Emerging Synthetic Methods for Routes Towards Molecules of Biological Relevance

Thesis submitted to the University of Strathclyde in fulfilment of the requirements for the degree of Doctor of Philosophy

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This thesis is a result of the author's original research. It has been composed by the author and has not been previously submitted for examination, which has led to the award of a degree.

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Ten years ago as I applied for a position at university I mentioned to my then girlfriend that chemistry would be a good subject to study. I thought that it was important to have a good education behind me in the unlikely event that my band didn't make it big – she thought this was quite a sensible plan! I have been lucky enough to have that girl by my side for the last ten years and she has encouraged me in everything I have ever attempted. She has pushed me on when I didn't have faith in myself and she has helped me pick myself back up when I have been knocked down. I am so happy to now call her my wife and am so incredibly grateful to her for all her support over the last ten years – don't worry Jen, I'll take the lead for the next ten!

“Education is an admirable thing, but it is well to remember from time to time that nothing that is worth knowing can be taught.”

— Oscar Wilde

“I learned very early the difference between knowing the name of something and knowing something.”

— Richard Feynman

“Whenever you find yourself on the side of the majority, it is time to pause and reflect.”

— Mark Twain

For Jen

Abstract

Investigations into the application of catalysts, of the type $[Ir(COD)(PR_3)(NHC)]PF_6$, within the realm of alkyne dimerization have been undertaken. These novel catalysts, previously synthesised within our research group, feature both a bulky phosphine ligand and a sterically-encumbered *N*-heterocyclic carbene ligand. The use of these iridium complexes in alkyne dimerization has been examined, with particular emphasis being placed upon tuning the selectivity of the dimerization whilst maintaining high yields. The relative paucity of iridium-mediated (*Z*)-selective dimerization procedures detailed in the literature rendered this transformation an appealing process to investigate. Subsequent studies led to a broadly employable system being developed which was applied to a range of aryl alkynes, resulting in the formation of the analogous (*Z*)-enynes in good yield.

Following this, a programme of research in collaboration with the Beatson Institute for Cancer Research, Glasgow, describes contributions towards the construction of specific '3D libraries' for potential application in fragment-based drug discovery. The chemistry investigated during this time forms the basis of the Beatson's contribution to the recently formed '3D libraries consortium' concerned with the fragment-based drug discovery. The ultimate goal was the preparation of an array of compounds featuring a non-planar conformation. It is hypothesised that the fragments will play key roles in inhibiting protein-protein interactions in key oncological processes. Further, it is envisaged that the conformational complexity imparted to the compounds will provide an advantage in overcoming difficulties associated with protein specificity. The aim of the project was to design a synthetic route to a novel pyridyl cyclopropane scaffold. The goal was that the preparative approach would allow for rapid access to a key late-stage intermediate, which in turn would then be able to undergo a series of transformations to allow for a range of fragments, based around a common scaffold, to be synthesised. The isolated compounds will form the basis of biophysical and biochemical based screening assays examining the compound's anti-cancer profile, with particular focus on identifying inhibitors of protein-protein interactions.

The final section of research centred on efforts towards the total synthesis of Agariblazeispirol C. As a result, significant steps towards the synthesis of the natural product have been achieved and a functionalised advanced intermediate has been reached. In this regard, a robust and efficient preparative pathway to the advanced intermediate has been designed. In addition, the key oxygenated sidechain has been installed in a late-stage species and represents an auspicious step towards the synthesis of the target molecule. The introduction of this key moiety was achieved following sustained synthetic efforts focusing on olefination and organometallic addition chemistry. The stereochemistry of the resulting intermediate has been deduced based on NMR studies. Subsequent synthetic investigations facilitated the formation of a suitable precursor for the ultimate synthetic transformation, a Pauson-Khand reaction. Preliminary attempts to promote the annulation protocol are discussed and it is likely that this work will significantly enhance the likelihood of accessing the natural product for the first time.

Abbreviations

°C	Degrees Celsius
3D	Three Dimensional
Ac	Acetyl
Ad	Adamantyl
ADME	Absorption, Distribution, Metabolism, and Excretion
Ar	Aryl
atm.	Atmospheres
BARF	Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
biph	Biphenyl
Bn	Benzyl
Bu	Butyl
CDK	Cyclin Dependent Kinase
COD	Cycloocta-1,5-diene
Cp*	1,2,3,4,5-Pentamethylcyclopentadienyl
Cy	Cyclohexyl
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DIAD	Diisopropyl Azodicarboxylate
DIBAL-H	Di*iso*butylaluminium Hydride
DMF	Dimethylformamide
DMP	Dess Martin Periodinane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(*1H*)-pyrimidinone
DMSO	Dimethyl Sulfoxide
Dod	Dodecyl
dppb	1,4-Bis(diphenylphosphino)butane

dppf	1,1'-Bis(diphenylphosphino)ferrocene
ee	Enantiomeric Excess
Et	Ethyl
Et_3N	Triethylamine
eq	Equivalents
FBDD	Fragment Based Drug Discovery
FCC	Flash Column Chromatography
g	Grammes
GC-MS	Gas Chromatograhy Mass Spectrometry
h	Hours
HATU	2-(1H-7-Azabenzotriazol-1-yl)-1,1,3,3-Tetramethyl Uronium Hexafluorophosphate Methanaminium
HIE	Hydrogen Isotope Exchange
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
HTS	High-throughput Screening
HWE	Horner-Wadsworth-Emmons
Hz	Hertz
IC_{50}	Concentration of an Inhibitor required for 50% Inhibition of Enzyme Activity
IAd	1,3-Bis(1-adamantyl)imidazoline-2-ylidene
ICy	1,3-Bis(cyclohexyl)imidazoline-2-ylidene
IMe	1,3-Bis(methyl)imidazoline-2-ylidene
IMes	1,3-Bis(2,4,6-trimethylphenyl)imidazoline-2-ylidene
I^{i}Pr	1,3-Bis(2,6-diisopropylphenyl)imidazoline-2-ylidene
^{i}Pr	Isopropyl
^{i}PrMgCl	Isopropylmagnesium chloride
IR	Infrared

KHMDS	Potassium Bis(trimethylsilyl)amide
kJ	Kilojoules
L	Ligand
LC-MS	Liquid Chromatography – Mass Spectrometry
LDA	Lithium Di*iso*propylamide
LE	Ligand Efficiency
LiHMDS	Lithium Bis(trimethylsilyl)amide
μM	Micromolar
M	Molar
mCPBA	*meta*-Chloroperoxybenzoic Acid
Me	Methyl
Mes	Mesityl
mg	Milligrammes
MHz	Megahertz
min	Minutes
ml	Millilitres
mM	Millimolar
mmol	Millimoles
mol	Moles
Ms	Methanesulfonyl
MW	Molecular Weight
MWI	Microwave Irradaiation
NaHMDS	Sodium Bis(trimethylsilyl)amide
NBS	*N*-Bromosuccinimide
^{n}BuLi	*n*-Butyllithium
nM	Nanomolar
NHC	*N*-Heterocyclic Carbene

NMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear Magnetic Resonance
	s – singlet
	d – doublet
	t – triplet
	q – quartet
	m – multiplet
	bs – broad singlet
	bd – broad doublet
	dd – doublet of doublets
	dt – doublet of triplets
	qt – quartet of triplets
	ddq – double doublet of quartets
NOESY	Nuclear Overhauser Effect Spectroscopy
o	*Ortho*
p	*Para*
Pd/c	Palladium on Carbon
Ph	Phenyl
PhMe	Toluene
Pin	Pinicolato
PKR	Pauson-Khand Reaction
PPI	Protein-Protein Interactions
ppm	Parts Per Million
PTSH	Phenyltetrazole Thiol
py	Pyridine
rt	Room Temperature
S	Solvent

S_NAr	Nucleophilic Aromatic Substitution
SIMes	1,3-Bis(2,4,6-trimethylphenyl)imidazolidin-2-ylidene
SIPr	1,3-Bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene
TBAF	Tetra-*n*-butylammonium Fluoride
TBAI	Tetra-*n*-butylammonium Iodide
TBS	*Tert*-butyldimethylsilyl
TDMPP	Tris(2,6-dimethoxyphenyl)phosphine
Temp.	Temperature
tert	Tertiary
THF	Tetrahydrofuran
Tf	Trifluoromethanesulfonyl
TLC	Thin Layer Chromatography
TMANO	Trimethylamine *N*-oxide
TMS	Trimethylsilyl
Tp	Trispyrazolylborate
Ts	Tosyl
UV	Ultraviolet

Contents

Abstract		**i**
Abbreviations		**iii**
Contents		**viii**

It should be noted that each Chapter is self-contained possessing individually associated experimental procedures and reference section.

Chapter 1	*Z*-Selective Dimerization of Aromatic Terminal Alkynes Catalyzed by an Iridium(I)-*N*-Heterocyclic Carbene-Phosphine System	**1**
Chapter 2	Development of Novel α-Helix Mimetics for Screening within Fragment-Based Drug Discovery	**125**
Chapter 3	Towards the Total Synthesis of Agariblazeispirol C	**214**

Chapter 1

Z-Selective Dimerization of Aromatic Terminal Alkynes Catalyzed by an Iridium(I)-*N*-Heterocyclic Carbene-Phosphine System

Contents

1.	**Introduction**	4
	1.1 Alkyne Dimerization	5
	1.2 Transition Metal-catalysed Alkyne Dimerization	7
	1.2.1 Palladium-catalysed Dimerization	7
	1.2.2 Nickel-catalysed Dimerization	8
	1.2.3 Ruthenium-catalysed Dimerization	9
	1.2.4 Rhodium-catalysed Dimerization	11
	1.2.5 Iridium-catalysed Dimerization	12
	1.3 Chemistry of Iridium	18
	1.3.1 Initial Employment within Organic Chemistry	18
	1.3.2 Catalyst Development	20
	1.4 Phosphines as Ligands	24
	1.5 *N*-Heterocyclic Carbenes as Ligands	26
	1.6 Kerr Group Catalysts	32
2.	**Previous and Proposed Work**	35
	2.1 Precedent for Investigation	35
3.	**Results and Discussion**	38
	3.1 Synthesis of Iridium(I) Complexes	38
	3.2 Application of Iridium(I) Complexes in Alkyne Dimerization	41
	3.3 Catalyst Comparison	42
	3.4 Reaction Mechanism	44
	3.5 Solvent Study	45
	3.6 Phosphine as an Additive	46
	3.7 Phosphine Loading	50
	3.8 Concentration Study	54
	3.9 COD Dissociation Study	55
	3.10 Temperature Study	57
	3.11 Time Study	58

3.12 Alternate Phosphine Study 60
3.13 Microwave Promotion 61
3.14 COD Hydrogenation Studies 63
3.15 Summary of Optimisation Studies 66
3.16 Expansions of the Substrate Scope 67
3.17 Corey-Fuchs Alkynylation 69
3.18 Dimerization of Aromatic Alkynes 72

4. Conclusion 78

5. Future Work 81

6. Experimental 83
6.1 General 83
6.2 General Procedures 85
6.3 Preparation of Iridium(I) Complexes 88
6.4 Alkyne Dimerization 92

7. References 122

1 Introduction

Transition metal complexes have played a major role in organic synthesis over the last fifty years.[1] Such species can facilitate transformations that would be difficult, or in some cases impossible, through the employment of traditional organic chemistry. Whilst many first- and second-row transition metals, particularly those found in groups 8-11, have been effectively employed as catalysts, there are much fewer examples of third-row complexes being utilised within organic synthesis. This is largely attributed to the increased stability, hence reduced reactivity, of the metal-carbon bond observed in complexes bearing a third-row transition metal.[1] As a result, during the formative years of organometallic chemistry it was generally accepted that third-row transition metals were inefficient catalysts for various synthetic transformations.

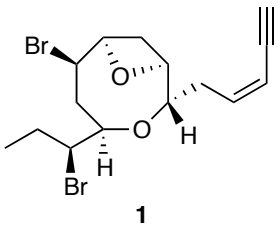
As a result of the initial hypothesis that third-row transition metals were synthetically less applicable, it was deemed that their perceived lack of reactivity could be exploited in order to access a range of substituted organometallic species. It was reasoned that these novel complexes could provide a more robust understanding of the elementary steps taking place during transition metal mediated transformations. In relation to this, an iridium species, $IrCl(CO)(PPh_3)_2$, commonly known as Vaska's complex, was employed in theoretical studies.[2] As predicted, the complex underwent a few rudimentary transformations and, as result of these investigations, chemists were able to identify the oxidative addition reaction pathway.[1] The general consensus around the time of these initial studies led to the belief that these types of complexes were too stable to be of any use in organic synthesis. As a result, the development of iridium catalysts received significantly less attention than rhodium and palladium catalysts.

It was not until the landmark discovery of Crabtree's catalyst, in the late 1970's, that the potential synthetic value of iridium complexes was realised.[3] This was the first homogenous catalyst capable of reducing tetrasubstituted olefins, an attribute lacking in the traditionally employed rhodium-based species, Wilkinson's catalyst.[4] Additionally, Stork and co-workers showcased the directing ability of Crabtree's catalyst, with the presence of

a hydroxyl group on the substrate leading to a strongly controlled diastereoselective hydrogenation.[5] Whilst the research into iridium-catalyzed processes received moderate interest through to the 1990's, since the turn of the century this has grown exponentially. As a result, there are now numerous examples of carbon-carbon and carbon-heteroatom bond forming reactions being catalysed by iridium complexes.[6] In addition, there are significant reports concerning the success of iridium catalysts within the field of C-H activation.[7] The functionalisation of an unactivated carbon-hydrogen bond represents the holy grail for many organic chemists. As such, the development of reaction protocols exploiting this ability has received considerable interest and represents a popular area of research within organic chemistry.

1.1 Alkyne Dimerization

The catalytic synthesis of π-conjugated enyne systems has attracted considerable interest in recent years. Enynes are recurring building blocks and, indeed, key components in a variety of pharmaceuticals, industrial intermediates, and natural products, such as (+)-3-(*Z*)-Laureatin **1**, (**Figure 1**).[8]

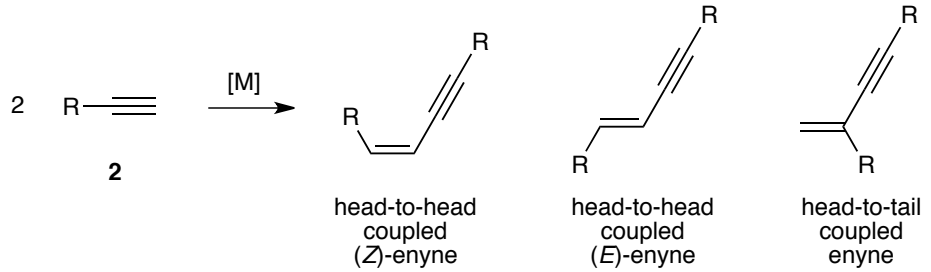


1

Figure 1

With regards to the synthesis of such moieties, there are a number of possible approaches, which mainly include metal-catalysed cross coupling reactions.[9] Of these, the palladium/copper co-catalysed alkynylation of aryl and vinyl halides is regarded as the most widely employed methodology to form enynes. However, there have been increased

endeavours to enhance the general atom economy of enyne formation, as well as improving the chemo-, regio-, and diastereoselectivity of the emerging processes. In this regard, alkyne dimerization facilitates the formation of these compounds with unprecedented atom economy, although the regiocontrol of this approach has proven challenging. As such, the establishment of methods that deliver desirable levels of regio- and stereocontrol provides a continuing challenge within this area. In this regard, the potential enyne isomers obtainable *via* alkyne dimerization are illustrated in **Scheme 1**.



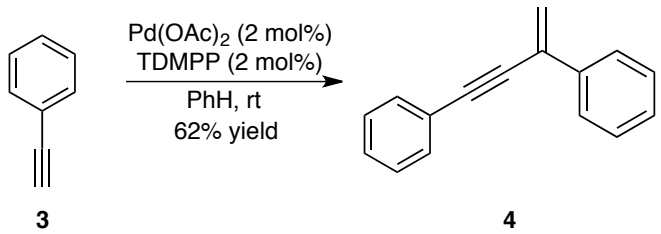
Scheme 1

As detailed in above, there is the potential to form either (*Z*) or (*E*) head-to-head coupled products, as well as the head-to-tail coupled enyne. In addition to this, a number of by-products can also be formed, most notably substituted aromatic rings, which are a result of [2+2+2] cyclotrimerization reactions.[10] Despite this, there has been a drive by the synthetic community to establish methods that deliver efficient levels of regio- and stereocontrol within this transformation (*vide supra*).

1.2 Transition Metal-catalysed Alkyne Dimerization

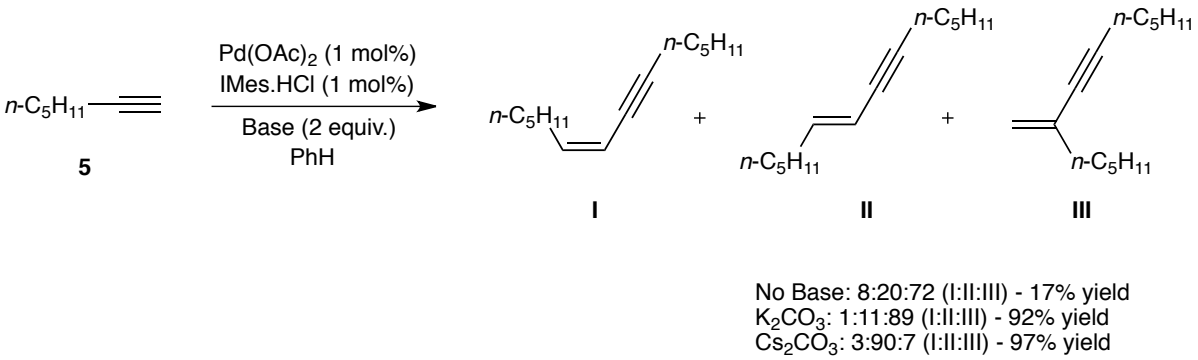
1.2.1 Palladium-catalysed Dimerization

Palladium-mediated dimerization of alkynes often results in the formation of the head-to-tail coupled product. In this regard, Trost and co-workers were able to facilitate the homodimerization of a number of alkynes by utilising palladium acetate in conjuction with tris(2,6-dimethoxyphenyl)phosphine (TDMPP) as a ligand.[11] The authors reported the successful head-to-tail dimerization of phenylacetylene in a 62% yield (**Scheme 2**). In addition, a broad range of substrates underwent head-to-tail dimerization in moderate to good yield.



Scheme 2

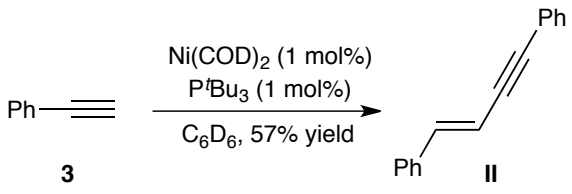
Following on from this, Nolan and co-workers investigated the use of a palladium-NHC species with the goal of elaborating on the scope of palladium catalysts in the reductive coupling of alkynes.[12] An array of terminal alkynes dimerized to the (*Z*)-enyne (**I**) and (*E*)-enyne (**II**), as well as the head-to-tail product (**III**) in good yield. With respect to the dimerization of heptyne, **5**, the authors reported a poor yield of 17% accompanied by a relatively unpronounced product distribution (**Scheme 3**). Interestingly, upon screening additives it was discovered that potassium carbonate facilitates a 92% yield of dimerized product with good selectivity for **III** being observed. Further still, employment of cesium carbonate as an additive led to an excellent 97% yield, with (*E*)-enyne **II** formed in a selective manner. It should be noted that the authors cannot account for the role that the base plays in the synthetic transformation. Based on this, the unpredictable nature of the transformation severely limits its synthetic utility.



Scheme 3

1.2.2 Nickel-catalysed Dimerization

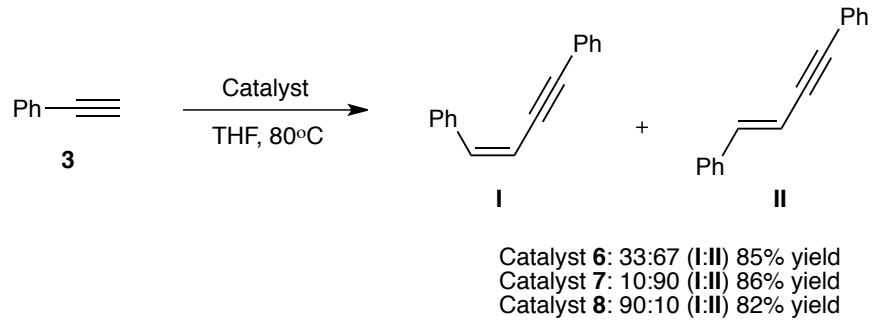
Nickel has also been successfully employed in alkyne dimerization. Ogoshi and co-workers envisaged that a tighter coordination sphere around the metal centre would be more efficient for the formation of the head-to-head (*E*)-enyne, with the steric effects of the ligands being maximised by the small radius of nickel.[13] Phenylacetylene, **3**, underwent a selective dimerization in a moderate 57% yield (**Scheme 4**). In addition, a limited range of alkynes underwent the selective dimerization protocol in moderate to good yield. In addition, the authors reported the first successful dimerization of tributylstannylacetylene, with the product of this reaction being able to undergo subsequent Stille coupling reactions.



Scheme 4

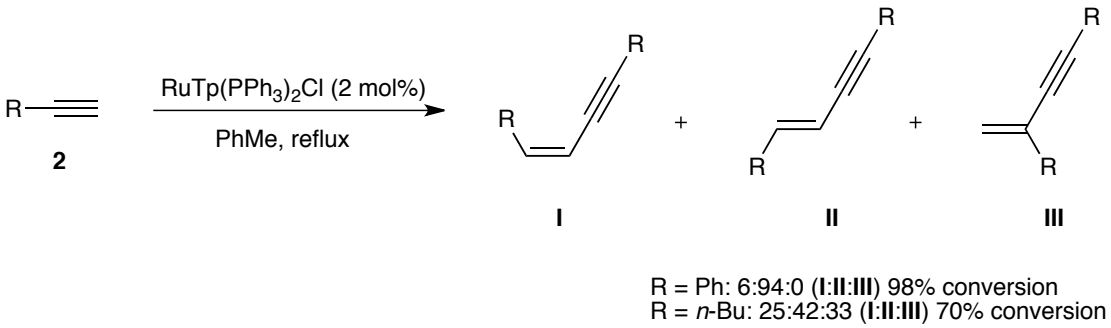
1.2.3 Ruthenium-catalysed Dimerization

Ruthenium hydride complexes have also proven effective within this arena. Yi and Liu applied a range of ruthenium complexes: $Cp^*Ru(PPh_3)H_3$, **6**, $Cp^*Ru(PCy_3)H_3$, **7**, and $Cp^*Ru(PMe_3)H_3$, **8**, to a small range of alkyne substrates and obtained reasonable selectivity with good yields of the desired dimerized products (**Scheme 5**).[14] Catalyst **6** promoted the dimerization in an impressive 85% yield, however the selectivity observed was moderate. However, the employment of catalyst **7** proved more successful and selectively formed **II** in an 86% yield. In contrast, catalyst **8** promoted the selective formation of **I** in an 82% yield. It is worth noting that, disappointingly, no one specific catalyst produced a uniform selectivity across the range of substrates investigated. Accordingly, it is thus unfeasible to accurately predict the main product of dimerization.



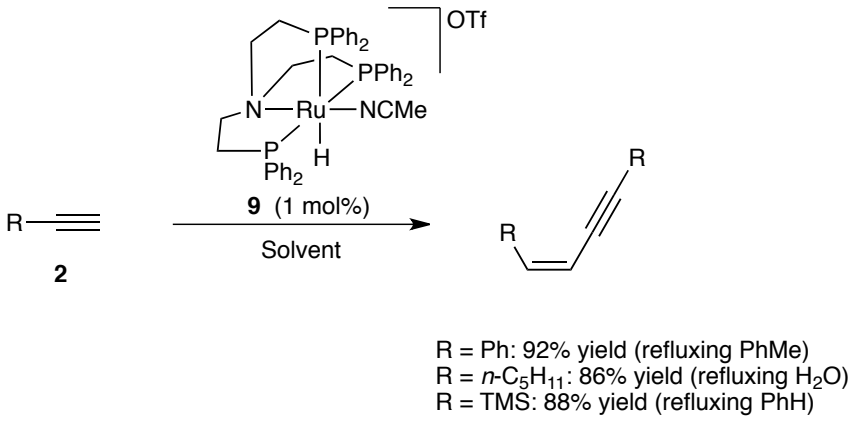
Scheme 5

The catalytic coupling of a limited range of substrates, through a ruthenium complex, was also reported by Kirchner *et al.*,[15] with the complex $RuTp(PPh_3)_2Cl$ successfully coupling phenylacetylene to yield (*E*)-1,4-diphenyl-1-buten-3-yne as the major product (**Scheme 6**). Unfortunately, alternative substrates, such as hex-1-yne, coupled with unexpected selectivity. Indeed, this proves detrimental to the overall employability of this catalytic system.



Scheme 6

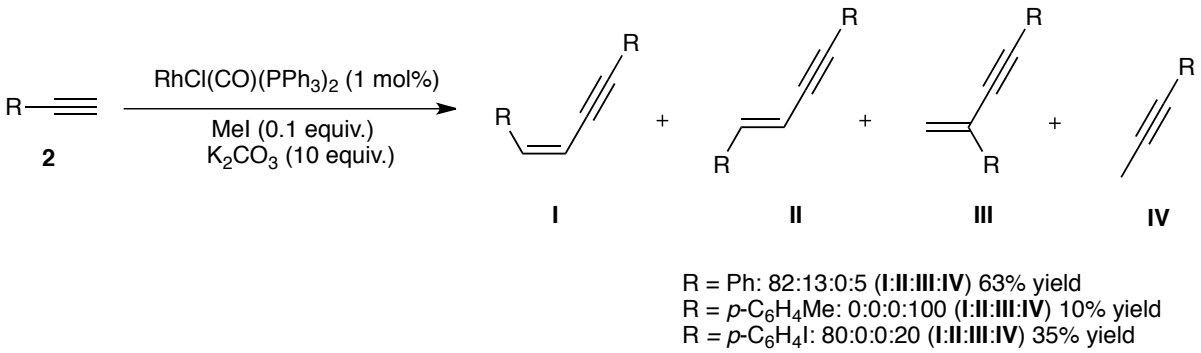
The most versatile ruthenium complex, $RuH(CH_3CN)(NPR_2R')OTf$, **9**, capable of facilitating reductive coupling was developed by Jia and co-workers in 2005.[16] This ruthenium catalyst is capable of facilitating (*Z*)-selective head-to-head dimerization of both aliphatic and aromatic alkynes (**Scheme 7**). Systems capable of achieving this feat are relatively rare. Having stated this, some of the aliphatic alkynes reacted in an inefficient manner in organic solvents, however, and required either aqueous or solvent-free conditions to deliver the products in good yields.



Scheme 7

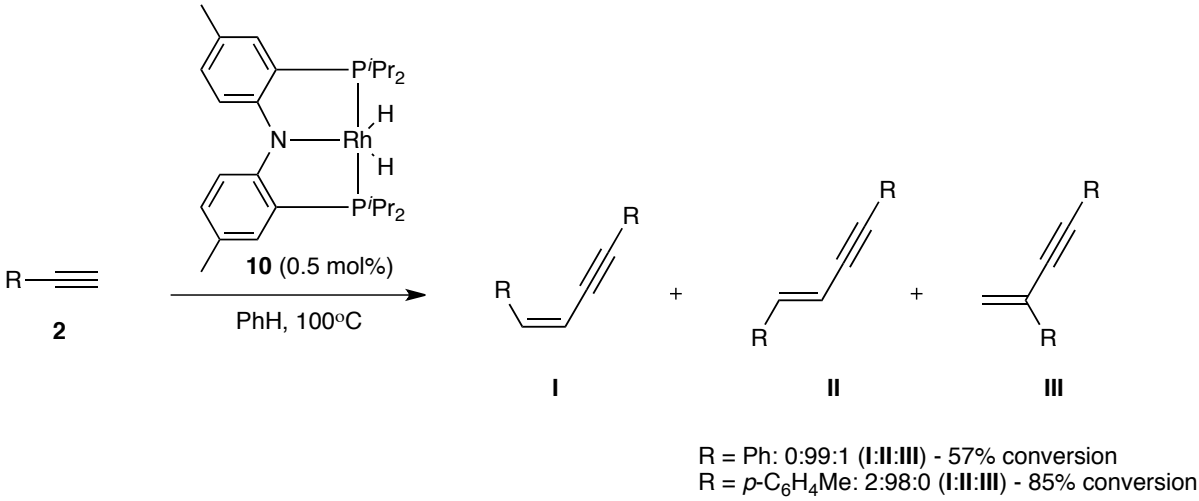
1.2.4 Rhodium-catalysed Dimerization

Lin and co-workers reported a rhodium-catalysed dimerization which was assisted by sub-stoichiometric quantities of methyl iodide (MeI) (**Scheme 8**).[17] The authors reported that the rhodium pre-catalyst underwent oxidative addition with MeI to form the active catalytic species *in situ*. Although the dimerization of phenylacetylene proceeded with impressive selectivity, the yield obtained was moderate. In addition, the attempted dimerization of *p*-tolylacetylene resulted in the exclusive formation of the undesired internal alkyne **IV**. Further yet, *p*-iodophenylacetylene dimerized to furnish the (*Z*)-enyne, **I**, in a relatively selective manner however a poor yield of 35% was obtained. As illustrated here, the outcome of the alkyne dimerization process is difficult to predict and, as such, necessitates a great deal of trial and error with respect to promoting the desired transformations.



Scheme 8

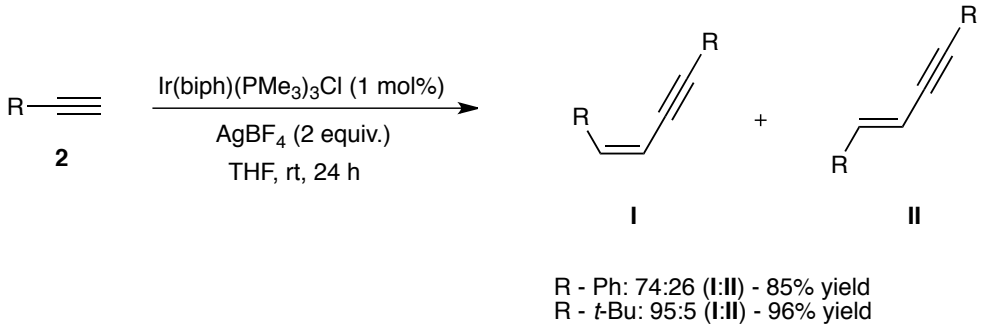
A further example of rhodium-based species being employed within the realm of alkyne dimerization was disclosed by Ozerov and co-workers.[18] The authors utilised a rhodium complex featuring a bulky PNP pincer ligand (**Scheme 9**) to facilitate the formation of (*E*)-1,4-disubstituted enynes, **II**. Alternative aromatic alkynes underwent dimerization to the analogous (*E*)-enyne products, **II**, equally well with moderate to very good conversions being observed for a range of substrates.



Scheme 9

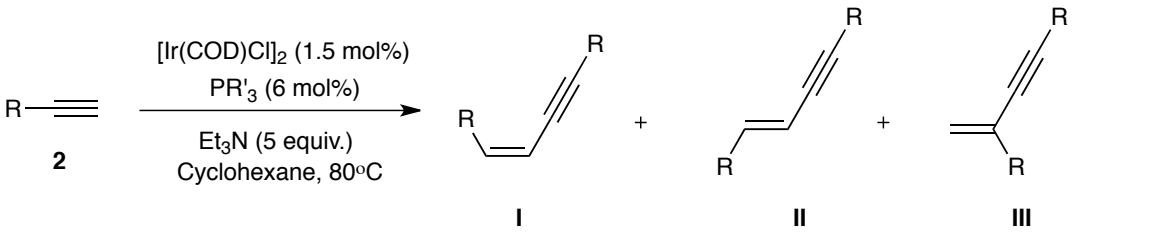
1.2.5 Iridium-catalysed Dimerization

One of the first examples of head-to-head alkyne dimerization, employing an iridium catalyst, was presented by Crabtree.[19] The complex Ir(biph)$(PMe_3)_3Cl$, with $AgBF_4$ acting as an additive, effectively dimerized a limited range of substrates (**Scheme 10**). Crabtree proposed that the $AgBF_4$ most likely facilitates abstraction of the chloride and/or phosphine ligand(s) to form the active catalyst. Phenylacetylene was shown to undergo (*Z*)-selective head-to-head dimerization, in an 85% yield in what was one of the first examples of iridium-catalysed alkyne dimerization. In addition, *tert*-buylacetylene was efficiently dimerized, in a 96% yield, under the reaction conditions. It should be noted that phenylacetylene was the only aryl alkyne species reported to undergo the selective dimerization protocol.



Scheme 10

The use of iridium complexes in alkyne dimerization was perhaps most aptly, and impressively, demonstrated by Miyaura and co-workers.[20] They reported that the stereoselectivity of the products formed was dependent on both the alkyne and the phosphine ligand on the catalyst. In these examples, the catalyst was generated *in situ* and the reaction greatly accelerated by the presence of a base (**Scheme 11**). The authors investigated the ability of triisopropylsilylacetylene to undergo selective dimerization. It was discovered that the strongly electron-donating tripropylphosphine ligand (PPr_3) was able to facilitate the (*Z*)-selective dimerization in a 70% yield. It should be noted that the electronic nature of phosphines will be discussed in a later section of the thesis. In contrast, the comparably less donating triphenylphosphine ligand (PPh_3) facilitated the (*E*)-selective dimerization in a 50% yield. In addition, *para*-tolylacetylene underwent (*Z*)-selective dimerization when PPr_3 was employed as the ligand and a 67% yield of the dimerized product was isolated. As before, the PPh_3 ligand promoted the (*E*)-selective dimerization process albeit in a poor 19% yield. As can be observed from **Scheme 11**, the selectivity of these processes is only relatively moderate. Further, *para*-tolylacetylene and *ortho*-tolylacetylene were the only aryl alkyne substrates reported to undergo the developed reaction protocol. As such, it is clear that this approach is not widely effective across a range of aryl alkynes.

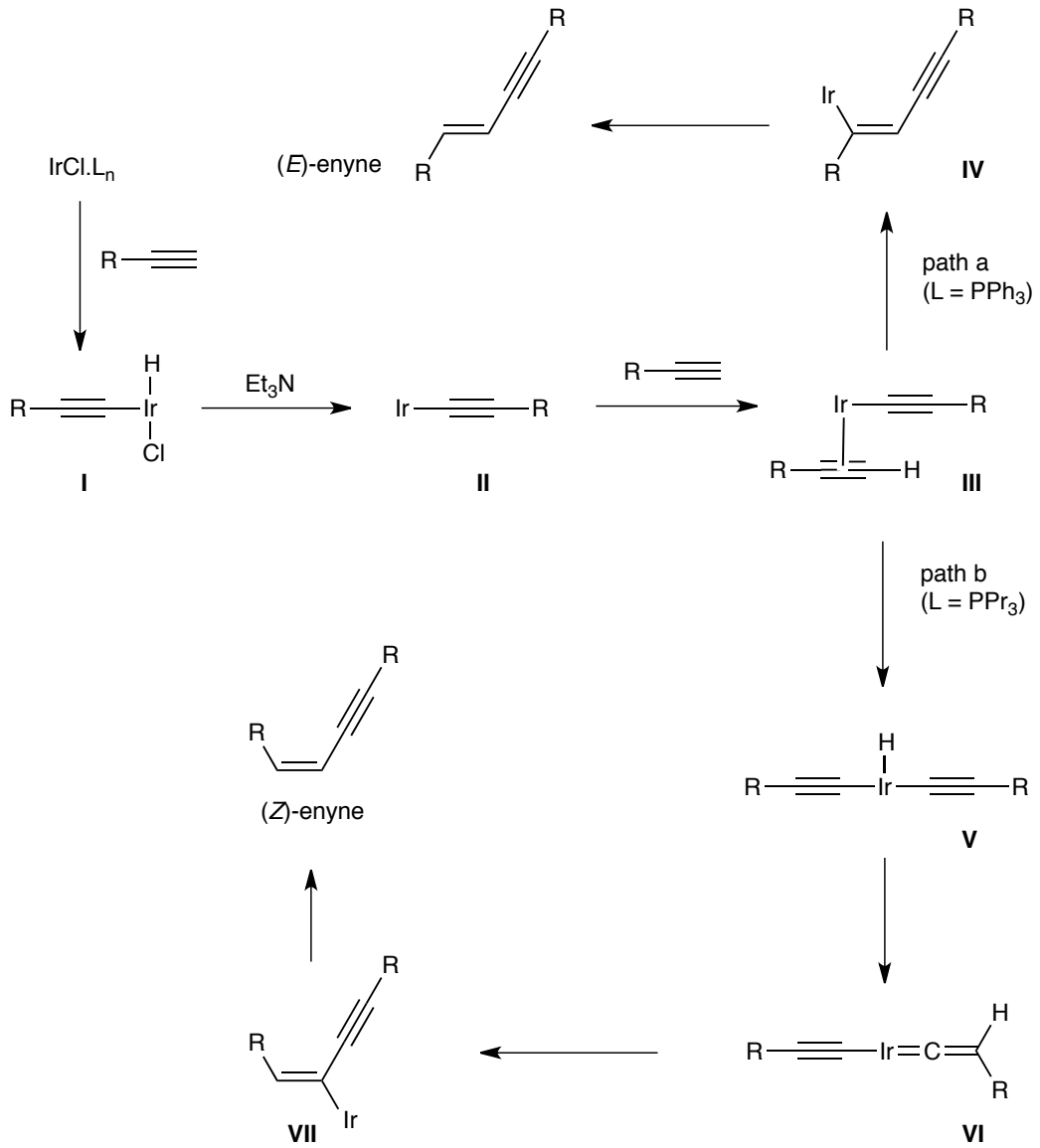


R - Si^{i}Pr$_3$, PR'$_3$ - PPr$_3$ 86:14:0 (**I**:**II**:**III**) - 70% yield
R - Si^{i}Pr$_3$, PR'$_3$ - PPh$_3$ 14:86:0 (**I**:**II**:**III**) - 50% yield
R - *p*-MeC$_6$H$_4$, PR'$_3$ - PPr$_3$ 76:24:0 (**I**:**II**:**III**) - 67% yield
R - *p*-MeC$_6$H$_4$, PR'$_3$ - PPh$_3$ 34:66:0 (**I**:**II**:**III**) - 19% yield

Scheme 11

Miyaura offered an explanation regarding the relationship between the selectivity obtained and ligand choice. It was theorised that highly electron-donating phosphines promote *Z*-selective dimerization, whereas phosphines donating comparably less electron density induce *E*-selective dimerization. This can be better understood by following the mechanism proposed by Miyaura *et al.* (**Scheme 12**). The authors propose that triethylamine promotes formation of the alkynl iridium complex **I**, which they believe is the active species for the catalytic transformation. Following on from this initial oxidative addition there is the potential for two separate mechanistic pathways. Firstly, when using a mildly electron-donating phosphine (PPh_3) the *E*-enyne is ultimately formed. It is proposed that following the initial complexation, **III**. The second alkyne species undergoes *syn*-insertion into the iridium-carbon bond, forming **IV**, which serves to liberate the *E*-enyne.

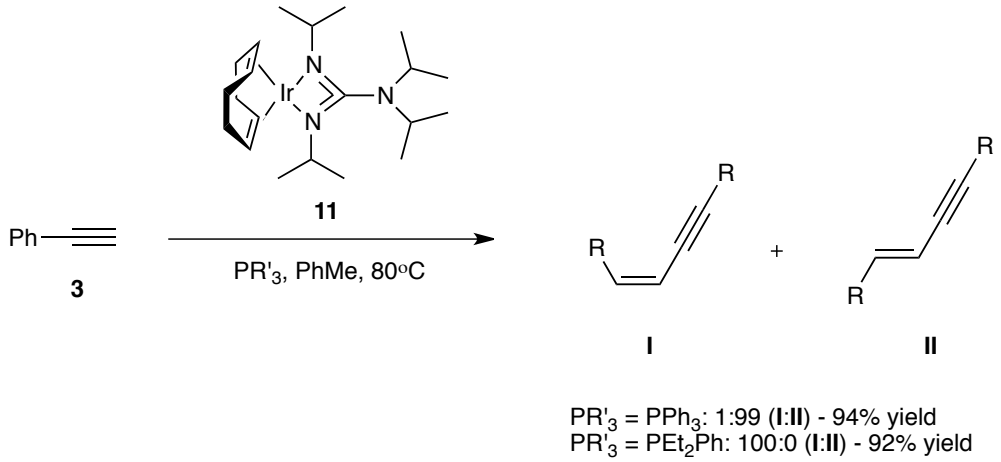
When using an appreciably more donating phosphine, such as PPr_3, the formation of the *Z*-enyne occurs predominantly. Pathway b represents the author's mechanistic rationale for the *Z*-selective products. In this case, the second alkyne unit undergoes oxidative addition to yield **V**. The presence of a highly electron-donating phosphine may enhance the iridium's ability to undergo this second oxidative addition pathway; more electron density is pushed onto the metal, from the ligand, promoting the subsequent oxidative addition. The authors propose that this is followed by insertion into the Ir-H bond, resulting in alkynl vinylidene species **VI**. The resulting complex is believed to undergo a rearrangement to **VII**, which ultimately liberates the *Z*-enyne.



Scheme 12

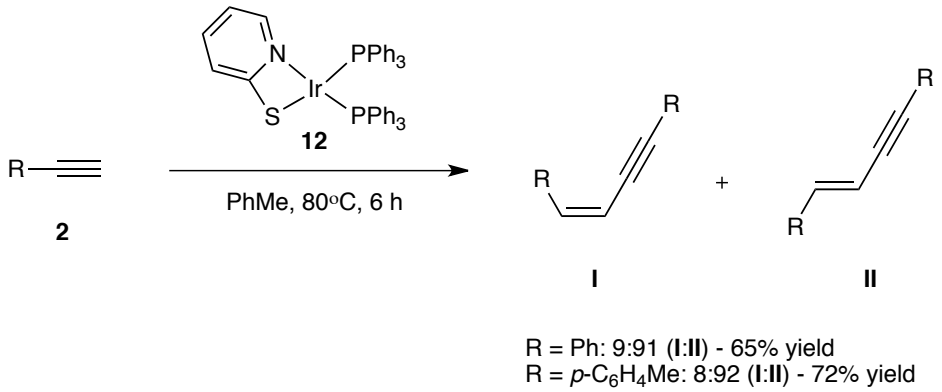
Miyaura's proposed mechanism, as delineated above, is without detailed experimental validation, however the authors highlight that the formation of vinylidene species **VI** is not uncommon within organometallic chemistry. Indeed, they appeal to the work of Wakatsuki *et al.* who reported an organometallic vinylidene species in a related catalytic system.[21] In addition, if a double oxidative addition pathway is taking place (path b) then it follows that an iridium(V) species is being formed during the course of the reaction. Miyaura *et al*. do not comment on this, however iridium(V) species have received considerable interest from the academic community in recent years.[22] Indeed, it is plausible that the above synthetic sequence, path b, does proceed *via* an iridium(V) intermediate.

A further example of iridium-mediated alkyne dimerization was reported by Fukuzawa and co-workers.[23] These authors reported the employment of iridium guanidinate complex, **11**, alongside a phosphine additive in the homo- and cross-dimerization of terminal alkynes. Species **11**, was employed with triphenylphosphine in the (*E*)-selective homodimerization of phenylacetylene (**Scheme 13**). In turn, a comparably more electron-donating phosphine, diethylphenylphosphine (PEt_2Ph) was employed in the (*Z*)-selective homodimerization of phenylacetylene. An impressive 92% yield was obtained of the (*Z*)-enyne, however, the (*Z*)-selective dimerization was not reproduced on any other aryl alkyne substrates. As such, there remains a paucity of iridium-mediated methods capable of promoting the (*Z*)-selective dimerization of a range of aryl alkynes.



Scheme 13

A final example of iridium-mediated alkyne dimerization, reported by Ogata and Toyota, is illustrated below (**Scheme 14**).[24] The authors successfully promoted the (*E*)-selective dimerization of phenylacetylene in a 65% yield and also successfully furnished the analogous *para*-methylphenylacetylene enyne in a 72% yield. These two aryl alkynes were the only such substrates to successfully undergo dimerization in a selective manner. Again, it is apparent that there is a distinct lack of methods available for promoting iridium-mediated (*Z*)-selective dimerization.



Scheme 14

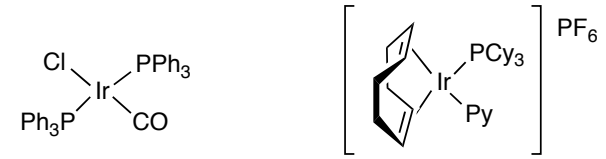
As discussed, the selective dimerization of alkynes represents an extremely efficient method of generating enyne moieties. There are a range of transition metal complexes that are capable of facilitating such a transformation, however promoting the (*Z*)-selective head-to-head dimerization has received significantly less attention than the analogous (*E*)-selective process (*vide supra*). More specifically, there is a distinct lack of iridum complexes that are capable of facilitating the (*Z*)-selective dimerization of a broad range of aryl alkynes. As such, this under populated research area represents a promising area to explore and could potentially lead to the expanded synthetic utility of iridium-based complexes.

The following overview provides a brief introduction to the properties of iridium and, more generally, grants insight into the attributes of ligands commonly associated with transition metal chemistry.

1.3 Chemistry of Iridium

1.3.1 Initial Employment within Organic Chemistry

As stated previously, the initial iridium-based species to emerge within the realm of organometallic chemistry was Vaskas' complex, **13** (**Figure 2**).[2] In the early 1960's Vaska's complex **13**, helped provide a fundamental understanding of the emerging field of homogenous catalysis. It was discovered that this coordinatively unsaturated complex, **13**, underwent a reaction with a range of electrophiles e.g MeI, to form an electronically saturated 18 (valence) electron species. These early experiments lead to a greater understanding of the oxidative addition pathway and, as such, played an integral role in the development of organometallic chemistry.[1] However, the synthetic utility of iridium was not fully appreciated until the late 1970's when Crabtree reported the isolation of complex **14**, which has come to be known as Crabtree's catalyst.[25]

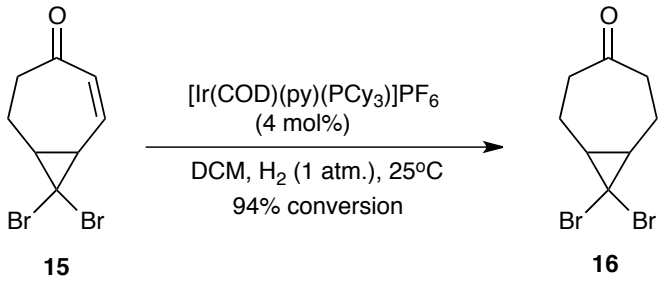


Vaska's Complex **13**

Crabtree's Complex **14**

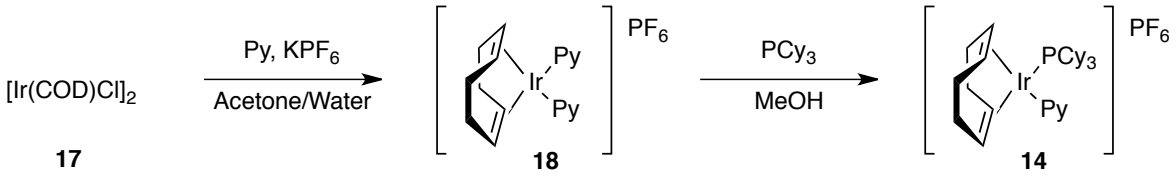
Figure 2

Following on from the initial isolation of complex **14**, significant synthetic studies were undertaken in the following years. Crabtree *et al*. reported that the novel complex was capable of promoting hydrogenation reactions on a wide range of substrates. Indeed, the hydrogenation of enone, **15**, proceeded in a 94% yield to the analogous saturated species, **16** (**Scheme 15**).[26] Hitherto, the rhodium-based complex, Wilkinson's catalyst, had proven the most effective homogenous hydrogenation catalyst.[27] However, Crabtree's catalyst was able to reduce tri- and even tetrasubstituted olefins,[28] an attribute lacking in Wilkinson's catalyst. The unprecedented activity displayed by Crabtree's catalyst in homogenous hydrogenation reactions has led to its widespread use in both industry and academia.



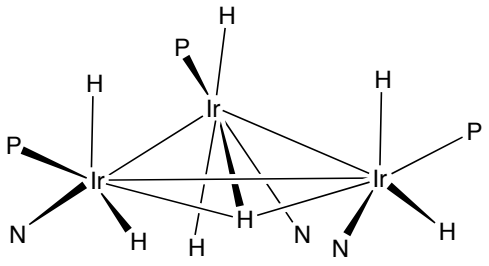
Scheme 15

Initially, an exchange reaction was employed to access **14**, however Crabtree disclosed an improved synthesis of **14**, whereby the iridium(I) chloride 1,5-cyclooctadiene complex dimer, **17**, was treated with pyridine and potassium hexafluorophosphate to furnish **18**. Following this, displacement of one of the pyridine ligands with tricyclohexylphosphine (PCy_3) facilitated access to the desired catalyst, **14** (**Scheme 16**).[29]



Scheme 16

Despite its previously unprecedented levels of activity, use of Crabtree's catalyst is not without its drawbacks. The choice of solvent is critical when employing Crabtree's catalyst, as non-coordinating solvents result in the formation of catalytically inactive precipitates, whereas chlorinated solvents fare much better.[28] In addition, the catalyst becomes inactive at higher temperatures due to its limited thermal stability. Interestingly, diminished yields are observed with higher catalyst loadings; it is understood that this is attributable to the irreversible trimerization of the coordinatively unsaturated catalyst. This process leads to the formation of inactive, and insoluble, triiridium hydride bridged complexes (**Figure 3**). It was hypothesised, by Crabtree, that the incorporation of bulky ligands would result in reducing the potential for catalyst deactivation. [28]



19

Figure 3

1.3.2 Catalyst Development

For the reasons explained above, within the last decade there has been extensive research dedicated to the modification of Crabtree's catalyst. The isolation of *N*-heterocyclic carbenes (NHC), and subsequent demonstration of their properties as ligands in catalytic cycles, has led to synthesis of various novel iridium catalysts with a range of impressive properties and attributes. In this regard, Nolan investigated the effect of replacing the tricyclohexylphosphine ligand, within Crabtree's catalyst, with an NHC, before exploring the use of the complex in a series of hydrogenation reactions.[30] Previous reports revealed that replacing bulky phosphine ligands with sterically demanding NHCs such as 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes), **20**, 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (I^iPr), **21**, and 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene (SIMes), **22** (**Figure 4**) resulted in a marked increase in catalyst performance over a range of metal-mediated reactions including olefin metathesis[31] and C-C bond formation reactions.[32] It was envisaged that the introduction of an NHC would therefore result in a more active and thermally stable catalyst, relative to the parent compound, **14**.

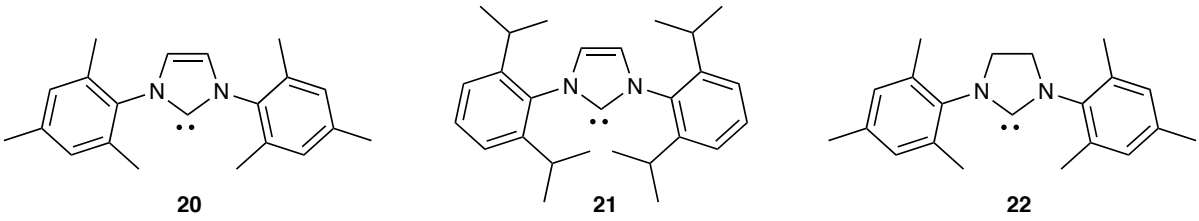
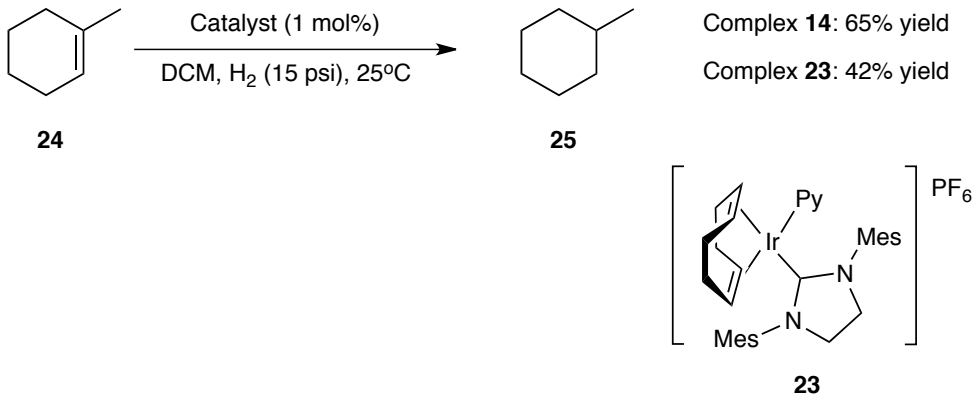


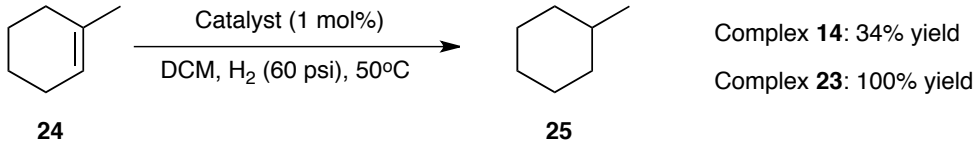
Figure 4

Accordingly, the catalytic activity of complex **23**, which featured an NHC ligand *in lieu* of PCy_3, was assessed in a range of hydrogenation reactions.[30] Based on this, the substituted cyclohexene species, **24**, was initially subjected to standard reduction conditions employing Crabtree's catalyst, **14**. The hydrogenation proceeded in an adequate 65% yield. In contrast, Nolan's amended NHC bearing analogue, **23**, was employed under the same reaction protocol and delivered the desired product in a less effective 42% yield (**Scheme 17**).



Scheme 17

However, when the reaction was repeated at elevated pressures and temperatures, a complete reversal in reactivity was observed. In this case, Crabtree's catalyst resulted in a much lower yield of 34%, whereas Nolan's catalyst, **23**, successfully hydrogenated the substrate to the corresponding saturated product in a 100% yield (**Scheme 18**).



Scheme 18

It is unsurprising that Crabtree's catalyst performed less well at elevated temperatures, as the thermal stability is relatively poor and catalyst deactivation tends to occur with increased temperatures (*vide supra*). In contrast, Nolan's complex, **23**, bearing a considerably bulky NHC, displayed excellent catalytic activity at elevated temperature and pressure. Accordingly, it is feasible to hypothesise that the bulky NHCs are serving to restrict the formation of dimerized/trimerized iridium complexes, whilst maintaining excellent catalytic performance.

In the following years, further modifications to Crabtree's catalyst, **14**, were undertaken by Buriak and co-workers. Where Nolan had replaced the phosphine moiety of Crabtree's catalyst, **14**, with a saturated NHC, Buriak and co-workers replaced the pyridine ligand with an unsaturated NHC, resulting in a mixed phosphine/NHC complex.[33] The resulting novel complexes are illustrated below **26**-**29** (**Figure 5**).

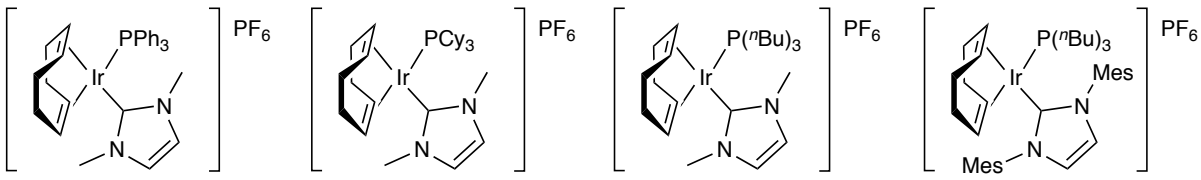
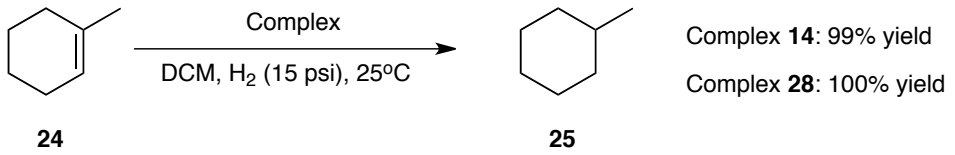


Figure 5

Across the board, the mixed phosphine/NHC complexes were found to be extremely robust and efficient catalysts. More specifically, complex **28** was capable of facilitating the complete hydrogenation of 1-methyl-1-cyclohexene, **24**, in an extremely efficient manner (**Scheme 19**). This was the first example of an NHC analogue of Crabtree's catalyst performing on par with the parent compound at room temperature.



Scheme 19

In subsequent studies Buriak *et al.* carried out further modifications of the mixed NHC/phosphine catalysts and introduced an alternative counter-ion. Where Crabtree's catalyst and the NHC derivatives thereof featured hexafluorophosphate (PF_6) as the counter-ion, Buriak and co-workers introduced the tetrakis(3,5-bis (trifluoromethylphenyl)borate (BARF) counter-ion (**Figure 6**).[34] The BARF counter-ion is considered less coordinating than the PF_6 species, due to the fact that the negative charge is spread out over the four electron-poor aryl rings.

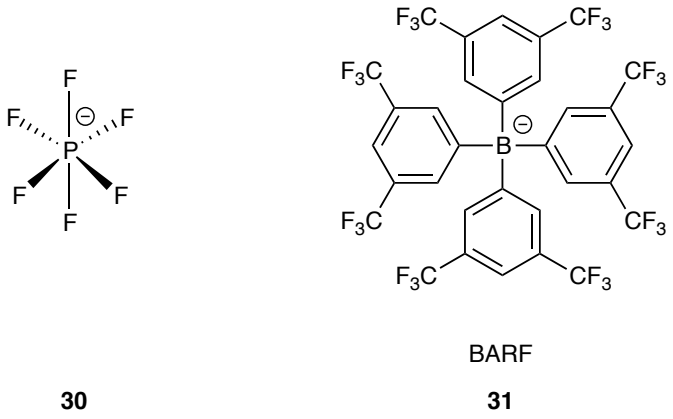


Figure 6

Buriak's catalysts were similarly employed as catalysts in the hydrogenation of mono-, di-, tri- and tetrasubstituted alkenes. Again, it was found that the BARF catalysts generally outperformed the PF_6 analogues in terms of both catalytic rate and long-term stability.[34]

1.4 Phosphines as Ligands

As can be seen from the examples shown previously, the properties of transition metal complexes can be manipulated by careful selection of the appropriate phosphine ligand. This has led to the widespread use of phosphines as ligands in organometallic chemistry. With respect to tertiary phosphines, the substituents present can be altered allowing control of both the electronic and steric properties of the phosphine. The bonding present between phosphines and their adjacent metal centre is comprised of two elements (**Figure 7**).[1] A σ-bond is formed by donation of the lone pair of electrons, from an sp^3 orbital, on the central phosphorus atom to the empty d-orbitals of the metal. In addition to this, phosphorus can also participate in π-backbonding, accepting electron density from filled d-orbitals of the metal. It is noteworthy to highlight that it is not the empty, low-lying d-orbitals of phosphorus that accommodate this electron density but instead the σ* orbital of the P-R bond.

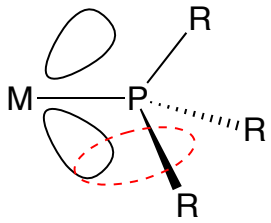


Figure 7

The steric and electronic parameters of phosphines must be quantified in order to fully appreciate the behaviour they induce in the resulting complexes. The steric influence of the phosphines is perhaps best understood by employing a model system developed by Tolman,[35] whereby the phosphines are defined in terms of their cone angle, θ, calculated by measuring the angle of a cylindrical cone, the apex of which is occupied by the metal centre (**Figure 8**). The outermost atoms of the substituents represent the maximum of the cone and, as such, the steric bulk associated with each phosphine can be determined.

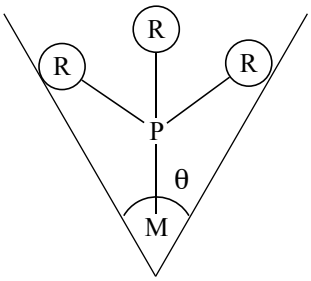


Figure 8

Thus, altering the R group of the phosphine can result in changes in the ligand bulk, which can, in turn, be fine-tuned to optimise the catalytic performance of the metal. This may be applied in cases where the subsequent coordination of other ligands is not desired; by using bulky phosphines the coordination of ensuing ligands is restricted. The cone angle measurements of some of the most widely employed phosphines are detailed in **Table 1**.

Phosphine	***Cone Angle (°)***
PMe_3	118
$P(O^iPr)_3$	130
PEt_3	132
$PMePh_2$	136
PPh_3	145

Table 1

The electronic parameters of phosphines were also quantified by Tolman.[35] This was achieved by measuring the infrared (IR) carbonyl stretch of a model nickel complex, $Ni(CO)_3L$, featuring different phosphines. It was found that as the σ-donation from the

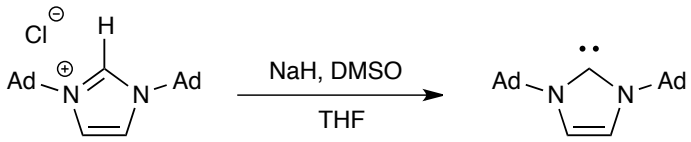
phosphine ligand increased, and π-acidity decreased, more electron density is pushed onto the metal centre. As a result, the electron density present in the π* orbital of the C-O is increased, which in turn lowers the stretching frequency observed by IR spectroscopy. The stretching frequencies obtained for some of the most commonly encountered phosphines are displayed in **Table 2**. With the most electron-donating phosphine, PCy_3, a low stretching frequency is observed. The converse is true for the least electron-donating phosphine shown, PPh_3.

Phosphine	***vCO cm^{-1} of Ni(CO)$_3$PR$_3$***
PPh_3	2068.9
PMe_3	2064.1
$P(^iPr)_3$	2059.2
PCy_3	2056.4

Table 2

1.5 *N*-Heterocyclic Carbenes as Ligands

The seminal work on NHCs was carried out by Öfele[36] and Wanzlick[37] in the late 1960's. The researchers, independently, synthesised the first organometallic complexes featuring NHC ligands. It was much later, in the early 1990's, that the isolation of free carbenes was eventually realised by Arduengo.[38] The first stable crystalline NHC, 1,3-di(adamantly)imidazol-2-ylidene, was prepared by deprotonation of the imidazolium salt **32** by either the dimsyl anion or KO^{t}Bu, allowing **33** to be isolated as colourless crystals (**Scheme 20**).



32 **33**

Scheme 20

The somewhat unique electronic properties of NHCs are responsible for their stability. NHCs are singlet carbenes and, as such, feature a pair of non-bonding electrons, which occupy an sp^2 orbital in the plane of the ring.[39] The stability of NHCs is attributed to the push-pull effect exhibited by these electrons (**Figure 9**). Firstly, the electron-withdrawing nitrogen stabilises the σ-nonbonding orbital through induction. Secondly, the vacant p-orbital on the carbene carbon can accept electron density from the adjacent heteroatoms. NHCs typically feature a nitrogen-carbene carbon bond length of 1.365Å, which is characteristic of a double bond. This gives further evidence to the nature of the interaction of the nitrogen lone pair with the p-orbital of the carbene carbon.

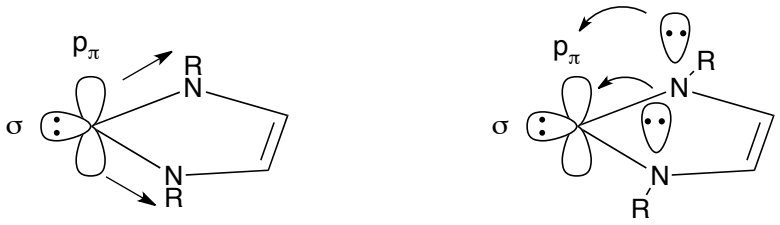
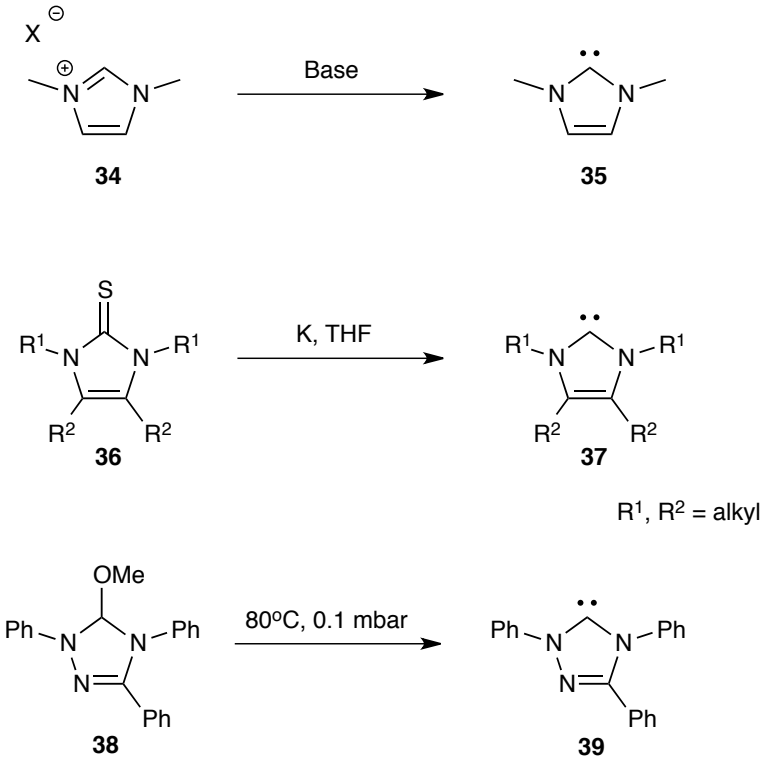


Figure 9

These electronic properties have led to the widespread use of NHCs as ligands in organometallic chemistry. The excellent σ-electron donating properties of NHCs and minimal π-backbonding results in very strong NHC-metal bonds and prevents decomposition of the various complexes being used as catalysts.

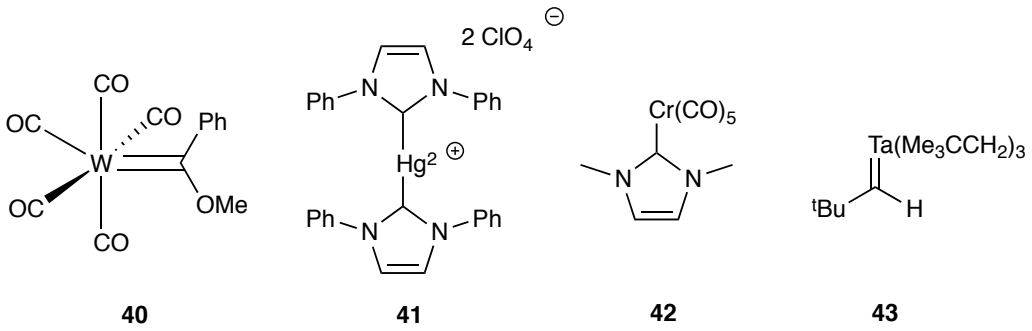
From a practical viewpoint, there are several main methods available for the formation of NHCs. These include deprotonation of the appropriate imidazolium salt, desulfurisation of thioureas, and thermolysis of methanol adducts (**Scheme 21**).[39]



Scheme 21

In relation to the above, the most widely used method to prepare NHCs is deprotonation of the corresponding imidazolium salt, **34**. Typically, NaH/KH in THF in the presence of DMSO (to generate the dimsyl anion) is employed. Indeed, Arduengo employed such a protocol to isolate the first NHC.[38] Reduction of the appropriate thiourea species, **36**, to the resulting imidazolin-2-ylidene using metallic potassium is an alternative route,[40] however, there have been reported issues regarding the reproducibility of this approach. The thermolysis of methanol adducts, resulting in NHCs, was developed by Enders and resulted in the formation of the corresponding triazol-2-ylidene, **39**, in good yields.[41] Having stated this, this method is complicated by the extreme sensitivity of the starting methanol adduct.

It is important to highlight, and reiterate, the seminal work in the development of metal-carbene complexes. The first carbene complex formed was that of complex **40**, which was discovered by Fischer,[42] with the subsequent independent research of Öfele and Wanzlick resulting in the formation of the first metal-NHC complexes, **41** and **42**, respectively (*vide supra*).[36,37] In 1974, a further class of carbenes was discovered by Schrock, as exemplified by complex **43** (**Figure 10**).[43] These new carbenes exhibited completely different reactivity from the preceding Fischer-type carbenes.



40 **41** **42** **43**

Figure 10

It is important to recognise, with regards to both Fischer- and Schrock-type carbenes, that the complexes formed feature a double bond between the metal and carbene. However, the polarity is different in the two cases, as the electron density is distributed differently for each class (**Figure 11**). This is a result of the different energy between the d_π orbital of the metal and the p_π orbital of the carbene. If the d_π orbital is lower in energy than the p_π orbital, then the metal carbon bond is polarised δ- on the metal and δ+ on the carbene, resulting in a Fischer carbene. If the opposite is true then the polarity of the metal-carbon bond is reversed and, as such, a Schrock carbene is formed. As stated previously, NHCs fall into the realm of Fischer carbenes. The p_π orbital of NHCs are extremely high in energy, due to the adjacent heteroatoms donating electron density into the p_π orbital.[39] As a result, there is poor interaction between the p_π and d_π orbital, rendering the potential for π-backbonding minimal.

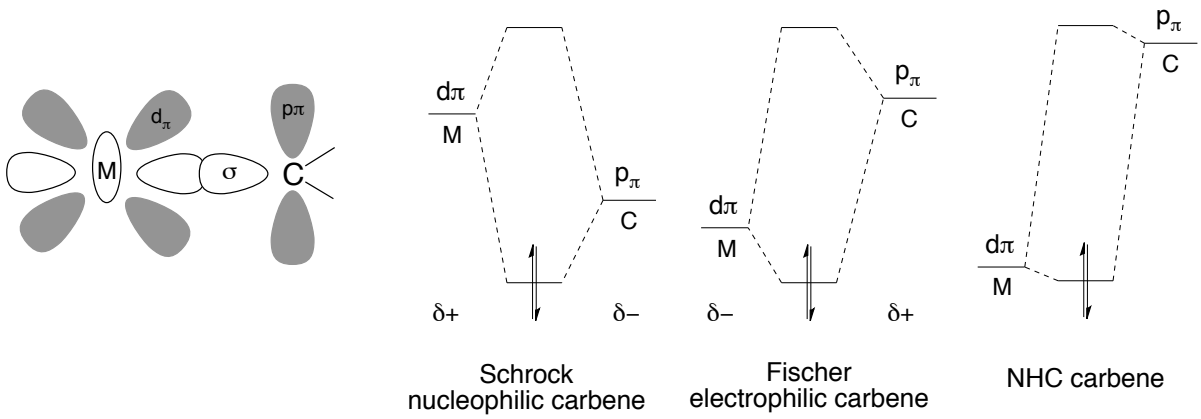


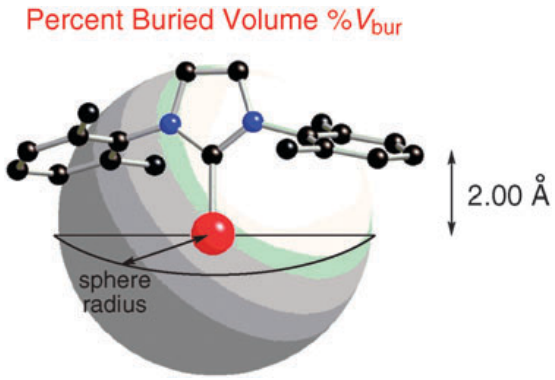
Figure 11

In an analogous manner to Tolman, Nolan and co-workers employed [(NHC)Ir(CO)$_2$Cl] as a standard to quantify both the electronic and steric parameters of the most frequently used NHCs.[44] Measurement of the IR carbonyl absorption frequency revealed that NHCs showed increased donor capacity relative to even the most donating phosphines. Moreover, the results of these investigations concluded that there was very little difference in the donor capacity of varying NHCs. The most electron-donating NHCs are, unsurprisingly, alkyl-substituted NHCs, with the IAd ligand exhibiting the greatest donor ability (**Table 3**).

NHC	***vCO cm^{-1} of (NHC)Ir(CO)$_2$Cl***
SIMes	2051.5
IMes	2050.7
ICy	2049.6
IAd	2049.5

Table 3

Quantifying the steric parameters of NHCs has proved more challenging. In relation to this, Nolan has introduced the concept of 'percent buried volume' ($\%V_{bur}$) as a model to determine the spatial occupation of various ligands.[45] The $\%V_{bur}$ is defined as the percent of the total volume of a sphere occupied by a ligand. The volume of this sphere represents the potential coordination sphere space around the metal occupied. By appealing to the information in **Table 4**, it can be observed that the metal (red) is positioned in the centre of a hypothetical sphere possessing a radius of 3.50 Å. In addition, a coordinated NHC ligand is positioned 2 Å from the metal. Based on this, the volume of the sphere occupied by the NHC ligand can be deduced, this provides integral information relating to the steric bulk of the NHC. By utilising this method the resultant calculations can be compared for each NHC, with the findings for the most readily utilised NHCs summarised below.



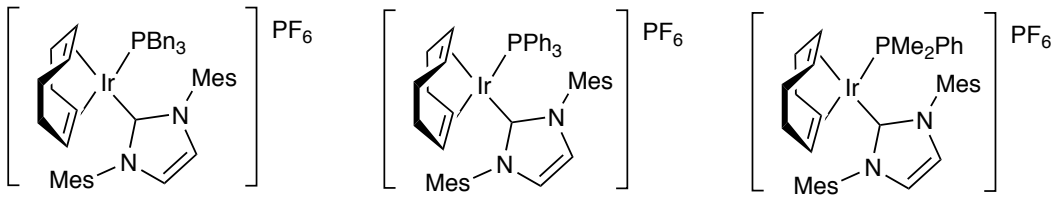
NHC	***$\%V_{bur}$ of (NHC)AuCl***
IMes	36.5
SIMes	36.9
IPr	44.5
SIPr	47.0
IAd	39.8

Table 4[46]

1.6 Kerr Group Catalysts

As discussed, there has been significant interest in further enhancing the efficiency and robustness of iridium-based catalysts. As stated previously, the formation of inactive dimers and trimers is a significant problem with Crabtree's catalyst, **14**. Indeed, Crabtree hypothesised that bulky ligands would circumvent this issue and lead to an enhancement of the catalyst's stability. In this vein, Nolan developed a range of iridium-centred catalysts featuring an NHC/pyridine ligand sphere. In a further development, Buriak employed an NHC/phosphine ligand environment in order to access a range of novel iridium complexes. However, Buriak stated that the formation of an iridium species featuring both a bulky phosphine and a sterically encumbered NHC could not be achieved.

Concurrently, research within the Kerr group was focused on developing novel iridium complexes featuring both an appreciably bulky phosphine ligand and also a sterically encumbered NHC ligand. Kerr and co-workers theorised that it was, indeed, possible to form such complexes through careful manipulation of the synthetic route. Pleasingly, this proved to be the case and a suite of novel complexes, including **44**, **45**, and **46**, were formed with good levels of efficiency (**Figure 12**).[47]

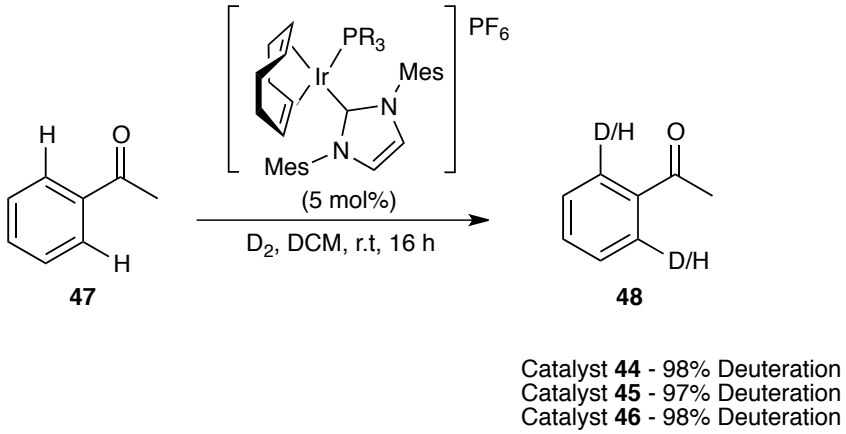


44 **45** **46**

Figure 12

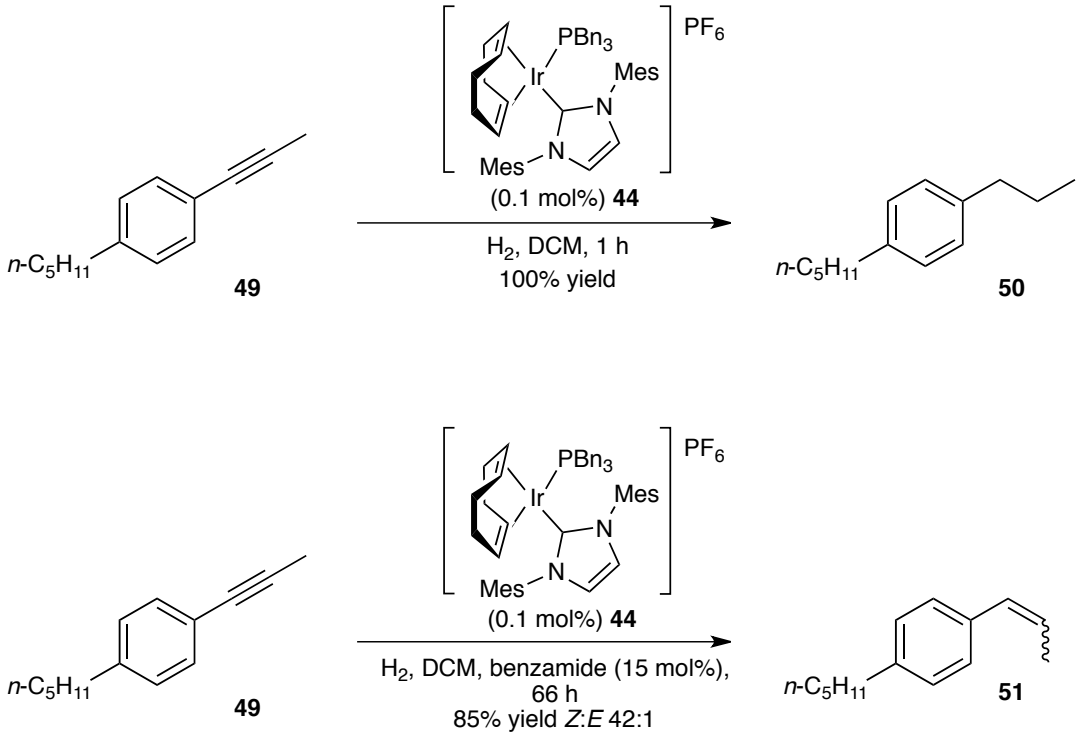
These complexes had been specifically designed for applications within the field of hydrogen-isotope exchange (HIE). Accordingly, this is where the synthetic applicability of these compounds was first investigated. The HIE process is widely utilised within the pharmaceutical industry as it facilitates the labelling of potential drug candidates. Based on this, the resulting labelled moieties can be monitored within drug metabolism and

pharmacokinetic studies, as this represents an integral part of the drug discovery programme. In relation to this, the selective labelling of acetophenone, **47**, was performed with the novel iridium complexes, **44**-**46** (**Scheme 22**). Pleasingly, the selective deuteration occurred with near quantitative conversion in all cases. In addition, the novel complexes were found to outperform Crabtree's catalyst, the industry standard, over a range of labelling reactions and across a spectrum of substrates.[47]



Scheme 22

In an attempt to further expand the scope and application of these novel complexes, a series of studies pertaining to the catalysts' ability to perform hydrogenations were undertaken (**Scheme 23**).[48] Initially, when employing an extremely low catalyst loading of complex **44**, alkyne **49** was reduced to the analogous alkyl species, **50** over the course of 1 hour. This result was indicative of the powerful synthetic attributes possessed by the novel iridium complexes. In addition, a partial hydrogenation reaction akin to a homogenous example of Lindlar's catalyst, was conducted. Pleasingly, the strategic employment of a suitable catalyst poison, benzamide, alongside complex **44**, resulted in the partial hydrogenation of the substrate to the corresponding alkene species, **51**. In addition, the reduction proceeded in a selective manner to afford the (*Z*)-olefin in an almost exclusive manner.



Scheme 23

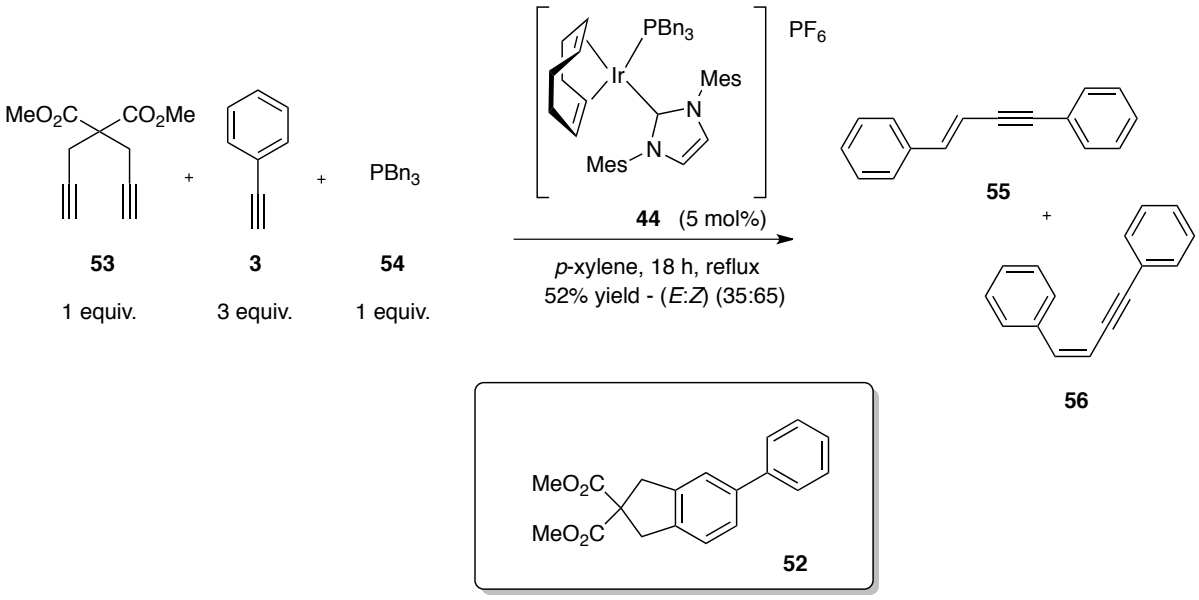
As discussed, the novel iridium complexes developed by Kerr *et al.* possess a range of powerful synthetic attributes. In addition, the ability of the catalysts to facilitate the promotion of carbon-carbon bond formation would serve to further enhance the synthetic potential of these catalysts. In relation to this, it is envisaged that the iridium complexes will prove to be extremely versatile catalysts, capable of promoting an array of organic transformations.

2 Previous and Proposed Work

2.1 Precedent for Investigation

The organoiridium complexes developed within our laboratories have shown excellent synthetic applicability with respect to the aforementioned hydrogen-isotope exchange processes and hydrogenation reactions.[47,48] Having stated this, it was desirable to further elaborate upon the synthetic utility of the novel iridium catalysts. Initially, research began with regards to the synthesis of functionalised aromatic species from diyne and alkyne precursors. It was anticipated that the novel iridium species would be able to participate in [2+2+2] cyclotrimerization reactions to afford aromatic moieties in an economical and expedient fashion. As such, the ability of our complexes to facilitate the formation of carbon-carbon bonds would serve to enhance the synthetic utility of the iridium complexes.

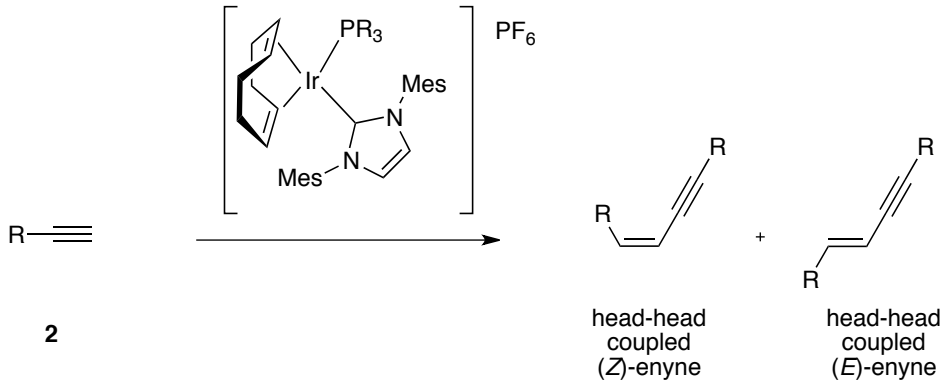
Initial attempts within our laboratories to promote an iridium-mediated [2+2+2] cyclotrimerzation process employed diyne, **53**, alongside phenylacetylene, **3** (**Scheme 24**).[49] However, the major product observed in the reaction profile was not the anticipated cyclotrimerization product, **52**, but instead the homodimerized alkyne product, **55**/**56**. This was very surprising, yet not unwelcome. As discussed previously in the overview of dimerization processes, the head-to-head (*Z*)-selective coupling process is somewhat rare. Accordingly, we were pleased to find that the reaction yielded the *Z*-product of this dimerization pathway and, indeed, this was the major product of the reaction in a 52% yield.



Scheme 24

As stated previously, the formation of carbon-carbon bonds represents one of the most synthetically useful transformations within organic chemistry. As such, the ability of our iridium complexes to facilitate such a transformation would serve to enhance their synthetic appeal. Accordingly, it was envisaged that the yield, and indeed selectivity, of the unexpected alkyne dimerization process could be significantly enhanced following a sustained optimisation programme. The relative paucity of (*Z*)-selective, transition metal catalysed alkyne dimerization processes would allow the development of a novel and useful reaction protocol that grants access to a synthetically useful organic structure. In turn, it was envisaged that the optimised reaction conditions could ultimately be transposed to more functionalised substrates in order to facilitate the formation of a range of functionalised (*Z*)-enynes.

Accordingly, the ability of our iridium complexes to promote alkyne dimerization will be investigated (**Scheme 25**). An initial programme to determine the most prolific catalyst will be carried out, subsequently leading to optimisation studies. In due course, it is believed that this will expand the synthetic utility of our iridium complexes.

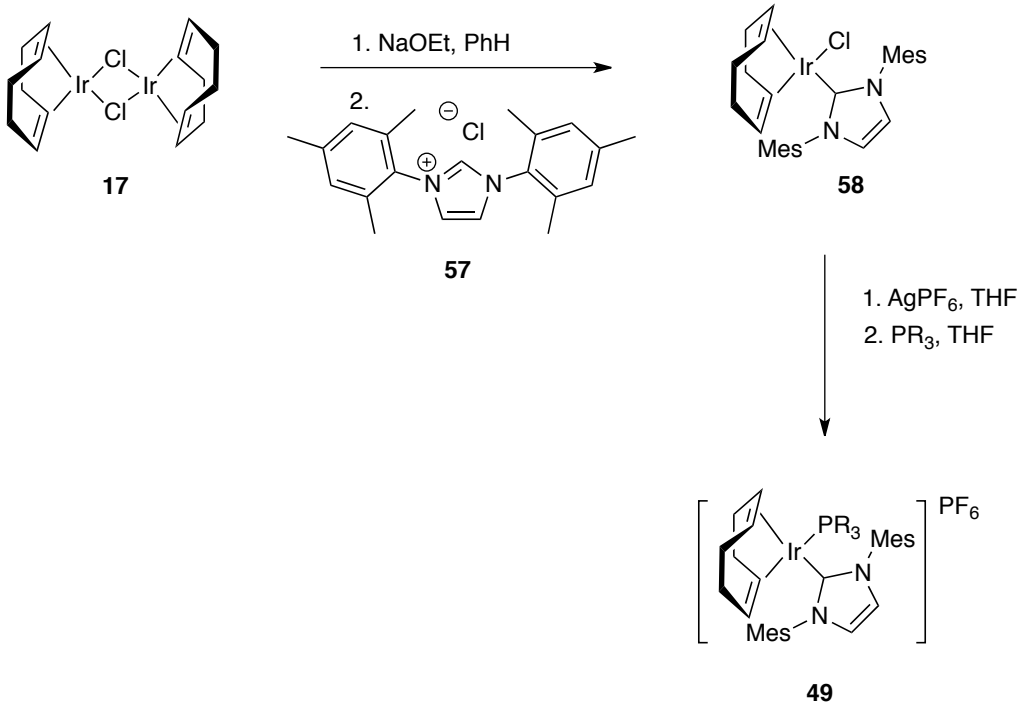

PR3
PF6
Ir
Mes
N
N
Mes
R
R
R
R
+
R
2
head-head
coupled
(Z)-enyne
head-head
coupled
(E)-enyne

Scheme 25

3 Results and Discussion

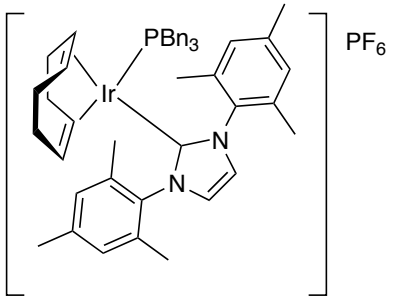
3.1 Synthesis of Iridium(I) Complexes

At the outset of the project the initial priority was to perfect the techniques required to synthesise the iridium complexes in optimum yield. The general route for preparation of the catalysts is outlined below (**Scheme 26**). Upon treatment of a solution of $[Ir(COD)Cl]_2$, **17**, in benzene with NaOEt, a red to yellow colour change was observed. After allowing the mixture to stir for a short time, the imidazolium salt, **57**, was added, enabling formation of the stable Ir(COD)(IMes)(Cl) intermediate, **58**. Subsequent addition of silver hexafluorophosphate resulted in the formation of a dark precipitate, which is indicative of halide abstraction occurring. Following filtration through celite under an inert atmosphere, the final step of the synthesis involves addition of phosphine, causing a distinct orange to red colour change. Recrystallisation techniques were then employed to isolate the desired complex.



Scheme 26

By adhering to this procedure, the first catalyst synthesised was complex **44**, bearing the sterically encumbered IMes NHC ligand and tribenzylphosphine (**Figure 13**). The initial attempt proved relatively successful with an isolated yield of 44%. However, subsequent attempts resulted in a marked decrease in the yields obtained (**Table 5**). This was attributed to the quality of silver hexafluorophosphate, which had likely degraded due to its extreme moisture- and light-sensitivity. As a result, the use of fresh silver hexafluorophosphate was able to facilitate the synthesis of the desired complex in improved and consistent yields. Pleasingly, a yield of 63% was attained; which was indicative of a sound grasp of the practical techniques required for the synthesis of the catalyst.



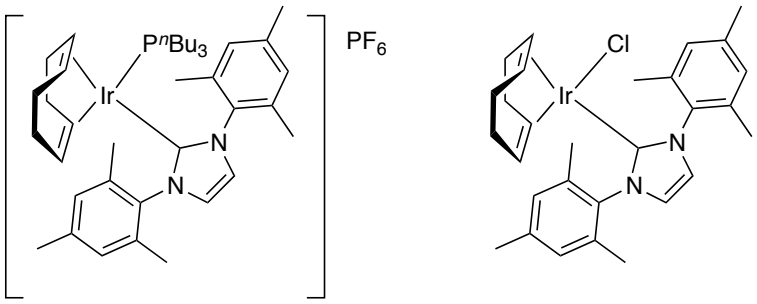
44

Figure 13

Entry	*Yield of Complex 44 (%)*
1	44
2	25
3	26
4	63

Table 5

Due to the precedented ability of complex **44** to facilitate hydrogen isotope exchange processes and hydrogenation reactions, it was desirable to further enhance the catalysts applicability. In relation to this it was envisaged that, after optimisation, complex **44** could be an efficient catalyst for the promotion of (*Z*)-selective alkyne dimerization. Having stated this, it was important to probe the catalytic ability of related analogues in order to verify that complex **44** represented a suitable candidate for the optimisation programme. In relation to this, iridium complex, **29**, featuring an alternative phosphine ligand, tri-*n*-butylphosphine (PBu_3) was also synthesised (**Figure 14**, **Table 6**). This particular phosphine ligand was selected as tributylphosphine is more strongly electron-donating and, accordingly, it was reasoned that this particular attribute could potentially enhance the performance of the iridium centre to undergo oxidative addition in a facile manner. In contrast, in a bid to further explore the role of the phosphine ligand it was decided that the intermediate chloro-NHC species, **58**, would also be trialled in a dimerization reaction. With this in mind, complex **58** was formed as described in **Scheme 26** and instead of reacting on to afford a phosphine-NHC complex, the intermediate was simply isolated from the reaction mixture. Pleasingly, the chloro-NHC complex, **58**, was formed in an 76% yield.



29 **58**

Figure 14

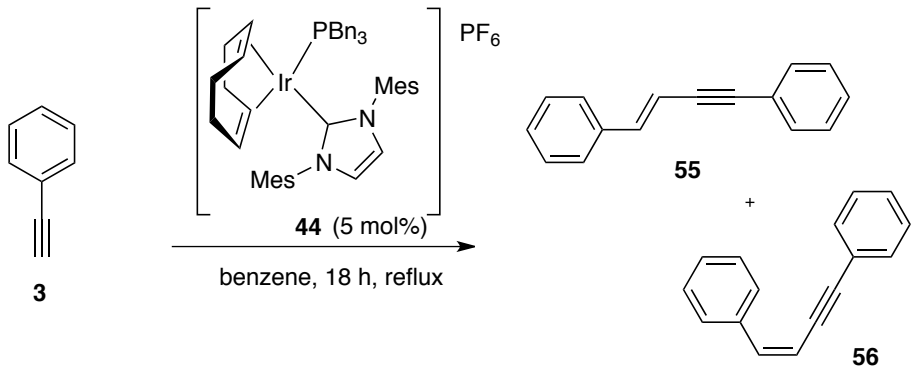
Entry	*Complex*	*Yield (%)*
1	Complex **29**	61%
2	Complex **58**	76%

Table 6

Pleasingly, several catalysts were now at hand and available for trial in alkyne dimerization reactions. To date, complex **44** had proven a versatile and broadly applicable catalyst within the respective fields of hydrogen-isotope exchange and hydrogenation.[47,48] As such, it was desirable to further enhance the synthetic utility of complex **44**. Having stated this, it was pertinent to investigate the performance of the comparably more electron-rich complex **29** and, indeed the neutral complex **58**, featuring a more electron-poor ligand environment.

3.2 Application of Iridium(I) Complexes in Alkyne Dimerization

With a cross section of potential catalysts in hand, attention turned to their application in alkyne dimerization reactions. The initial experiments employed 5 mol% of complex **44**, with phenylacetylene employed as the model substrate (**Scheme 27**). The goal of these early experiments was to gain familiarity with the reaction, purification, and analytical techniques. The head-to-head dimerized products were obtained as inseparable isomers with the ratio of (*E*) to (*Z*) being calculated by ^{1}H NMR. It should be noted that the head-to-tail dimerized product was not encountered within this research programme. As illustrated below (**Table 8**), the yields obtained were modest, despite the selectivity being relatively pronounced in favour of the (*Z*)-isomer. Pleasingly however, consistent results were obtained which were indicative of a sound grasp of the requisite practical techniques.



Scheme 27

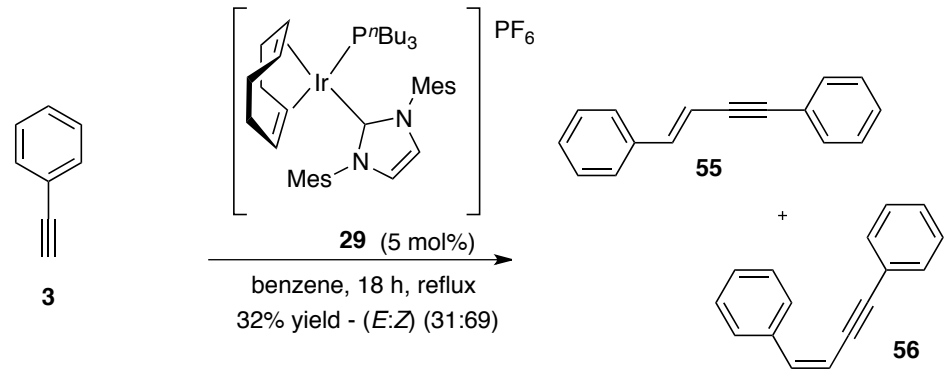
Entry	*Selectivity (E:Z)*	*Yield (%)*
1	25:75	31
2	24:76	27

Table 7

3.3 Catalyst Comparison

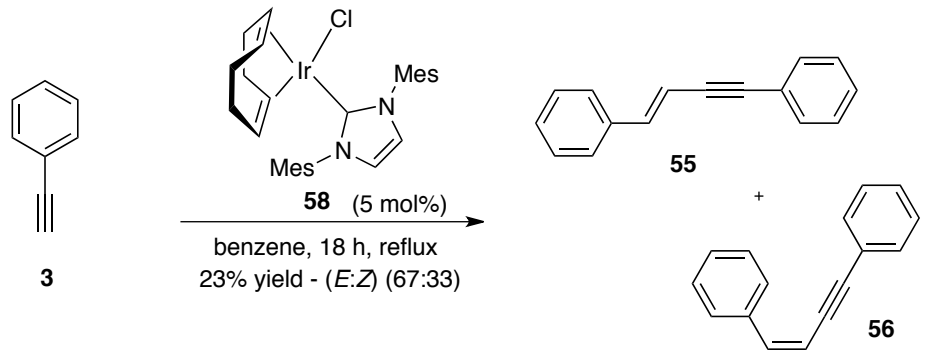
Before the optimization studies began in earnest it was logical to conduct a brief set of experiments in order to assess the performance of a small range of iridium complexes established and employed within the Kerr group.

As stated previously, it was rationalised that complex **29**, bearing an appreciably electron-donating tributylphosphine ligand, would offer a comparably more electron-rich catalyst over complex **44**. Accordingly, complex **29** was employed in the benchmark dimerization reaction (**Scheme 28**). The reaction outcome was very similar to that observed with complex **44**, with a yield of 32% being obtained. In addition, the selectivity of the exclusive head-to-head dimerization process was remarkably similar to that observed with complex **44**.



Scheme 28

In order to further investigate the perceived requirement for the catalyst to possess an electron-donating phosphine ligand, it was decided to trial a complex that did not feature a such a ligand. Accordingly, complex **58**, which lacked a strongly electron-donating phosphine was applied in the dimerization of phenylacetylene (**Scheme 29**). As anticipated, the yield obtained with complex **58** was modest, however it was surprising to observe that the selectivity was reversed, resulting in a greater proportion of the (*E*)-enyne being obtained. Based on this result with chloro complex **58**, the presence of an electron-donating phosphine on the catalytic species seems imperative.

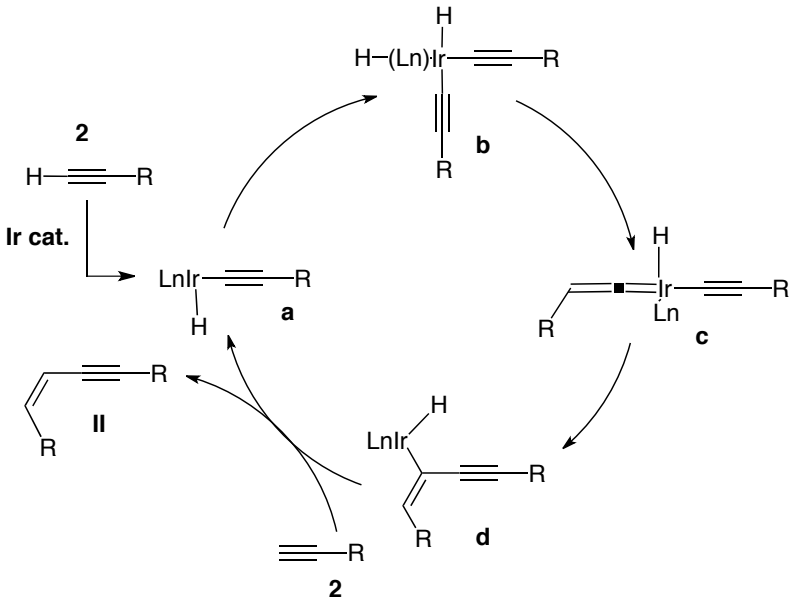


Scheme 29

The results obtained with complexes **44** and **29**, possessing the tribenzylphosphine and tributylphosphine, respectively, were remarkably similar. However, it was decided to employ complex **44** in subsequent optimisation studies. This decision was based on the fact that complex **44** had previously facilitated impressive results in hydrogenation and hydrogen isoptope exchange reactions, and it was desirable to further expand the synthetic utility of this species.

3.4 Reaction Mechanism

Before further optimsation studies could be carried out, it was important to consider the mechanism by which the reaction proceeds. It is likely that the reaction pathway progresses through a similar mechanism to that proposed by Miyaura.[20] The iridium(I) complex can be regarded as a pre-catalyst and the formation of the active catalyst, **a**, occurs upon dissociation of the COD ligand and oxidative addition of the alkyne species (**Scheme 30**). Complex **a** will then undergo a second oxidative addition to form complex **b**. Following this, complex **b** can isomerise to vinylidene species **c** *via* intraligand hydrogen transfer.[21] In turn, the *cis*-enyne species **d** is afforded by intramolecular migration of the alkyne unit onto the α-carbon of the vinylidene moiety. As supported by the detailed observations of Wakatsuki when employing ruthenium complexes within related processes,[21] the establishment of the *cis* form of the enyne unit within **d** is believed to be favoured. This is attributable to the fact that this would minimise any repulsive interactions between the (alkenyl) R group and the specific bulky ligand sphere around iridium. Following this, protodemetalation affords the desired enyne **II**, and returns intermediate **a**.

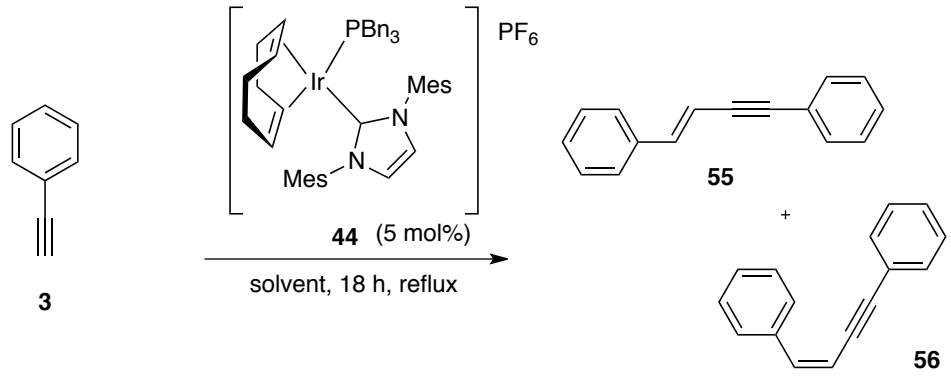


Scheme 30

Based on the above mechanistic rationale, it is likely that the combination of a bulky and electron-rich ligand environment of both complexes **44** and **29** facilitates the double oxidative addition pathway necessary for (*Z*)-selective dimerization.

3.5 Solvent Study

With respect to preparative chemistry, judicious solvent choice remains of paramount importance, as solubility, boiling point, and coordinating ability of the solvent must all be considered. This philosophy is especially true for transition metal-catalysed processes as many transition metals are capable of coordinating heteroatoms present in a range of common reaction media.[1] In this respect, iridium behaves in a similar manner to other transition metals, with various solvents facilitating the formation of undesired inactive iridium complexes. Having stated this, the use of a non-coordinating solvent is likely to prove advantageous within the iridium promoted dimerization process. Accordingly, benzene, toluene, and *p*-xylene were trialled, with all three being able to facilitate the reaction to some degree (**Scheme 31, Table 8**). In addition, in order to probe the effectiveness of a comparatively more coordinating solvent, THF, was employed in the dimerization protocol (**Entry 4**). As anticipated, THF proved ineffective and resulted in a poor yield being observed with minimal selectivity being achieved.



Scheme 31

Entry	*Solvent*	*Selectivity (E:Z)*	*Yield (%)*
1	Benzene	25:75	31
2	Toluene	13:87	40
3	*p*-Xylene	35:65	31
4	THF	40:60	8

Table 8

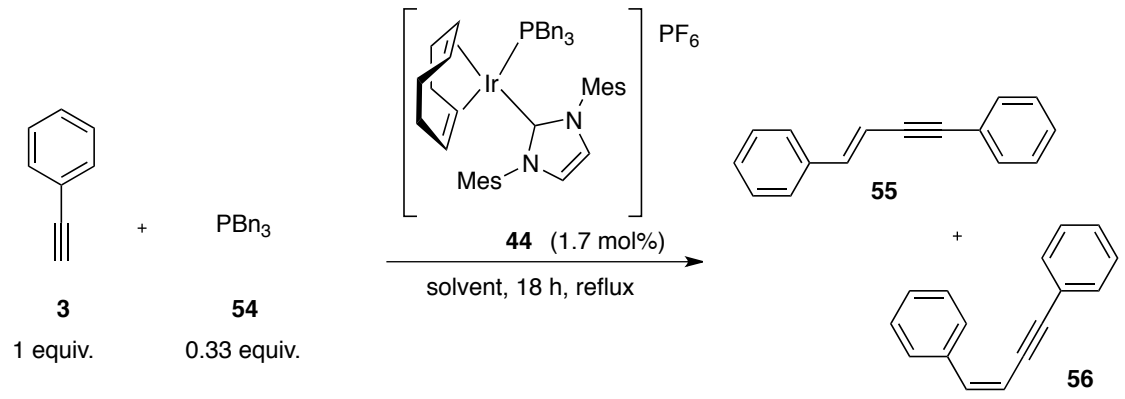
Considering the results in greater detail, benzene and *p*-xylene were relatively effective in the context of the solvent screening. However, toluene proved to be the most efficient solvent in terms of promoting good levels of selectivity whilst also affording the desired product in a moderate 40% yield. Unsurprisingly, the use of THF led to a poor yield and selectivity being observed. This is most likely a result of the THF coordinating to the iridium center, which would result in lower accessibility for the alkyne. Previous work carried out within our laboratory had focused on the application of complex **44** in the selective hydrogenation of alkynes to alkenes.[48] Indeed, in such studies, THF was identified as an efficient catalyst poison.

3.6 Phosphine as an Additive

As stated previously, the ability of our novel iridium complexes to furnish the products of alkyne dimerization was discovered as a result of preliminary attempts to promote a related cyclotrimerization process. More specifically, it was during an additive study employing a tribenzylphosphine additive that the dimerization products were first observed. To this stage it has been shown that the dimerization proceeds in the absence of the phosphine additive. Having stated this, it was apposite to investigate the performance of the tribenzylphosphine additive within the developed dimerization protocol.

As discussed, the [2+2+2] annulation studies employed 1 equivalent of the diyne moiety **53**, 3 equivalents of the alkyne coupling partner, **3**, 1 equivalent of tribenzylphosphine, **54**, and 5 mol% of the appropriate iridium catalyst (**Scheme 24**). These values were reasoned to offer access to the cyclotrimerization product. However, as the dimerization product was obtained from this preliminary reaction, the stated values need to be amended. With respect to the dimerization process, 1 equivalent of phenylacetylene, **3**, is actually exposed to 0.33 equivalents of the phosphine additive and 1.7 mol% of the iridium catalyst. In order to reproduce this relationship in subsequent studies, the catalyst loading was lowered from 5 mol% to 1.7 mol% in order to reproduce the conditions employed in the preliminary investigations.

Based on the above rationale, complex **44** (1.7 mol%) and tribenzylphosphine (0.33 eq.) were added to toluene. The resulting suspension was heated to reflux, followed by addition of phenylacetylene, and stirred for 18 hours. After this time it was revealed that the excess phosphine, in this particular reaction setup, had failed to enhance the overall yield of the head-to-head coupled products (**Scheme 32**, **Table 9**). Nonetheless, the *E*:*Z* selectivity was impressive with ratios reaching 13:87.

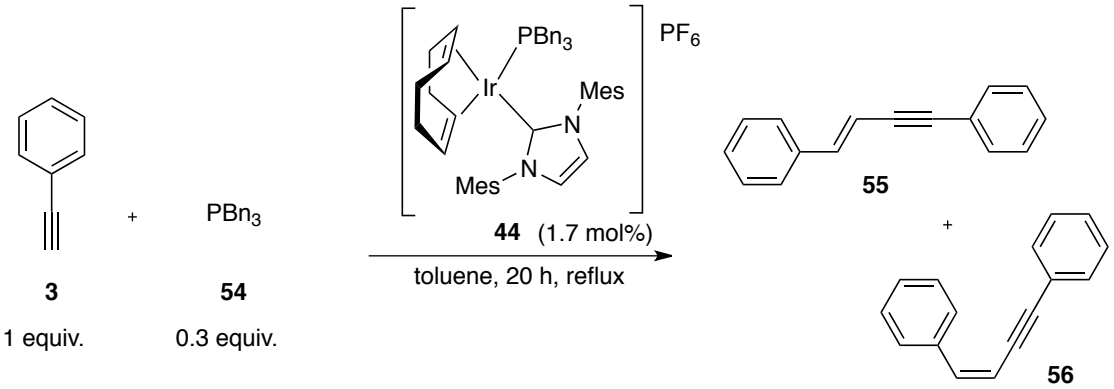


Scheme 32

Entry	*Solvent*	*Selectivity (E:Z)*	*Yield (%)*
1	Toluene	13:87	46
2	*p*-Xylene	15:85	39

Table 9

Upon considering the outcomes above, it was theorised that the tribenzylphosphine additive may not have had the opportunity to fully react with complex **44**, prior to the addition of the reaction substrate. As such, the active catalyst may have failed to form in sufficient quantity to impact the course of the reaction. It was therefore decided to stir the catalyst and phosphine under reflux for 2 hours, before the addition of alkyne **3** (**Scheme 33**, **Table 10**).



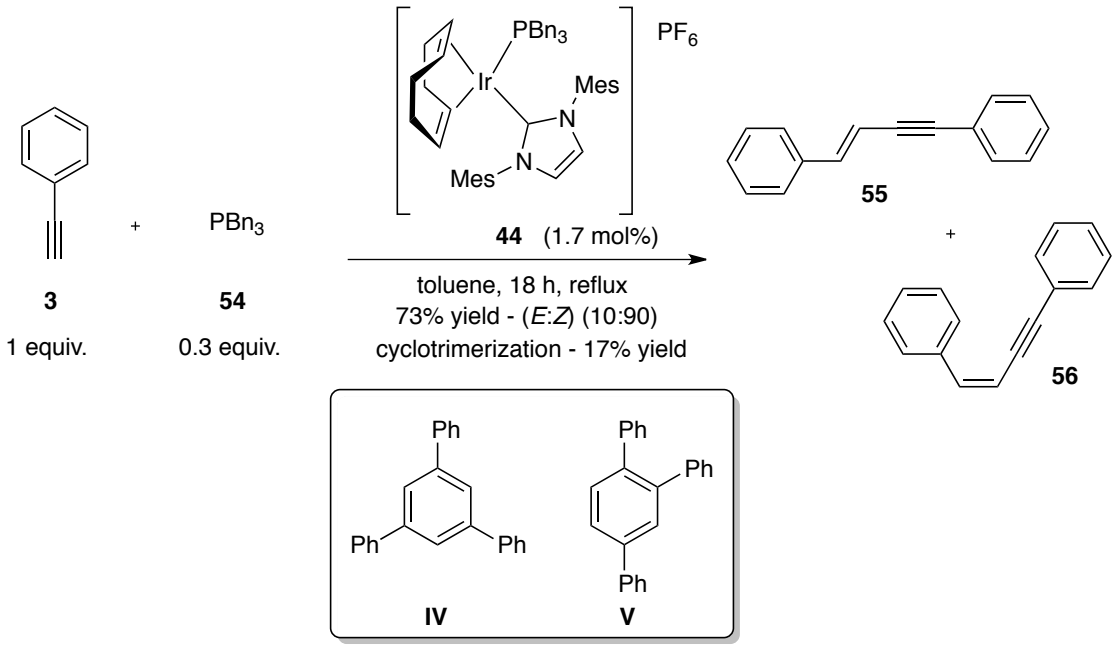
Scheme 33

Entry	*Selectivity (E:Z)*	*Yield (%)*
1	48:52	30
2	51:49	31

Table 10

Disappointingly, this approach proved ineffective with relatively poor yields being obtained alongside a lack of any *E*:*Z* selectivity. It seemed likely that over the initial 2 hour time period, the large excess of phosphine coordinates to the iridium center, rendering the catalyst less effective in terms of its ability to coordinate the reaction substrate.

Based on the poor outcome of the stepwise addition protocol, it was reasoned that an alternative order of addition may facilitate the formation of the desired enyne(s) in improved yield and selectivity. It was anticipated that the addition of all reactants from the outset, prior to any heating, would potentially enhance the reaction efficiency and deliver the desired product in good yield (**Scheme 34**). Interestingly, for the first time, upon completion and attempted purification of the reaction mixture, an impurity was identified in the ^{1}H NMR spectrum of the product(s) **55**/**56**. More specifically, the ^{1}H NMR featured extra signals in the aromatic region. Initially, it was reasoned that residual phosphine additive was present in the reaction product and this was responsible for the additional proton signals. Based on this, a ^{31}P NMR spectrum of the reaction product was obtained. Upon analysis of the spectrum it was obvious that there was no phosphorus-based species present. As a result, it was hypothesized that the extra aromatic signals, present in the ^{1}H NMR spectrum, could be attributed to the formation of the undesired 1,3,5- and 1,2,4-triphenylbenzene products. Indeed, upon comparison with literature data, it seemed that this scenario was likely.[50,51] As such, the NMR data could be interpreted to provide a yield for the dimerized product and, indeed, the cyclotrimerized product. Gratifyingly, this amended addition protocol led to a much-improved yield of 73%, and excellent selectivity of 10:90 in favour of the (*Z*)-isomer obtained. This reaction represents a considerable success within the context of this dimerization research programme, as previously, poor yields had been consistently attained. In addition, based on analysis of the ^{1}H NMR data, the cyclotrimerization products had formed in a 17% yield.



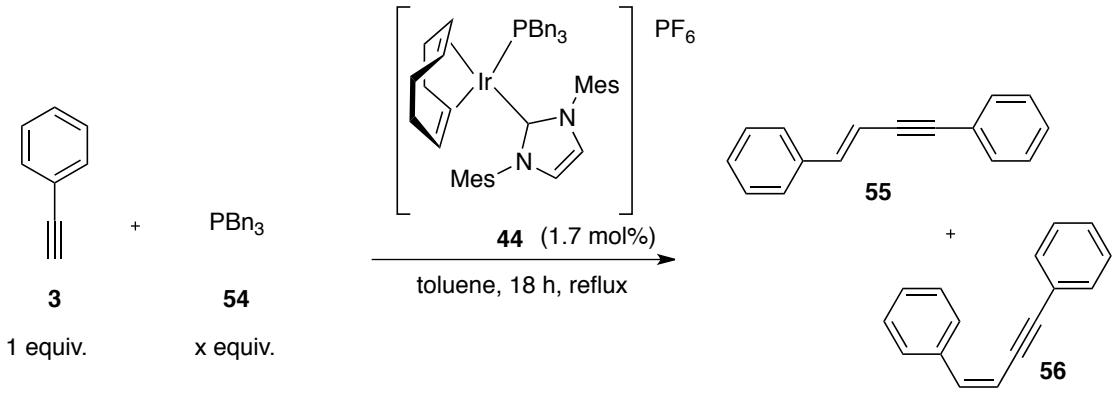
Scheme 34

As stated above, the amended reaction protocol afforded an excellent result, however, the role of the phosphine additive could only be speculated upon: is the phosphine forming a new iridium complex *in-situ*, what is the optimum level of phosphine incorporation, and how does the formation of by-products fare with varying levels of phosphine addition? In order to address some of the questions arising from the above findings, it was decided to investigate the role of the additive.

3.7 Phosphine Loading

With promising reaction conditions in hand, attention turned to investigating the optimum levels of tribenzylphosphine required within the developed reaction protocol. The study below illustrates the varying results obtained from different loadings of PBn_3 (**Scheme 35**, **Table 11**). As discussed previously, the yield of the cyclotrimerization by-product(s) can be calculated from analysis of the ^1H NMR spectra of the purified reaction mixture. This allows the by-product formation to be quantified and as such provides key information with respect to efficiently promoting the desired dimerization protocol. Upon analysing the

results of the study, three key observations were made. Firstly, when employing between 0 and 0.2 equivalents of PBn_3 the yield of the reaction was poor (**Entries 1 - 5**). In turn, employing greater than, and including, 0.3 equivalents of tribenzylphosphine resulted in a considerably improved yield of the enyne product (**Entries 6 - 8**). Secondly, the *Z*-selectivity was most pronounced when employing 0.2 equivalents or greater of PBn_3 (**Entries 5 - 8**). Finally, the yield of the by-product was diminished with increased loadings of the phosphine additive (**Entries 6 – 8**).

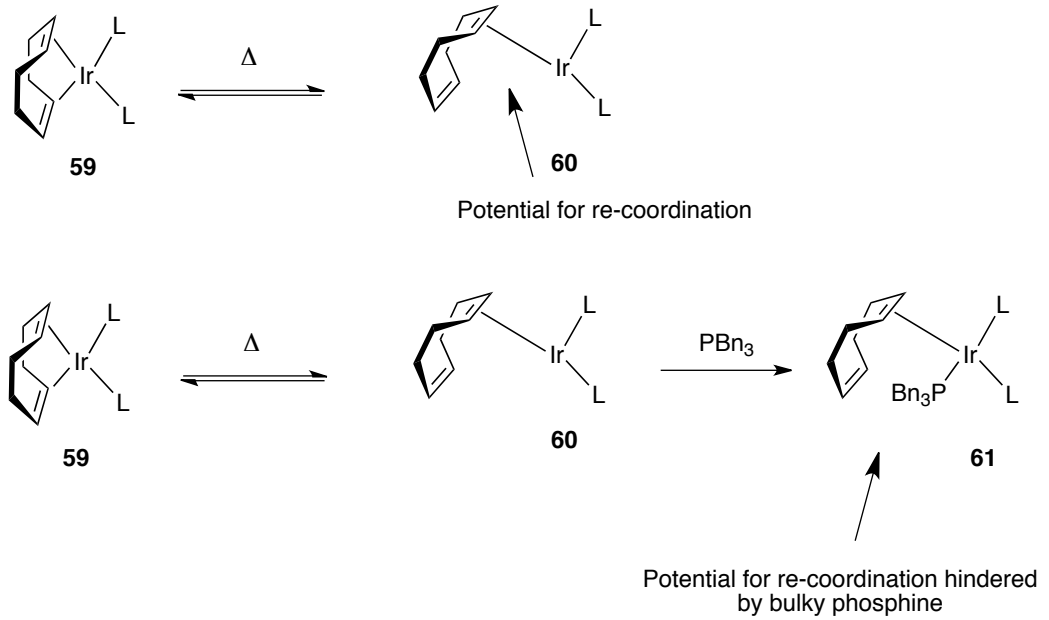


Scheme 35

Entry	*Phosphine Equivalents*	*Selectivity (E:Z)*	*Yield of 55 & 56 (%)*	*Yield of Cyclotrimerization Product (%)*
1	0	20:80	11	36
2	0.017	42:58	26	22
3	0.05	55:45	34	21
4	0.1	49:51	28	20
5	0.2	13:87	41	19
6	0.3	10:90	83	12
7	0.4	12:88	78	12
8	0.5	13:87	80	14

Table 11

The findings of the phosphine loading study allude to several, non-exclusive, potential roles of the phosphine additive. It is possible that one of the roles involves the excess phosphine being able to facilitate the dissociation of the COD ligand from the iridium center (**Scheme 36**). The COD ligand is coordinated to the metal centre at two separate points and, as such, it is feasible that one of the olefin moieties dissociates but complete dissociation is hindered due to the other olefin moiety remaining coordinated. Indeed, this potentially allows the dissociated olefin to re-coordinate to the iridium centre. It can be rationalised that the excess phosphine may coordinate to the iridium metal and block re-coordination of the COD olefin, **61**.



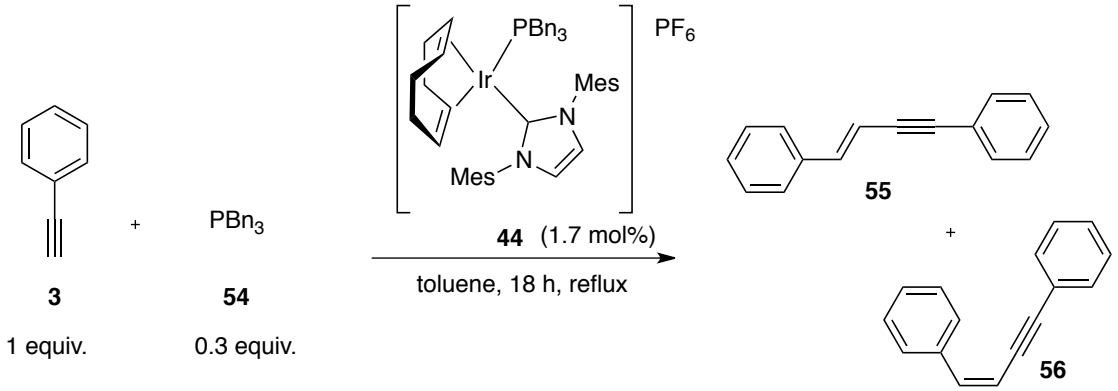
Scheme 36

Alternatively or additionally, the excess phosphine potentially results in the formation of the active catalyst *in-situ*. Perhaps, the presence of two phosphine species, ligated to the catalyst, results in a complex which readily undergoes oxidative addition. This theory would give credence to the argument for the reaction proceeding *via* an iridium(V) species. However, the formation of a congested iridium(V) species is a non-trivial process, although not without precedent.[22]

The two potential roles elaborated upon above are further potentially complemented by a third function. It is feasible that the excess phosphine may be responsible for limiting the access of the alkyne, to the metal centre. In this case, one can envisage the phosphine restricting the amount of alkyne around the catalyst and, as such, limiting the formation of the cyclotrimerization product. It follows that a decrease in the formation of the undesired cyclotrimerization product would effectively enhance the yield of the selectively dimerized product. In a similar vein, when on considering the proposed mechanistic rationale (pages 44 - 45), the presence of excess bulky phosphine should also enhance the *Z*-selectivity of the dimerization process. In relation to all of this, it was decided that a comprehensive study relating to reaction concentration would shed further light on the role of the phosphine additive and, simultaneously, serve to further increase the chemical yield of the dimerization process.

3.8 Concentration Study

Inspired by the observation that high phosphine loadings limit the formation of the cyclotrimerization process, a study relating to the reaction concentration was initiated. It was envisaged that employing a more dilute system would result in the alkyne being less concentrated around the metal centre of the catalyst. As such, this implies that the potential cyclotrimerization reaction pathway would be limited, resulting in a lower yield of the undesired aromatic byproduct(s). In turn, this would hopefully allow the desired enyne to form, selectively, in greater yield. The results of the concentration study are displayed below (**Scheme 37**, **Table 12**). At comparatively low levels of concentration (200 mM to 600 mM) the formation of the cyclotrimerization product is restricted (**Entries 1 – 4**). In contrast, and as anticipated, more concentrated systems promoted the formation of the cyclotrimerization product in greater yield (**Entries 5 – 6**). However, the benefits of a more dilute system are not as pronounced as was originally envisaged. Having stated this, there is a marginal increase in the yield of the desired dimerization product at lower concentrations. Based on this, it was decided to maintain a reaction concentration of approximately 600 mM for employment within subsequent dimerization studies. It is noteworthy that the selectivity remained relatively consistent across the range of concentrations investigated.



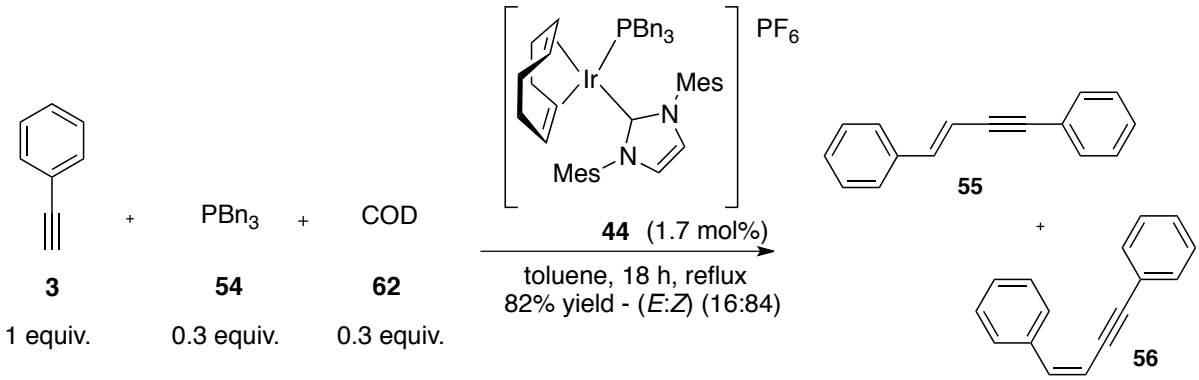
Scheme 37

Entry	*Concentration*	*Selectivity (E:Z)*	*Yield of Enyne (%)*	*Yield of Cyclotrimerization Product (%)*
1	200 mM	25:75	71	12
2	300 mM	27:73	74	13
3	400 mM	27:73	76	14
4	600 mM	30:70	74	14
5	800 mM	29:71	68	20
6	900 mM	30:70	67	19

Table 12

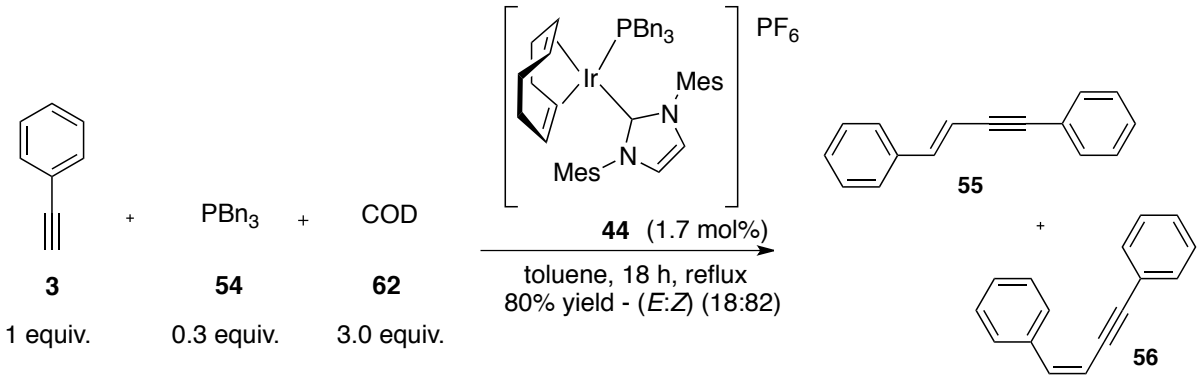
3.9 COD Dissociation Study

As proposed above, it was rationalised that the tribenzylphosphine additive was aiding the COD dissociation process that was key to the formation of the active catalyst. As such, it was pertinent to design suitable experiments that would probe the role of the phosphine additive. Accordingly, it was theorised that performing the reaction with an excess of COD, **62**, may result in the reaction being shut down. If this proved to be the case, it stands to reason that the phosphine additive is involved in promoting COD dissociation. As a result it could be deduced that the tribenzylphosphine additive was key to facilitating rapid COD dissociation. With this in mind, 0.3 equivalents of COD were added, alongside the traditional 0.3 equivalents of tribenzylphosphine (**Scheme 38**). Upon completion of the reaction it was obvious that the excess COD had no negative effect on the reaction and an 82% yield of the desired enyne, exhibiting impressive selectivity, was obtained. It should be noted that this was the highest yield obtained to-date.



Scheme 38

In order to further probe this result, the reaction was repeated employing 3.0 equivalents of COD. Surprisingly, the reaction proceeded, again, in an excellent 80% yield with pronounced (*Z*)-selectivity observed (**Scheme 39**).

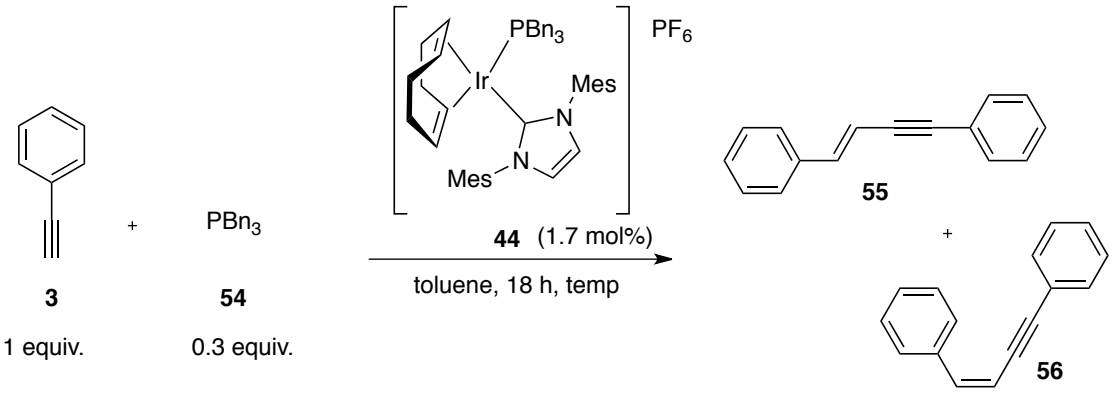


Scheme 39

Based on these results, and indeed on those of the concentration study, it is highly unlikely that the tribenzylphosphine additive aids COD dissociation or has a pronounced effect on minimising cyclotrimerization product. As such, it is likely that over the course of the dimerization process the initial phosphine ligand present on the iridium center dissociates under the reaction conditions. Accordingly, the presence of additional phosphine maintains the phosphine-NHC ligand environment around the iridium metal, and indeed it this specific ligand environment that seems to be key to promoting the reaction in good yield with enhanced levels of selectivity.

3.10 Temperature Study

In spite of the preliminary rationale, it has been experimentally determined that COD dissociation is not suitably enhanced by the phosphine additive. However, COD dissociation represents an integral part of catalyst activation. More specifically, the liberation of the COD ligand generates the requisite vacant coordination sites on the iridium centre, and it is through these vacant sites that substrate coordination takes place. It is presumed that high temperatures facilitate COD dissociation but the exact temperature at which this occurs is unknown. The temperature dependence of the reaction was therefore investigated (**Scheme 40**, **Table 13**). At lower temperatures, the desired reaction failed to occur and the alkyne starting material remained unreacted (**Entries 1 – 4**). Upon raising the temperature to 75˚C the dimerization occurred, albeit in a poor yield (**Entry 5**). Based on this result, it is likely that that the COD dissociation occurs at this temperature. An incremental increase in the temperature to 85˚C resulted in a similar result to that obtained previously (**Entry 6**). In turn, an increase in the reaction temperature to 110˚C led to an 80% yield with pronounced (*Z*)-selectivity observed (**Entry 7**)



Scheme 40

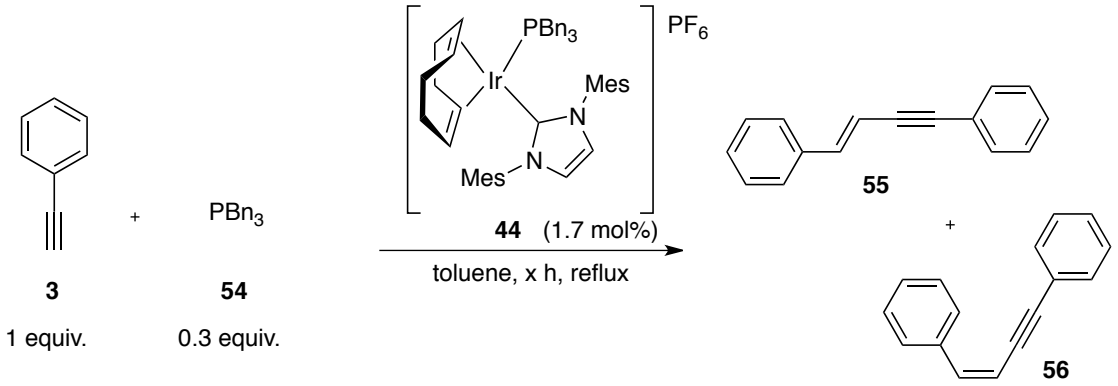
Entry	*Temperature*	*Selectivity (E:Z)*	*Yield of Enyne (%)*	*Yield of Cyclotrimerization Product (%)*
1	25˚C	-	-	-
2	50˚C	-	-	-
3	60˚C	-	-	-
4	70˚C	-	-	-
5	75˚C	46:54	45	8
6	85˚C	42:58	42	7
7	110˚C	19:81	80	10

Table 13

3.11 Time Study

To this point, the stability of the enyne products over a prolonged length of time, under the established reaction conditions, was unknown. It is possible that upon formation, the enyne may undergo subsequent reactions to form undesired byproducts or, indeed, isomerisation of the olefin moiety may occur. It was decided that a tandem reaction process would offer insight into the potential degradation of the enyne product (**Scheme 41**, **Table 14**). As such, the first of the two reactions was analysed after 2.5 hours and resulted in an excellent 80% yield with pronounced (*Z*)-selectivity obtained (**Entry 1**). The second reaction was allowed to run for a full 18 hours before being analysed. Interestingly the comparably longer reaction time did not have a negative effect on the reaction outcome (**Entry 2**). Based on the above findings, it can be deduced that the enyne product is stable under the reaction conditions. It should be noted that although excellent results were obtained after

2.5 h reaction time, the decision was made to implement the standard 18 hour reaction time in future studies. As the optimisation study was drawing to a close, alternative substrates were being considered for extension of the scope of the reaction. Accordingly, it was rationalised that more elaborately functionalised compounds may require the extended reaction time. As such, the implementation of an 18 hour reaction as standard, would maintain a uniform set of reaction conditions to be investigated for each substrate.



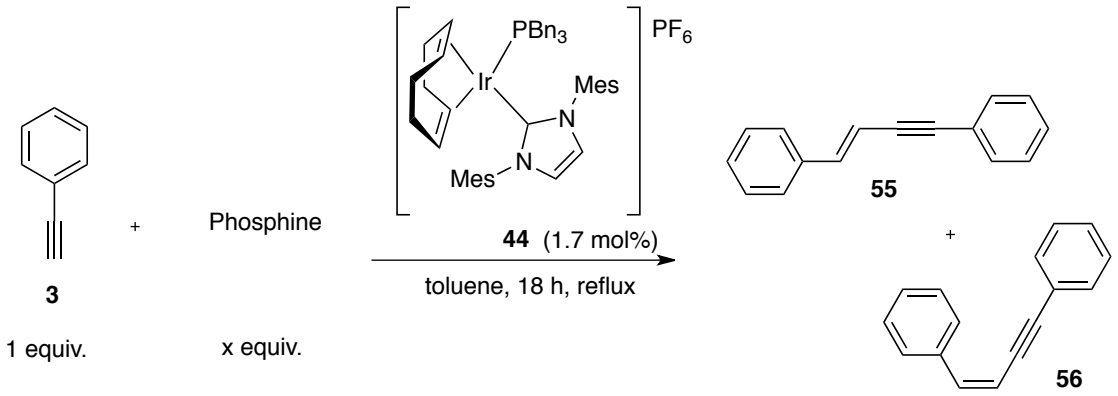
Scheme 41

Entry	*Time*	*Selectivity (E:Z)*	*Yield of Enyne (%)*	*Yield of Cyclotrimerization Product (%)*
1	2.5 h	13:87	80	13
2	18 h	11:89	81	9

Table 14

3.12 Alternate Phosphine Study

At this juncture, the optimisation study had developed in a pleasing fashion with a robust reaction protocol at hand. However, in relation to the phosphine additive, one question remained: would an alternative phosphine additive improve the reaction yield and selectivity? With this in mind, it was hypothesised that using a mixed phosphine type catalyst may result in a further improvement in the selectivity. Accordingly, a small range of alternative phosphine additives were trialled in the reaction protocol. The results of this study are summarised below (**Scheme 42**, **Table 15**). The use of tributylphosphine resulted in an unexpected reversal of the selectivity of the resultant enyne and a significant drop in the yield (**Entry 1**). This was surprising as it was anticipated that the electron-rich phosphine would facilitate the proposed double oxidative addition pathway associated with the dimerization process. However, the steric bulk of the phosphine is reduced relative to PBn_3 and, consequently, this may be the reason behind the lowered *Z*-selectivity. In addition, 1,4-bis(diphenylphosphino)butane (dppb), a bidentate phosphine ligand, was employed in order to investigate the impact that a bidentate ligand would have on the reaction (**Entries 2** & **3**). However, the bulky ligand proved to be too sterically encumbered to facilitate any reaction and resulted in the inactivation of the catalyst.



Scheme 42

Entry	*Phosphine* (*Equivalents*)	*Selectivity (E:Z)*	*Yield of Enyne (%)*	*Yield of Cyclotrimerization Product (%)*
1	PBu_3 (0.33)	66:34	38	12
2	dppb (0.17)	-	-	-
3	dppb (0.33)	-	-	-

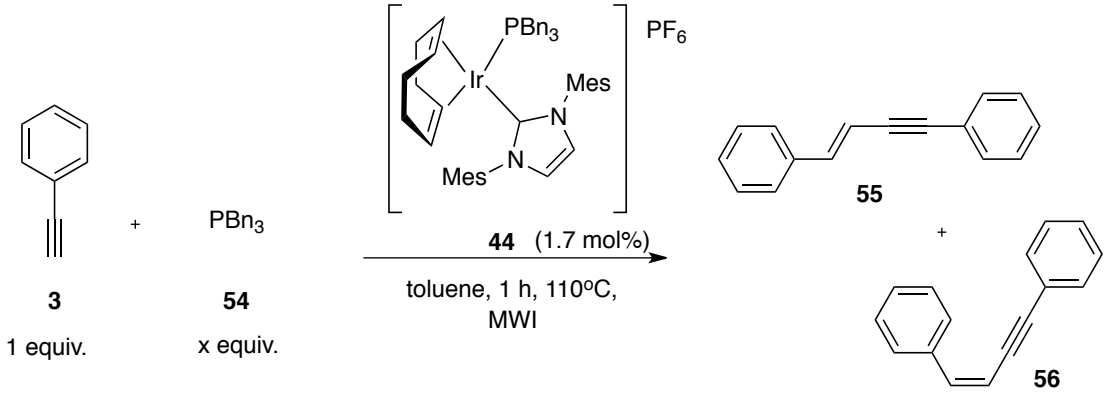
Table 15

Based on the above results, it is obvious that the delicate nature of the electronics and sterics are clearly disrupted with this mixed phosphine set-up. Accordingly, tribenzylphosphine remained the additive of choice in the iridium catalysed alkyne dimerization process.

3.13 Microwave Promotion

A comprehensive optimisation study had facilitated the development of a high yielding and robust dimerization protocol. Having stated this, it was felt that alternative methods of promoting the reaction may result in a rapid, and higher yielding, process. Accordingly, microwave irradiation was employed in the hope of facilitating expedient access to the selectively dimerized product (**Scheme 43**, **Table 16**). During the course of the optimisation study, the phosphine additive had proven of paramount importance, with respect to efficiently promoting the dimerization process. Based on this, it was decided to conduct a brief phosphine loading study with regards to the microwave-promoted reactions. Initially, the optimised conditions for the thermal reaction were transposed to the preliminary attempt employing microwave irradiation (**Entry 1**). Disappointingly, a slight drop in yield and selectivity was observed employing the benchmark reaction protocol. Based on this, extreme cases of phosphine loading, 0 and 1.0 equivalents, respectively,

were trialled in the microwave promoted reaction (**Entries 2** & **3**). Unfortunately, these alternative reaction protocols resulted in a loss of selectivity and a poor yield of the enyne.

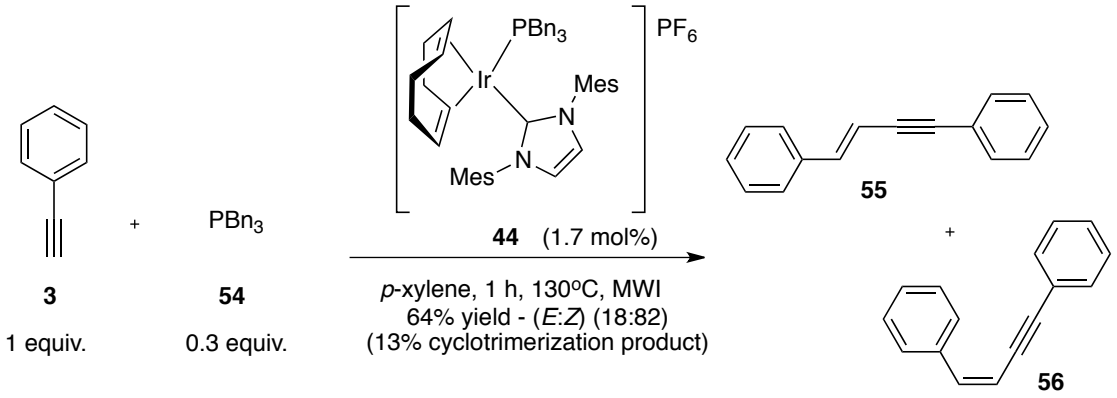


Scheme 43

Entry	*Phosphine Equivalents*	*Selectivity (E:Z)*	*Yield of Enyne (%)*	*Yield of Cyclotrimerization Product (%)*
1	0.3	21:79	71	12
2	0	44:56	16	34
3	1.0	22:78	45	17

Table 16

As stated previously, the transposed conditions were marginally poorer than the optimised thermally-promoted conditions. Based on this, it was reasoned that the use of an alternative solvent may enhance the yield. Accordingly, *p*-xylene was employed in the microwave reaction in the hope that it may furnish the desired product in enhanced yield (**Scheme 44**). Owing to the increased boiling point of the solvent, the reaction was carried out at 130°C. Unfortunately, despite proceeding in a (*Z*)-selective manner, the higher boiling solvent failed to suitably enhance the yield of the reaction.

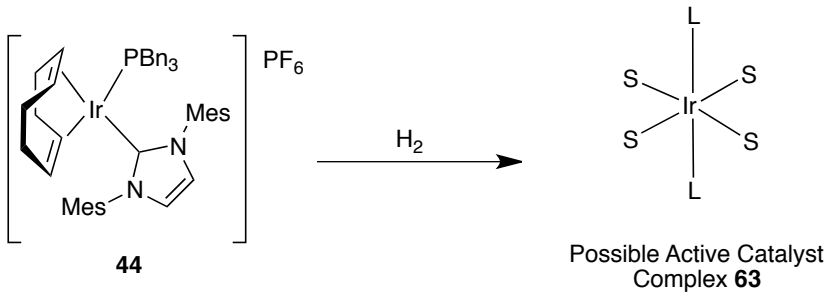


Scheme 44

The attempts to promote the reaction *via* microwave irradiation failed to appreciably enhance the selectivity and yield. As such, the thermally-promoted reaction remained the most efficient promotion method. However, before embarking on expanding the substrate scope of the reaction, it was decided to further investigate the formation of the active catalyst *via* COD dissociation.

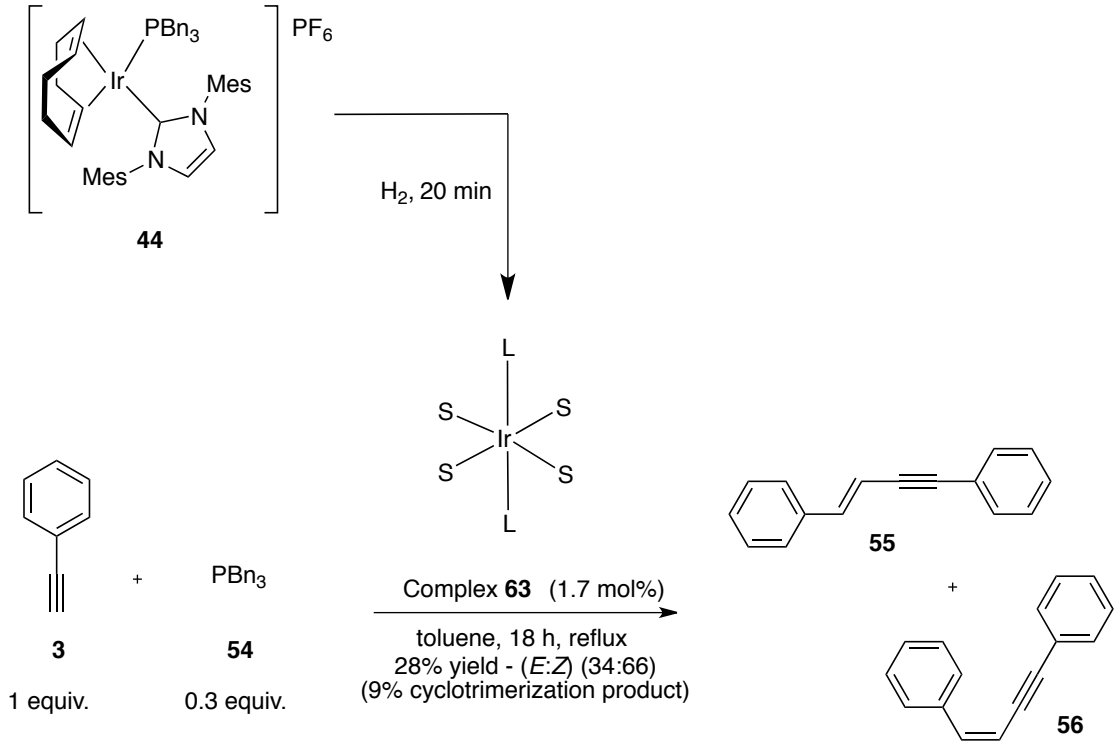
3.14 COD Hydrogenation Studies

The thermally-assisted promotion of COD dissociation has been employed throughout the optimisation study. Indeed, this has previously granted access to the desired enyne in excellent yield with appreciable levels of selectivity. However, an alternative method of catalyst activation remained univestigated, it could be deduced that hydrogenation of the COD moiety would form the active catalyst in a contrasting manner (**Scheme 45**).



Scheme 45

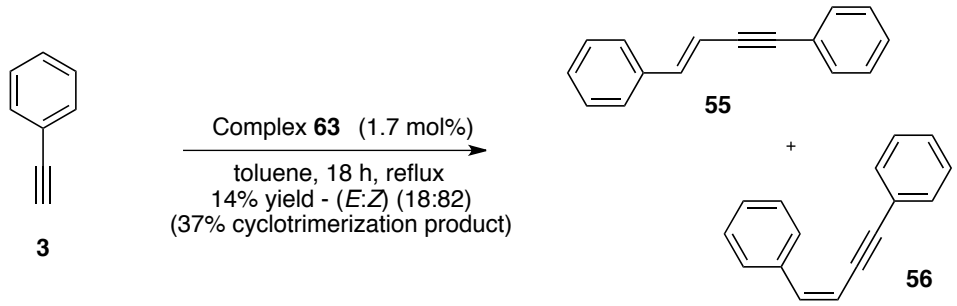
In order to probe this activation method, complex **44** was subjected to a hydrogenation reaction with the resulting species being employed directly in an alkyne dimerization reaction (**Scheme 46**). The initial hydrogenation was carried out in toluene, with the catalyst being stirred at room temperature under an atmosphere of hydrogen for 20 minutes. After this time the hydrogen was removed and the system placed under an atmosphere of argon, this was followed by addition of phenylacetylene and tribenzylphosphine as a mixture in solution. Unfortunately, the results of the reaction were disappointing with a poor 28% yield and only moderate *E*:*Z* selectivity being obtained; it is likely that the COD hydrogenation proceeded rapidly, however, following this, the catalyst's vacant coordination sites were swamped by the excess phosphine present. Accordingly, the potential for the alkyne to interact with the catalyst would be severely restricted.



Scheme 46

Based on the theory that the excess phosphine was serving to deactivate the catalyst, it was logical to implement a strategy in the absence of phosphine additive. As such, it follows that there would be decreased competition for coordination sites and this may serve to

enhance the effectiveness of this system (**Scheme 47**). Unfortunately, as before, the yield obtained was disappointing. Therefore it was obvious that this approach failed to offer an enhancement to the reaction protocol. Interestingly, the yield of the cyclotrimerization by-product significantly increased. This is potentially attributable to the increased concentration of the alkyne substrate around the iridium centre.

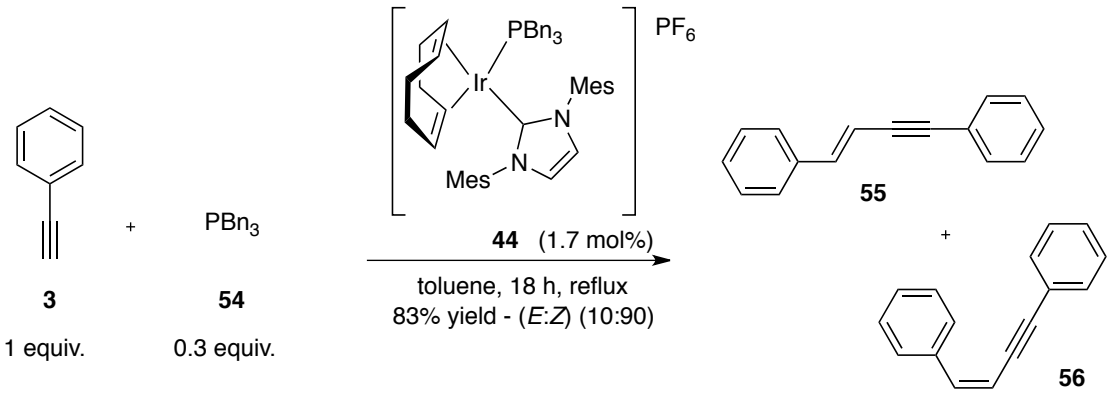


Scheme 47

Based on the results of the above experiments it is likely that the vacant iridium centres dimerize, and indeed trimerize, with themselves. This issue has plagued researchers employing Crabtree's catalyst over extended periods of time. It is probable that the hydrogenation activation pathway deactivates the catalyst due to the rapid formation of inactive iridium clusters.

3.15 Summary of Optimisation Studies

After an extensive optimisation process, which encompassed a range of variables and promotion methods, an optimised system was identified. This optimised protocol granted access to the desired enyne in a yield of 83% with (*E*:*Z*) selectivity of (10:90) (**Scheme 48**).



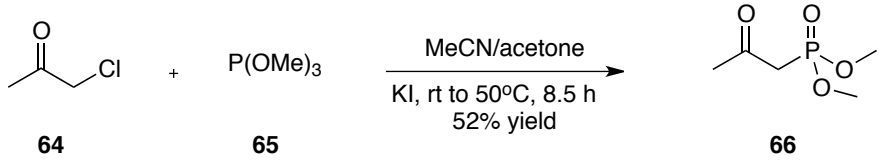
Scheme 48

Pleased with the development of the dimerization protocol attention turned to expansion of the substrate scope. Accordingly, it was envisaged that the optimised system could be transposed to a range of alternative alkynes.

3.16 Expansion of the Substrate Scope

In order to probe the scope of the developed reaction protocol, attention turned to alternative alkynes that would serve to illustrate the applicability of the optimised system. As such, consideration was given to the initial substrates to be trialled. It was decided that aryl alkynes featuring electronically different substituents would serve as the substrates for the initial screening programme. With this approach in mind, attention turned to the synthesis of suitable aryl alkynes. Accordingly, it was decided that the Ohira-Bestmann alkynylation would grant expedient access to the desired compounds.[52] Before this could be attempted, the Ohira-Bestmann reagent had to first be synthesised.

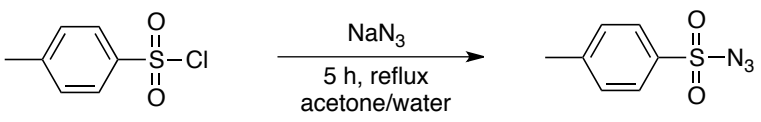
The Ohira-Bestmann reagent, **69**, is formed *via* a diazo transfer reaction, using tosyl azide **68** and the enolate of the required phosphonate **66**. Pleasingly, the phosphonate **66** can be prepared from very inexpensive starting materials *via* a sequential Finkelstein/Arbuzov reaction (**Scheme 49**).[53] Through employment of this reaction protocol, the desired phosphonate ester, **66**, was isolated in a 52% yield.



64 **65** **66**

Scheme 49

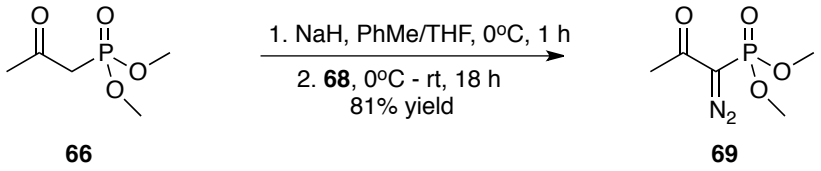
Before diazo transfer could take place, formation of tosyl azide **68** was required. This was achieved without incident, from tosyl chloride **67** and sodium azide, in excellent yield (**Scheme 50**).



67 **68**

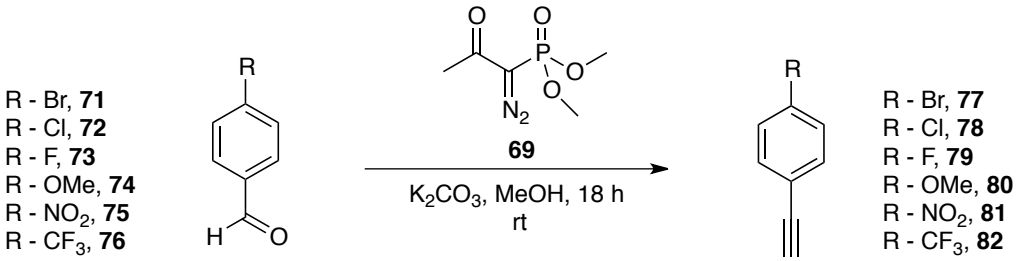
Scheme 50

With both components in hand, attention turned to the diazo transfer reaction which would facilitate the formation of the desired Ohira-Bestmann reagent **69**. Pleasingly, this transformation proceeded in an 81% yield (**Scheme 51**).



Scheme 51

Having prepared the Ohira-Bestmann reagent, in good quantities, attention turned to the alkynylation of functionalised benzaldehyde moieties (**Scheme 52**, **Table 17**). The *para*-halogenated benzaldehydes, **71**-**73**, reacted without incident to afford the analogous alkyne species in good yield (**Entries 1** – **3**). In addition, *para*-methoxy, **74**, and *para*-nitro, **75**, substituted benzaldehydes underwent alkynylation to furnish the analogous alkyne compounds in an efficient manner (**Entries 4** & **5**). Unfortunately, the formation and isolation of the *para*-trifluoromethyl product **76** was extremely problematic (**Entry 6**). It was observed that the starting material was readily oxidised, in air, to the analogous acid. Fortunately, the acid was a solid and filtration was effective in removing this contaminant. Nonetheless, rapid oxidation of the isolated aldehyde remained a problem. As the reaction protocol employs an excess of base it was decided to press on in the hope that the acid would fail to interfere with the progress of the reaction. As such, the aldehyde (with a small amount of acid present) was treated with an excess of potassium carbonate in methanol, and this was stirred for 30 minutes followed by the addition of the Ohira-Bestmann reagent, **69**. Pleasingly, the use of excess base facilitated reasonable conversion to the desired alkyne. Subsequent isolation of the alkyne was attempted by employing column chromatography, however, the alkyne proved unstable and decomposed upon contact with silica. Undeterred, an alternative approach was devised.



Scheme 52

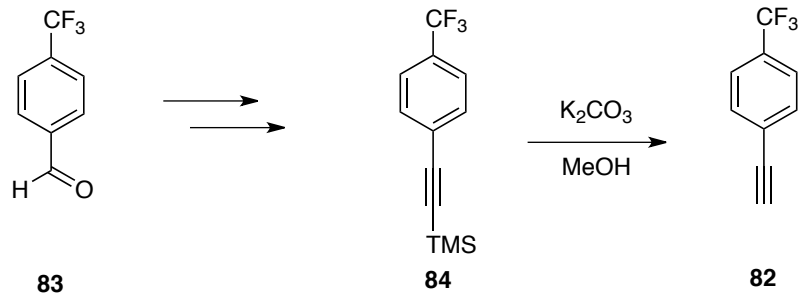
Entry	*Alkyne*	*Yield (%)*
1	**77**	83
2	**78**	82
3	**79**	88
4	**80**	74
5	**81**	72
6	**82**	-

Table 17

3.17 Corey-Fuchs Alkynylation

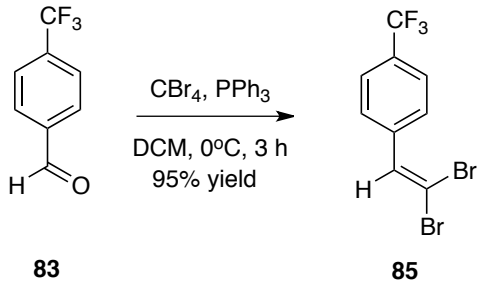
The Corey-Fuchs alkynylation involves converting an aldehyde to a dibromo olefin, which is subsequently transformed to an alkyne.[54] It was envisaged that the previously inaccessible *para*-trifluoromethyl phenylacetylene **82**, could be formed *via* this approach. It was proposed that trimethylsilyl protected alkyne, **84**, could be formed and subsequently isolated *via* column chromatography. Accordingly, it was anticipated that the TMS protected alkyne would prove more stable. As such, it follows that the trimethylsilyl

protecting group could be removed immediately prior to attempting the dimerization protocol (**Scheme 53**).



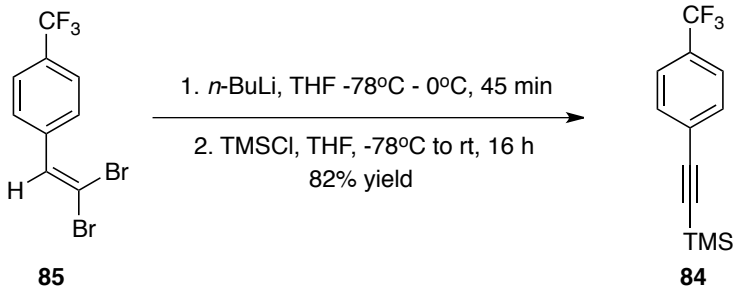
Scheme 53

With this synthetic strategy in mind, aldehyde **83**, was subjected to Corey-Fuchs reaction conditions. Pleasingly, this approach granted access to the corresponding dibromo olefin, **85**, in a 95% yield (**Scheme 54**).



Scheme 54

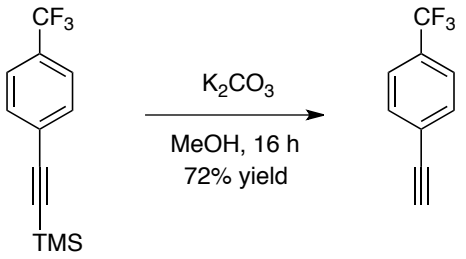
With this product in hand, attention turned to accessing the protected alkyne in a one-pot fashion. Accordingly, dibromo olefin, **85**, was treated with *n*-BuLi in order to promote the formation of the lithiated alkyne species. Upon complete conversion of the dibromo moiety, the anionic intermediate was quenched with chlorotrimethylsilane. Gratifyingly, this facilitated access to the desired alkyne, **84**, in an 82% yield (**Scheme 55**).



85 **84**

Scheme 55

With protected alkyne **84** in hand, attention turned to the removal of the silyl unit, in order to liberate the terminal alkyne moiety, **82**. This transformation was facilitated by treating alkyne **84** with potassium carbonate in methanol, which cleanly provided the desired species in a 72% yield (**Scheme 56**). Unfortunately, as before, the freshly installed terminal alkyne readily underwent degradation pathways. Based on this, it was decided to liberate the terminal alkyne immediately prior to future dimerization attempts.



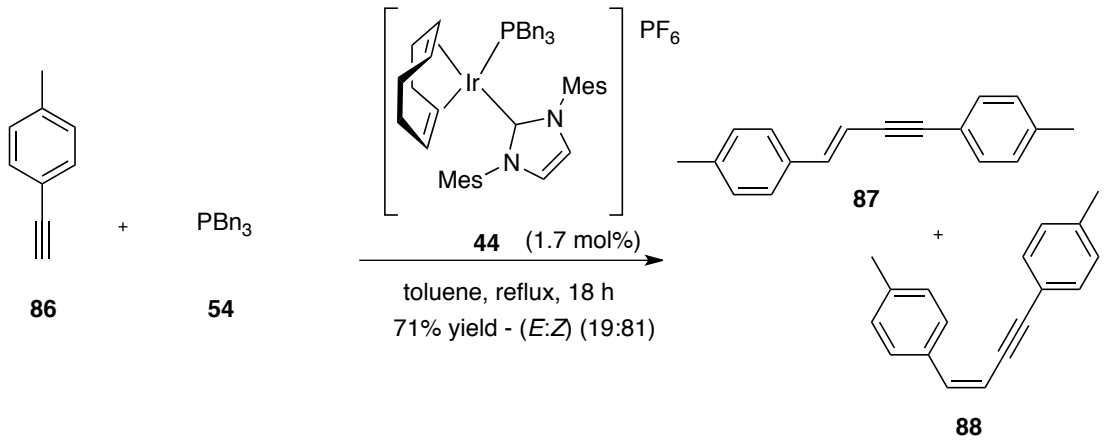
84 **82**

Scheme 56

Pleased with the synthesis of a broad set of aryl alkynes, attention turned to the performance of these species within the optimised dimerization protocol. It was envisaged that the aryl alkynes, featuring contrasting electronics, would behave in a similar manner to phenylacetylene and grant expedient access to the (*Z*)-selective dimerization product.

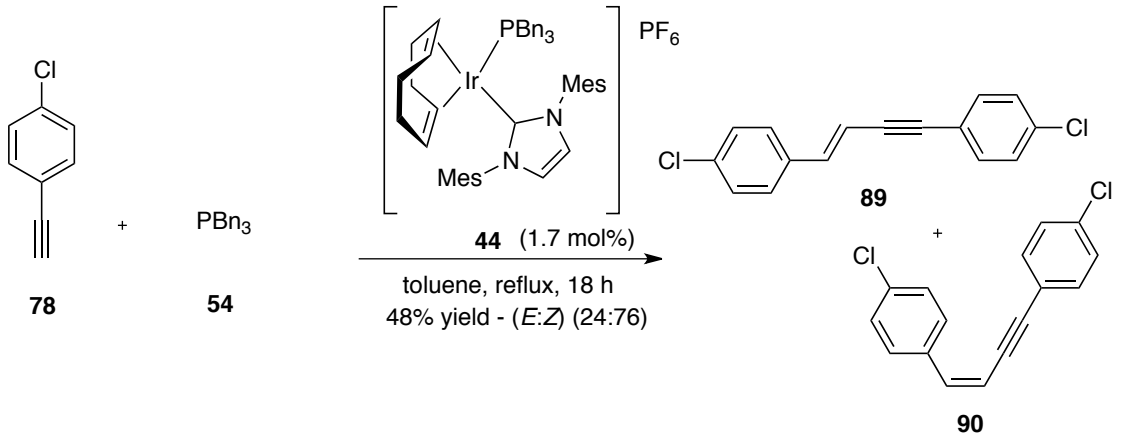
3.18 Dimerization of Aromatic Alkynes

The ability of aromatic alkynes to undergo homo dimerization was investigated initially with the commercially sourced *p*-methylphenylacetylene **86** (**Scheme 57**). Pleasingly, under the optimised reaction conditions, the homo dimerization of *p*-methylphenylacetylene **86** proceeded in a 71% yield with good (*Z*)-selectivity being obtained. In addition, it should be noted that the product(s) of cyclotrimerization were not observed in the reaction profile. Indeed, this proved to be the case for all the substrates screened under the optimised reaction protocol.



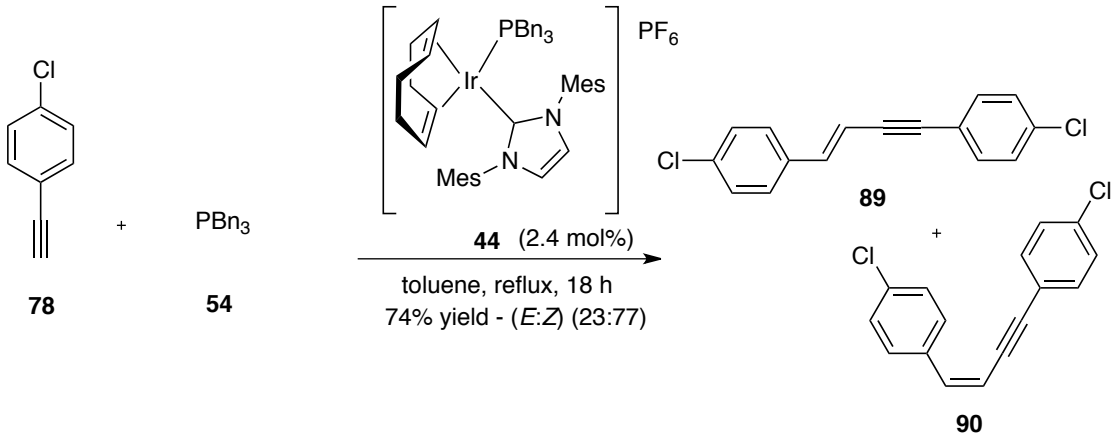
Scheme 57

Having trialled a relatively electron-neutral species, attention turned to the dimerization of a halogen-bearing substrate. Accordingly, *p*-chlorophenylacetylene **78** was subjected to the reaction conditions. Upon analysing the product of the reaction the *E*:*Z* selectivity was relatively pronounced, however the overall yield was disappointing (**Scheme 58**).



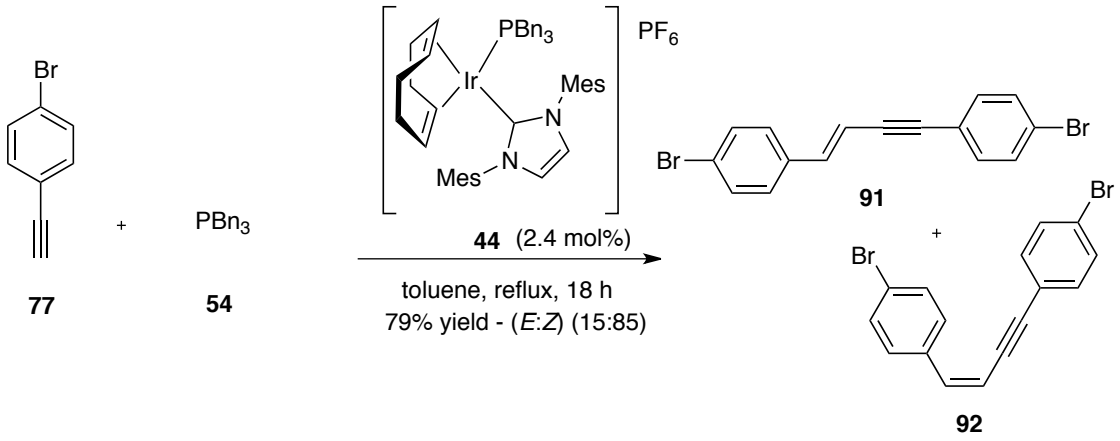
Scheme 58

Aryl halides are incredibly useful building blocks within organic chemistry and in order to effectively showcase the developed methodology it was imperative to facilitate the transformation of such compounds in appreciable yield. It was hypothesised that the poor yield obtained in this dimerization could potentially be attributed to the chloro functionality partially ligating to the iridium complex, which may serve to lower the catalyst activity. In a bid to combat this effect, an increased catalyst loading of 2.4 mol% was employed (**Scheme 59**). Gratifyingly, an improved yield of 74%, coupled with similarly good selectivity for the *Z*-enyne, was obtained. In addition, the chloro functionality remained intact. This outcome illustrates the mild nature of the iridium catalyst; in this regard many other transition metal catalysts would facilitate the undesired protodehalogenation pathway. Extremely pleased with this outcome, it was decided that the increased catalyst loading would be implemented for the remainder of the substrate screening.



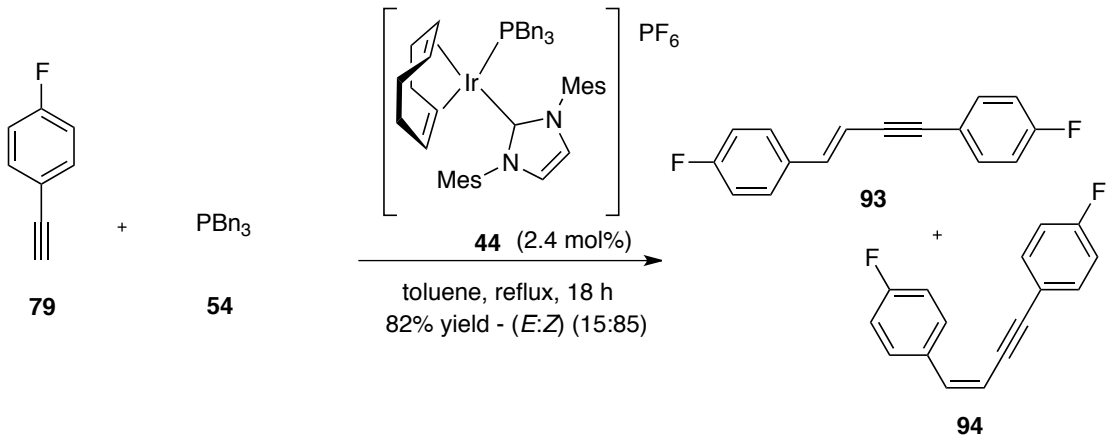
Scheme 59

The successful dimerization of *p*-bromophenylacetylene **77** would set complex **44** apart from many other transition metal catalysts in terms of facilitating dimerization. This metal-mediated transformation is not readily encountered in the chemical literature. This is presumably attributable to the potential for undesired protodehalogenation to occur. Accordingly, it would be incredibly pleasing to facilitate a (*Z*)-selective dimerization process, whilst retaining the halo functionality. Accordingly, *p*-bromophenylacetylene **77** was subjected to the optimised reaction conditions (**Scheme 60**). Pleasingly, dimerization proceeded in an excellent yield with very good selectivity observed.



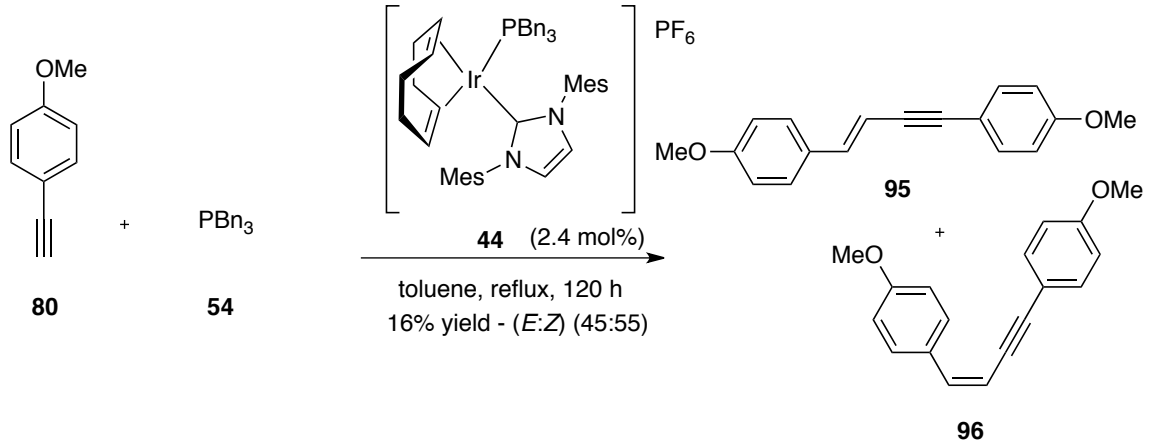
Scheme 60

Due to the ubiquitous nature of fluorinated species within medicinal chemistry it seemed appropriate to investigate the dimerization of a suitably fluorinated species. Accordingly, the previously synthesised *p*-fluorophenylacetylene **79** was exposed to the dimerization protocol. Gratifyingly, the desired product was obtained in a very good yield with pleasing selectivity exhibited (**Scheme 61**).



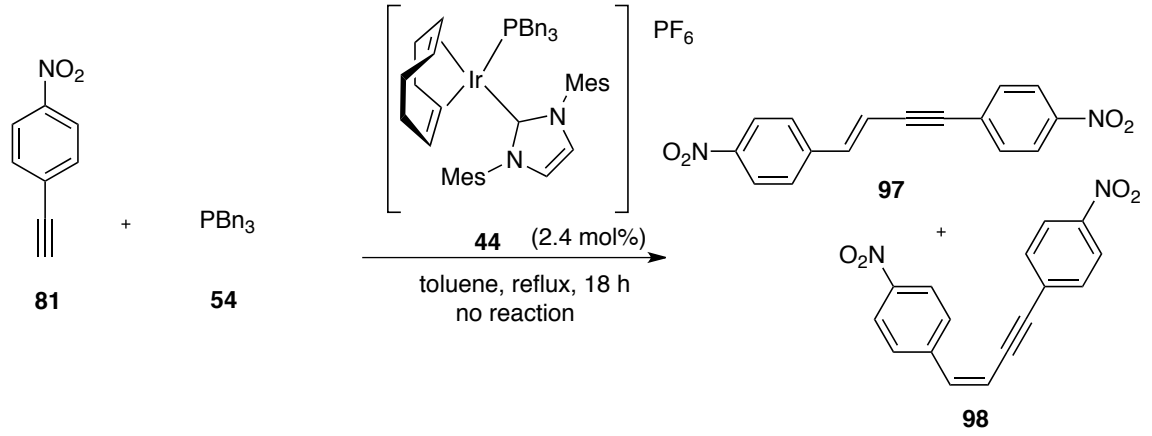
Scheme 61

It was particularly pleasing to considerably expand the scope of the reaction. Accordingly, it was decided to employ the previously prepared *p*-methoxyphenylacetylene **80**, a substrate featuring an electron-donating group (**Scheme 62**). It was envisaged that this would render the initial oxidative addition step more difficult. Disappointingly, although not wholly unexpectedly, the reaction proceeded in poor yield with a loss in the selectivity observed even after a prolonged reaction time. It would appear that the electron-donating nature of the substrate impedes the reaction as predicted.



Scheme 62

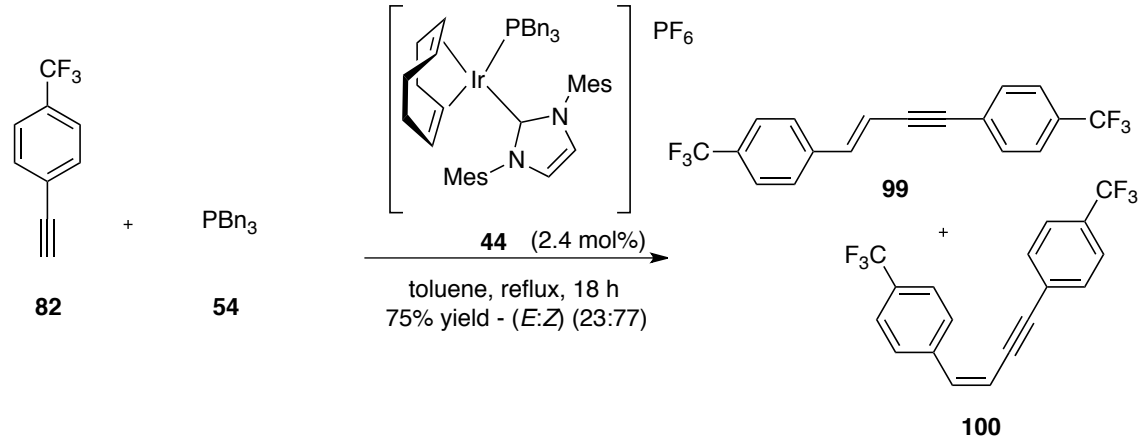
In contrast to the electronic nature of the above example, *p*-nitrophenylacetylene **75** was investigated. It follows that electron-withdrawing nature of the nitro-substituent should render the substrate more susceptible to rapid oxidative addition (**Scheme 63**). Unfortunately, the substrate failed to undergo dimerization and instead underwent degradation. This is most likely attributed to the nitro group coordinating to the iridium centre, resulting in deactivation of the catalyst.



Scheme 63

Inspite of the disappointing result obtained with *p*-nitrophenylacetylene **81**, it remained pertinent to investigate the ability of an aryl alkyne featuring an electron-withdrawing group to undergo selective dimerization. It was envisaged that *p*-trifluoromethylphenylacetylene **82** would be capable of undergoing dimerization and, indeed, was unlikely to poison the iridium catalyst (**Scheme 64**). As predicted, alkyne **82**

proved an efficient substrate for dimerization with pleasing selectivity and chemical yield being observed.



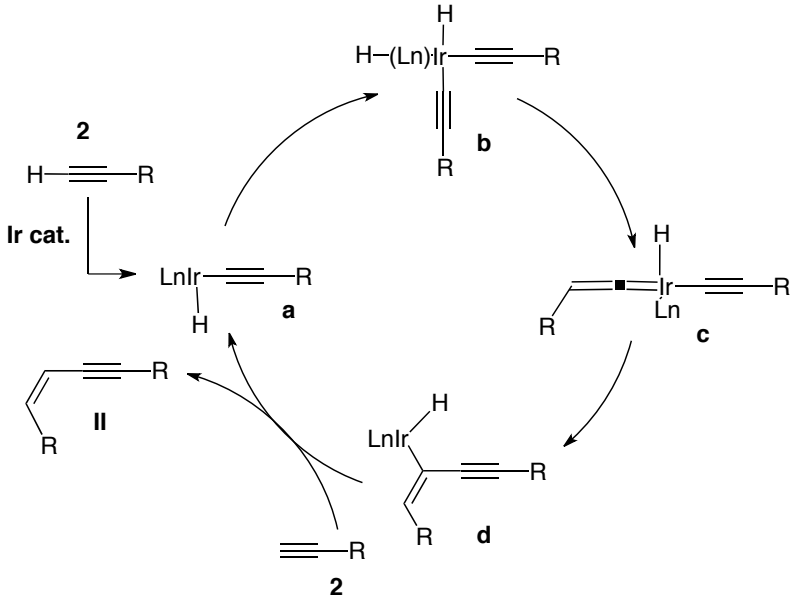
Scheme 64

In summary, a variety of aryl alkynes have effectively underwent dimerization in a regiochemical and stereoselective fashion. It has been illustrated that electron-rich substrates react in poor yield with a lack of selectivity observed. In contrast, electron-poor and electron-neutral aryl alkynes undergo dimerization in good yield and diastereoselective control being exhibited. In addition, it should be noted that an undisclosed substrate screening led to the above synthetic protocol being applied to several alkyl alkynes. However, these preliminary attempts failed to deliver the dimerized product(s) and efforts were concentrated on expanding the scope of aryl alkynes, as detailed above.

4 Conclusion

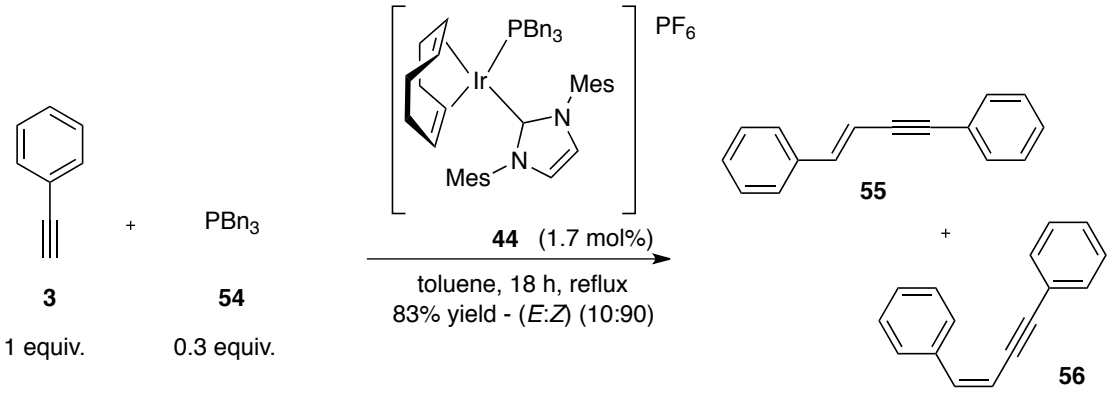
The (*Z*)-selective head-to-head homodimerization of aryl alkynes has been achieved through the use of a novel iridium(I) catalyst bearing a mixed NHC/phosphine ligand environment. Not only is this important in terms of adding to a limited number of complexes capable of facilitating such a transformation, it also illustrates a further application of the mixed NHC/phosphine catalysts developed within our laboratory.

As discussed, the employment of tribenzylphosphine as a ligand is integral to the selective dimerization process. The subtle electronic and steric balance of the phosphine unit underpins the synthetic protocol. This can be better understood by appealing to our proposed reaction mechanism (**Scheme 65**). In order to access the key intermediate **b**, the iridium centre must undergo two successive oxidative additions. These transformations are likely to be aided by the electron rich ligand environment afforded by the tribenzylphosphine additive. In addition, it is believed that the formation of intermediate **d** is responsible for imparting the observed (*Z*)-selectivity, as this species avoids repulsive interactions between the alkynyl substituents and the ligand sphere of the iridium catalyst. Based on the above, the strategic employment of tribenzylphosphine as an additive, alongside our novel iridium catalyst, promotes the selective and efficient dimerization of aryl alkynes.



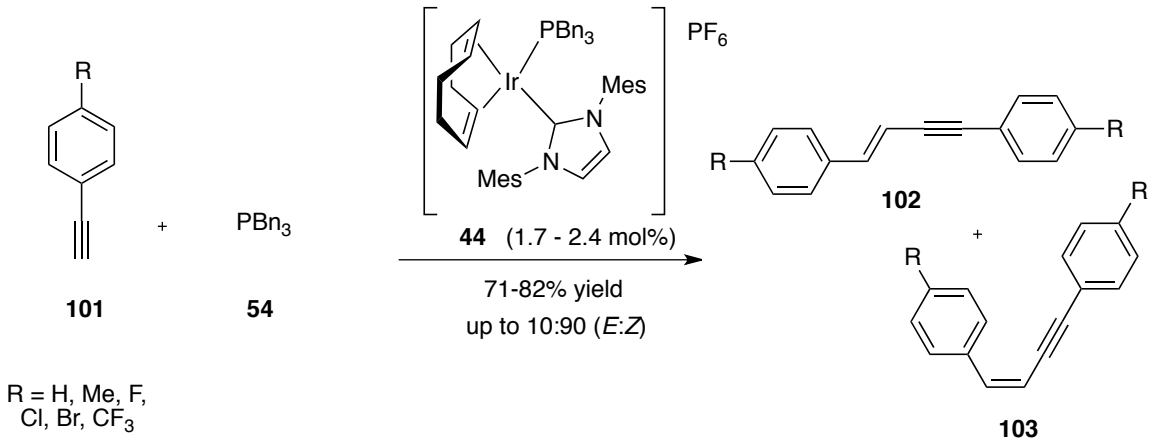
Scheme 65

Further still, the system has been subjected to extensive optimisation studies with a range of conditions investigated. More specifically, employing only 1.7 mol% of the iridium catalyst, alongside a phosphine additive, granted access to the desired (*Z*)-enyne product in an excellent 83% yield (**Scheme 66**). In addition, a range of experiments were designed, and performed, in order to gain a more complete understanding of the role of the phosphine additive. It is proposed that the phosphine additive is unlikely to aid in the initial dissociation of the COD ligand, and instead maintains the phosphine-NHC ligand environment.



Scheme 66

Upon completion of these studies a range of alternative alkynes were exposed to the optimised reaction conditions. This proved successful for a range of electron-poor and electron-neutral aromatic alkynes which underwent dimerization with very good regio- and stereoselective control (**Scheme 67**).



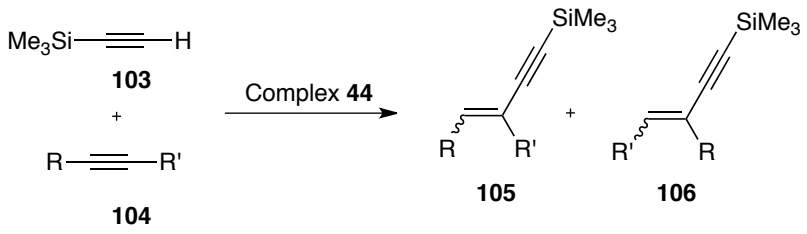
Scheme 67

Pleasingly, the reaction protocol enabled the dimerization of haloaryl alkynes, which are traditionally considered capricious substrates under transition metal catalysed processes. The optimisation process, and subsequent substrate screening, was recently disclosed in the chemical literature.[55]

5 Future Work

The most obvious development of the dimerization protocol is expansion of the substrate scope. Indeed, the employment of heteroaryl and alkyl substrates would significantly enhance the utility of this transformation. As such, this represents an interesting area for future research.

In a further extension of this project, the delivery of terminal alkynes into internal alkynes may be investigated (**Scheme 68**). It is envisaged a suitable terminal alkyne may be able undergo cross-dimerization with an electronically-tuned coupling partner. For example, trimethylsilylacetylene, **103**, could potentially undergo cross dimerization with a suitable alkyne such as **104**, to furnish enyne **94** and/or enyne **95**.



Scheme 68

In order to promote cross-dimerization in a regio- and stereoselective manner, extensive optimisation would be required. Having stated this, the cross-dimerization approach could potentially grant expedient access to a range of functionalised enyne units. This would undoubtedly prove useful to synthetic chemists and serve to further expand the scope of the novel phosphine-NHC iridium complexes.

A final point to consider is returning to the [2+2+2] annulation studies. As noted, the dimerization programme detailed herein was initiated after preliminary attempts to promote the cyclotrimerization protocol. Indeed, it was identified that the aromatisation process was failing to occur due to the alkyne moieties undergoing dimerization. It follows that employing alkynes that do not react under the dimerization protocol within the

cyclotrimerization setup may facilitate access to a range of substituted aromatic products from [2+2+2] cyclisation processes. As such, this may prove to further enhance the synthetic utility of the novel iridium complexes developed within our laboratory.

6 Experimental

6.1 General

All reagents were obtained from commercial suppliers (Aldrich, Alfa Aesar or Strem) and used without further purification, unless otherwise stated. All reactions were carried out under an inert, dry nitrogen atmosphere, unless otherwise stated. Purification was carried out according to standard laboratory methods.[56]

- Tetrahydrofuran and diethyl ether were dried by heating to reflux over sodium wire, using benzophenone ketyl as an indicator, and then distilled under nitrogen.
- Benzene was dried by heating to reflux over sodium wire then distilled under nitrogen.
- Dichloromethane was dried by heating to reflux over calcium hydride, and then distilled under nitrogen.
- Toluene was obtained from a PureSolv SPS-400-5 Solvent Purification System.
- Acetone was dried by refluxing over flame dried potassium carbonate and then distilled prior to use.
- Phenylacetylene was dried by heating to reflux over calcium hydride, and then distilled under nitrogen.
- *p*-Methylphenylacetylene was dried by heating to reflux over calcium hydride, and then distilled under nitrogen.
- *n*-BuLi was obtained as a solution in hexanes and standardised using salicyldehyde phenylhydrazone.[57]
- Triphenylphosphine was purified by recrystallisation from ethanol.
- Petrol refers to petroleum ether in the boiling range of 40-60°C.

Thin Layer Chromatography was carried out using Camlab silica plates coated with fluorescent indicator UV254. These were then analysed using a Mineralight UVGL-25 lamp and developed using vanillin or potassium permanganate solutions.

Flash Column Chromatography was carried out using Prolabo silica gel (230-400 mesh).

IR spectra were obtained on a Perkin Elmer Spectrum 1 machine.

1H and 13C NMR spectra were recorded on a Bruker DPX 400 spectrometer at 400 MHz and 100 MHz, respectively, or a Bruker DRX 500 spectrometer at 500 MHz and 125 MHz, respectively. 31P NMR spectra were recorded on a Bruker DPX 400 spectrometer at 162 MHz. Chemical shifts are reported in ppm. Coupling constants are reported in Hz and refer to 3JH-H interections, unless otherwise stated. Note: CDCl3 solvent signals were used as internal reference points at δ 7.26 and 77.16 ppm in 1H and 13C NMR respectively.

Melting points were obtained (uncorrected) on a Gallenkamp Griffin melting point apparatus.

Reactions performed under microwave irradiation were carried out in a CEM Discover instrument using sealed glass tubes.

Liquid Chromatography – Mass Spectrometry was carried out using an Agilent 6130 Liquid Chromatography system, fitted with a BEH C18 5.0 μm 4.6 x 150 mm column. Employing either a basic gradient of 5-95% 0.1% ammonium hydroxide in MeCN : 0.1% ammonium hydroxide in 10 mM aqueous ammonium bicarbonate solution or an acidic gradient of 5-95% 0.1% Formic Acid in MeCN : 0.1% formic acid in H_2O.

6.2 General Procedures

General Procedure A – Preparation of Iridium(I) complexes

A 1 M sodium ethoxide solution was prepared by dissolving sodium metal (0.25 g) in ethanol (10 ml) within a previously flame dried 2-neck flask under nitrogen. To a flame-dried Schlenk tube containing η^4-cycloocta-1,5-dieneiridium(I) chloride dimer **17**, dissolved in dry benzene (10 ml), was added 1 M sodium ethoxide solution, resulting in a red to yellow colour change. The solution was stirred at room temperature for 10 minutes, followed by the addition of the imidazolium salt. The solution was stirred under an atmosphere of argon for 5 h, after which time the solvent was removed under high vacuum. The residue was triturated with dry diethyl ether (15 ml) and filtered through celite under argon. The solvent was again removed under high vacuum, yielding a yellow solid, which was dissolved in dry THF (10 ml). Addition of silver hexafluorophosphate resulted in a yellow to orange colour change, and the formation of a precipitate was observed. The solution was stirred for 20 minutes prior to filtration through celite under argon, to give a clear orange solution. On addition of the phosphine, the solution turned from orange to deep red. After stirring for 90 minutes, the solvent was once again removed under high vacuum, yielding a red solid. The product was isolated by recrystallisation and analysed by ^{1}H, ^{31}P, and ^{13}C NMR, and IR spectroscopy.

General Procedure B – Alkyne Dimerization

A round bottom flask, fitted with a reflux condenser, was flame-dried under vacuum and allowed to cool under nitrogen prior to being charged with the desired alkyne, iridium complex, and dry solvent. The reaction mixture was then heated to reflux and allowed to stir for 18 hours. The mixture was then concentrated *in vacuo* and the products were isolated by column chromatography (eluent: 0-2.5% diethyl ether in petrol).

General Procedure C – Alkyne Dimerization

A round bottom flask, fitted with a reflux condenser was flame-dried under vacuum and allowed to cool under nitrogen prior to being charged with complex **44**, tribenzylphosphine **54**, and dry solvent. The reaction mixture was then heated to reflux, at which point phenylacetylene **3** was added and the mixture stirred for 18 hours. The mixture was then concentrated *in vacuo* and the products were isolated by column chromatography (eluent: 0-2.5% diethyl ether in petrol).

General Procedure D – Alkyne Dimerization

A round bottom flask, fitted with a reflux condenser was flame-dried under vacuum and allowed to cool under nitrogen prior to being charged with complex **44**, tribenzylphosphine **54**, and dry solvent. The reaction mixture was then heated to reflux and allowed to stir for 2 hours, prior to the addition of phenylacetylene **3**. The resulting mixture was stirred for 18 hours. The mixture was then concentrated *in vacuo* and the products were isolated by column chromatography (eluent: 0-2.5% diethyl ether in petrol).

General Procedure E – Alkyne Dimerization

A round bottom flask, fitted with a reflux condenser was flame-dried under vacuum and allowed to cool under nitrogen prior to being charged with the desired alkyne, complex **44**, tribenzylphosphine **54**, and dry solvent. The reaction mixture was then heated to reflux and allowed to stir for the allotted time. The mixture was then concentrated *in vacuo* and the products were isolated by column chromatography (eluent: 0-2.5% diethyl ether in hexane).

General Procedure F – Alkyne Dimerization

A round bottom flask, fitted with a reflux condenser, was flame-dried under vacuum and allowed to cool under nitrogen prior to being charged with the desired alkyne, complex **44**, phosphine, and dry solvent. The reaction mixture was then heated to reflux and allowed to stir for the allotted time. The mixture was then concentrated *in vacuo* and the products were isolated by column chromatography (eluent: 0-2.5% diethyl ether in petrol).

General Procedure G – Alkyne Dimerization

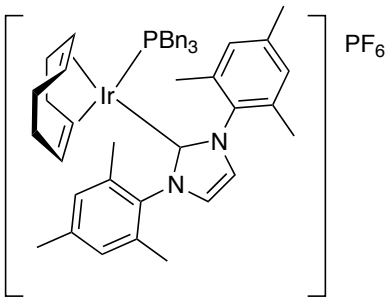
To a microwave vial was added: phenylacetylene, **3**, complex **44**, phosphine, and solvent. The mixture was then heated under microwave irradiation for 1 hour. The mixture was then concentrated *in vacuo* and the products were isolated by column chromatography (eluent: 0-2.5% diethyl ether in petrol).

General Procedure H – Preparation of Alkynes

A round bottom flask was flame dried under vacuum and allowed to cool under nitrogen prior to being charged with the desired aldehyde, potassium carbonate, and dry methanol. To the stirred slurry was added the Ohira-Bestmann reagent, dimethyl-1-diazo-2-oxopropylphosphonate **69**, and the mixture stirred at room temperature for 18 h. After this time, the mixture was diluted with ether and washed with saturated sodium bicarbonate. The organics were then pooled, dried over Na_2SO_4, concentrated *in vacuo*, and then purified by column chromatography (0-10% diethyl ether in petrol).

6.3 Preparation of Iridium(I) Complexes

Preparation of η^4-Cycloocta-1,5-diene(1,3-dimesitylimidazoline-2-ylidene)(tribenzylphosphine)iridium(I) hexafluorophosphate, ***44***[47]



Following *General Procedure A*, results are reported as a) amount of **17**, b) amount of NaOEt, c) amount of 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride, **57**, d) amount of $AgPF_6$, e) amount of tribenzylphosphine, f) recrystallisation solvents, and g) product yield.

Table 5, Entry 1

a) 0.4 g, 0.595 mmol, b) 1.2 ml, 1.2 mmol, c) 0.406 g, 1.191 mmol, d) 0.301 g, 1.191 mmol, e) 0.362 g, 1.191 mmol, f) DCM/Et_2O (1:1), and g) complex **44**, 0.556 g, 44%.

Table 5, Entry 2

a) 0.4 g, 0.595 mmol, b) 1.2 ml, 1.2 mmol, c) 0.406 g, 1.191 mmol, d) 0.301 g, 1.191 mmol, e) 0.362 g, 1.191 mmol, f) DCM/Et_2O (1:1), and g) complex **44**, 0.315 g, 25%.

Table 5, Entry 3

a) 0.2 g, 0.298 mmol, b) 0.6 ml, 0.6 mmol, c) 0.203 g, 0.596 mmol, d) 0.150 g, 0.596 mmol, e) 0.156 g, 0.596 mmol, f) DCM/Et_2O (1:1), and g) complex **44**, 0.163 g, 26%.

Table 5, Entry 4

a) 0.4 g, 0.595 mmol, b) 1.2 ml, 1.2 mmol, c) 0.406 g, 1.191 mmol, d) 0.301 g, 1.191 mmol, e) 0.362 g, 1.191 mmol, f) DCM/Et_2O (1:1), and g) complex **44**, 0.789 g, 63%.

Melting point: decomposed > 280˚C.

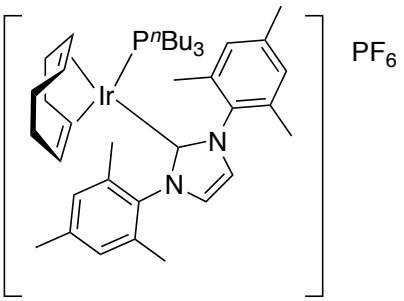
IR (DCM): 3003, 2920, 1607, 1577, 1485, 1433 cm^{-1}.

^1H NMR (400 MHz, d_6-acetone): δ 7.80 (s, 2H, olefinic CH), 7.40 (s, 2H, ArH), 7.35 (s, 2H, ArH), 7.30-7.29 (m, 9H, ArH), 6.99-6.97 (m, 6H, ArH), 4.72-4.70 (m, 2H, COD CH), 3.64-3.61 (m, 2H, COD CH), 3.02 (d, $^2J_{P\text{-}H}$ = 8.8 Hz, 6H, PCH_2Ar), 2.57 (s, 6H, $ArCH_3$), 2.47 (s, 6H, $ArCH_3$), 2.39 (s, 6H, $ArCH_3$), 1.80-1.77 (m, 2H, COD CH_2), 1.58-1.48 (m, 4H, COD CH_2), 1.36-1.34 ppm (m, 2H, COD CH_2).

^{13}C NMR (100 MHz, d_6-acetone): δ 176.2, 140.8, 137.1, 136.7, 135.9, 134.0, 134.0, 130.7, 130.6, 130.4, 129.2, 127.6, 127.4, 86.9, 75.5, 32.0, 30.7, 30.4, 20.8, 20.3 and 19.6 ppm.

^{31}P NMR (162 MHz, d_6-acetone): δ -6.26 ($P(CH_2Ph)_3$), -143.47 ppm (PF_6).

Preparation of η^4-Cycloocta-1,5-diene(1,3-dimesitylimidazoline-2-ylidene)(tri(^{n}butyl)phosphine)iridium(I) hexafluorophosphate, **29**[58]



Following *General Procedure A*, results are reported as a) amount of **17**, b) amount of NaOEt, c) amount of 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride, **57**, d) amount of $AgPF_6$, e) amount of tri^{n}butylphosphine, f) recrystallisation solvents, and g) product yield.

Table 6, Entry 1

a) 0.1 g, 0.149 mmol, b) 0.3 ml, 0.3 mmol, c) 0.101 g, 0.298 mmol, d) 0.760 g, 0.298 mmol, e) 0.060 g, 0.298 mmol, f) THF/hexane (1:1), and g) complex **29**, 0.178 g, 61%.

Melting point: decomposed > 270˚C.

IR (DCM): 3043, 2874, 2304, 1608, 1484 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (s, 2H, ArH), 6.96 (s, 2H, ArH), 6.90 (s, 2H, olefininc CH), 4.16-4.15 (m, 2H, COD CH), 3.73-3.68 (m, 2H, COD CH), 2.35 (s, 6H, $ArCH_3$), 2.29 (s, 6H, $ArCH_3$), 2.18 (s, 6H $ArCH_3$), 1.95-1.85 (m, 2H, COD CH_2), 1.75-1.60 (m, 2H, COD CH_2), 1.55-1.35 (m, 10H, alkyl CH_2 and COD CH_2), 1.31-1.25 (m, 6H, alkyl CH_2), 1.20-1.10 (m, 6H, alkyl CH_2), 0.88 ppm (t, J = 7.3 Hz, 9H, alkyl CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.3, 140.1, 136.1, 136.0, 134.5, 130.0, 129.9, 126.3, 82.2, 82.1, 74.0, 31.5, 31.1, 26.8, 24.6, 24.5, 24.4, 24.1, 21.2, 20.5, 19.6, 13.9 ppm.

^{31}P NMR (162 MHz, $CDCl_3$): δ -1.76 (P(^{n}Bu)$_3$), -143.58 ppm (PF_6).

Preparation of Chloro(η^4-Cycloocta-1,5-diene)(1,3-dimesitylimidazoline-2-ylidene iridium(I), **58**[59]

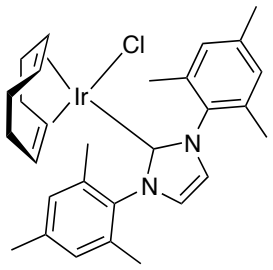


Table 6, Entry 2

To a previously flame-dried Schlenk tube containing η^4-cycloocta-1,5-dieneiridium(I) chloride dimer **17** (0.400 g, 0.595 mmol) dissolved in dry benzene (10 ml), was added a 1 M sodium ethoxide solution (1.2 ml), resulting in a red to yellow colour change. The solution was stirred at room temperature for 10 minutes, followed by the addition of 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride, **57** (0.406 g, 1.191 mmol). The solution was stirred under an atmosphere of argon for 5 hours, after which time the solvent was removed under high vacuum. The residue was triturated with dry diethyl ether (15 ml) and filtered through celite under argon. The solvent was again removed under high vacuum, and the crude residue purified by flash column chromatography (eluent: 0-50% ethyl acetate in hexane). The product **58** (0.607 g, 76%) was obtained as a solid following precipitation from petroleum ether.

Melting point: decomposed > 220˚C.

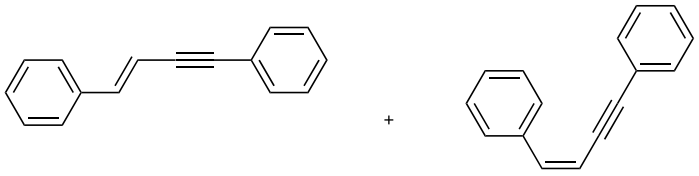
IR (DCM): 3092, 3009, 2916, 2876, 1609, 1485 cm^{-1}.

^1H NMR (400MHz, $CDCl_3$): δ 6.99-6.96 (2 x bs, 4H, ArH), 6.93 (s, 2H, olefinic CH), 4.14-4.10 (m, 2H, COD CH), 2.96-2.94 (m, 2H, COD CH), 2.34 (s, 12H, $ArCH_3$), 2.14 (s, 6H, $ArCH_3$), 1.74-1.59 (m, 4H, COD CH_2), 1.33-1.21 ppm (m, 4H, COD CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ 181.0, 138.8, 137.6, 136.3, 134.6, 133.0, 129.7, 128.3, 123.5, 82.8, 66.1, 51.6, 33.7, 29.3, 21.4, 19.9, 15.5 ppm.

6.4 Alkyne Dimerization

*(*E*)-1,4-Diphenyl-1-buten-3-yne,* **55**[60] and *(Z)-1,4-Diphenyl-1-buten-3-yne,* **56**[60]



The product of alkyne dimerization was isolated as a mixture of (*E*)- and (*Z*)-enynes with the ratio being determined by comparison to the published ^{1}H NMR data.

The following data is based on a 25:75 (*E*:*Z*) mixture:

IR (DCM): 2836, 2340, 1487 cm^{-1}.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.96 (d, *J* = 7.6 Hz, 0.75H, ArH) 7.51-7.34 (m, 9.25H, ArH), 7.07 (d, *J* = 16.2 Hz, 0.25H, *E*-olefin CH), 6.73 (d, *J* = 11.8 Hz, 0.75H, *Z*-olefin CH), 6.41 (d, *J* = 16.2 Hz, 0.25H, *E*-olefin CH) 5.95 ppm (d, *J* = 11.8 Hz, 0.75H, *Z*-olefin CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 141.3, 138.7, 136.6, 136.3, 131.5, 131.5, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.3, 128.2, 128.2, 126.3, 123.5, 123.4, 108.1, 107.4, 95.8, 91.7, 88.9, 88.2 ppm.

Following *General Procedure B*, results are reported as a) amount of phenylacetylene **3**, b) amount of catalyst, c) solvent, d) product yield, and e) product selectivity (*E*:*Z*).

Table 7, Entry 1

a) 0.150 g, 1.46 mmol, b) complex **44**, 0.077 g, 0.073 mmol, 5 mol%, c) benzene, 2.5 ml, d) 0.046 g, 31%, and e) 25:75.

Table 7, Entry 2

a) 0.150 g, 1.46 mmol, b) complex **44**, 0.077 g, 0.073 mmol, 5 mol%, c) benzene, 2.5 ml, d) 0.041 g, 27%, and e) 24:76.

Scheme 28

a) 0.150 g, 1.46 mmol, b) complex **29**, 0.069 g, 0.073 mmol, 5 mol%, c) benzene, 2.5 ml, d) 0.048 g, 32%, and e) 31:69.

Scheme 29

a) 0.150 g, 1.46 mmol, b) complex **58**, 0.047 g, 0.073 mmol, 5 mol%, c) benzene, 2.5 ml, d) 0.035 g, 23%, and e) 67:33.

Table 8, Entry 1

a) 0.150 g, 1.46 mmol, b) complex **44**, 0.077 g, 0.073 mmol, 5 mol%, c) benzene, 2.5 ml, d) 0.046 g, 31%, and e) 25:75.

Table 8, Entry 2

a) 0.150 g, 1.46 mmol, b) complex **44**, 0.077 g, 0.073 mmol, 5 mol%, c) toluene, 2.5 ml, d) 0.060 g, 40%, and e) 13:87.

Table 8, Entry 3

a) 0.150 g, 1.46 mmol, b) complex **44**, 0.077 g, 0.073 mmol, 5 mol%, c) *p*-xylene, 2.5 ml, d) 0.046 g, 31%, and e) 35:65.

Table 8, Entry 4

a) 0.150 g, 1.46 mmol, b) complex **44**, 0.077 g, 0.073 mmol, 5 mol%, c) THF, 2.5 ml, d) 0.012 g, 8%, and e) 40:60.

Following *General Procedure C*, results are reported as a) amount of phenylacetylene **3**, b) amount of catalyst, c) amount of tribenzylphosphine **54**, d) solvent, e) product yield, and f) product selectivity (*E*:*Z*).

Table 9, Entry 1

a) 0.153 g, 1.5 mmol, b) complex **44**, 0.026 g, 0.025 mmol, 1.7 mol%, c) 0.152 g, 0.5 mmol, d) toluene, 2.5 ml, e) 0.069 g, 46 %, and f) 13:87.

Table 9, Entry 2

a) 0.153 g, 1.5 mmol, b) complex **44**, 0.026 g, 0.025 mmol, 1.7 mol%, c) 0.152 g, 0.5 mmol, d) *p*-xylene, 2.5 ml, e) 0.059 g, 39%, and f) 15:85.

Following *General Procedure D*, results are reported as a) amount of phenylacetylene **3**, b) amount of catalyst, c) amount of tribenzylphosphine **54**, d) solvent, e) reaction time, f) product yield, and g) product selectivity (*E*:*Z*).

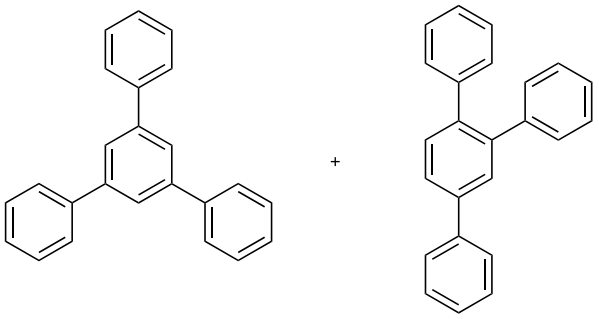
Table 10, Entry 1

a) 0.100 g, 0.97 mmol, b) complex **44**, 0.017 g, 0.017 mmol, 1.7 mol%, c) 0.097 g, 0.32 mmol, d) toluene, 2.0 ml, e) 0.045 g, 30%, and f) 48:52.

Table 10, Entry 2

a) 0.100 g, 0.97 mmol, b) complex **44**, 0.017 g, 0.017 mmol, 1.7 mol%, c) 0.097 g, 0.32 mmol, d) toluene, 2.0 ml, e) 0.047 g, 31%, and f) 51:49.

1,3,5-Triphenylbenzene[50] *and 1,2,4-Triphenylbenzene*[51]



^{1}H NMR (400MHz, $CDCl_3$): δ 7.89-7.23 ppm (m, 18H, ArH).

Following *General Procedure E*, results are reported as a) amount of phenylacetylene **3**, b) amount of catalyst, c) amount of tribenzylphosphine **54**, d) solvent, e) reaction time, f) product yield, g) product selectivity (*E*:*Z*), and h) cyclotrimerization product yield.

Scheme 34

a) 0.100 g, 0.97 mmol, b) complex **44**, 0.017 g, 0.017 mmol, 1.7 mol%, c) 0.090 g, 0.30 mmol, d) toluene, 1.6 ml, e) 18 hours, f) 0.073 g, 73%, g) 10:90, and h) 0.017 g, 17%.

Table 11, Entry 1

a) 0.100 g, 0.97 mmol, b) complex **44**, 0.017 g, 0.017 mmol, 1.7 mol%, c) N/A, d) toluene, 1.6 ml, e) 18 hours, f) 0.011 g, 11%, g) 20:80, and h) 0.036 g, 36%.

Table 11, Entry 2

a) 0.100 g, 0.97 mmol, b) complex **44**, 0.017 g, 0.017 mmol, 1.7 mol%, c) 0.003 g, 0.017 mmol, d) toluene, 1.6 ml, e) 18 hours, f) 0.026 g, 26 %, g) 42:58, and h) 0.022 g, 22%.

Table 11, Entry 3

a) 0.100 g, 0.97 mmol, b) complex **44**, 0.017 g, 0.017 mmol, 1.7 mol%, c) 0.015 g, 0.05 mmol, d) toluene, 1.6 ml, e) 18 hours, f) 0.034 g, 34%, g) 55:45, and h) 0.021 g, 21%.

Table 11, Entry 4

a) 0.100 g, 0.97 mmol, b) complex **44**, 0.017 g, 0.017 mmol, 1.7 mol%, c) 0.030 g, 0.10 mmol, d) toluene, 1.6 ml, e) 18 hours, f) 0.028 g, 28%, g) 49:51, and h) 0.020 g, 20%.

Table 11, Entry 5

a) 0.100 g, 0.97 mmol, b) complex **44**, 0.017 g, 0.017 mmol, 1.7 mol%, c) 0.060 g, 0.20 mmol, d) toluene, 1.6 ml, e) 18 hours, f) 0.041 g, 41%, g) 13:87, and h) 0.019 g, 19%.

Table 11, Entry 6

a) 0.100 g, 0.97 mmol, b) complex **44**, 0.017 g, 0.017 mmol, 1.7 mol%, c) 0.090 g, 0.30 mmol, d) toluene, 1.6 ml, e) 18 hours, f) 0.083 g, 83%, g) 10:90, and h) 0.012 g, 12%.

Table 11, Entry 7

a) 0.100 g, 0.97 mmol, b) complex **44**, 0.017 g, 0.017 mmol, 1.7 mol%, c) 0.120 g, 0.40 mmol, d) toluene, 1.6 ml, e) 18 hours, f) 0.078 g, 78%, g) 12:88, and h) 0.012 g, 12%.

Table 11, Entry 8

a) 0.100 g, 0.97 mmol, b) complex **44**, 0.017 g, 0.017 mmol, 1.7 mol%, c) 0.150 g, 0.50 mmol, d) toluene, 1.6 ml, e) 18 hours, f) 0.080 g, 80%, g) 13:87, and h) 0.014 g, 14%.

Table 12, Entry 1

a) 0.100 g, 0.97 mmol, b) complex **44**, 0.017 g, 0.017 mmol, 1.7 mol%, c) 0.090 g, 0.30 mmol, d) toluene, 4.8 ml, e) 18 hours, f) 0.071 g, 71%, g) 25:75, and h) 0.012 g, 12%

Table 12, Entry 2

a) 0.100 g, 0.97 mmol, b) complex **44**, 0.017 g, 0.017 mmol, 1.7 mol%, c) 0.090 g, 0.30 mmol, d) toluene, 3.2 ml, e) 18 hours, f) 0.074 g, 74%, g) 27:73, and h) 0.013 g, 13%.

Table 12, Entry 3

a) 0.100 g, 0.97 mmol, b) complex **44**, 0.017 g, 0.017 mmol, 1.7 mol%, c) 0.090 g, 0.30 mmol, d) toluene, 2.4 ml, e) 18 hours, f) 0.076 g, 76%, g) 27:73, and h) 0.014 g, 14%.

Table 12, Entry 4

a) 0.100 g, 0.97 mmol, b) complex **44**, 0.017 g, 0.017 mmol, 1.7 mol%, c) 0.090 g, 0.30 mmol, d) toluene, 1.6 ml, e) 18 hours, f) 0.074 g, 74%, g) 30:70, and h) 0.014 g, 14%.

Table 12, Entry 5

a) 0.100 g, 0.97 mmol, b) complex **44**, 0.017 g, 0.017 mmol, 1.7 mol%, c) 0.090 g, 0.30 mmol, d) toluene, 1.2 ml, e) 18 hours, f) 0.068 g, 68%, g) 29:71, and h) 0.020 g, 20%.

Table 12, Entry 6

a) 0.100 g, 0.97 mmol, b) complex **44**, 0.017 g, 0.017 mmol, 1.7 mol%, c) 0.090 g, 0.30 mmol, d) toluene, 1.0 ml, e) 18 hours, f) 0.067 g, 67%, g) 30:70, and h) 0.019 g, 19%.

Scheme 38

A round bottom flask, fitted with a reflux condenser, was flame-dried under vacuum and allowed to cool under nitrogen prior to being charged with phenylacetylene **3** (0.075 g, 0.73 mmol), complex **44** (0.013 g, 0.012 mmol), tribenzylphosphine **54** (0.070 g, 0.23 mmol), 1,5-cyclooctadiene (0.03 ml, 0.23 mmol), and dry toluene (2.5 ml). The reaction mixture was then heated to reflux and allowed to stir for 18 h. The mixture was then concentrated *in vacuo* and the products were isolated by column chromatography (0-2.5% Et_2O in hexane) to furnish **55**/**56** (0.062 g, 82%, 16:84 (*E*:*Z*)).

Scheme 39

A round bottom flask, fitted with a reflux condenser, was flame-dried under vacuum and allowed to cool under nitrogen prior to being charged with phenylacetylene **3** (0.075 g, 0.73 mmol), complex **44** (0.013 g, 0.012 mmol), tribenzylphosphine **54** (0.070 g, 0.23 mmol), 1,5-cyclooctadiene (0.3 ml, 2.30 mmol), and dry toluene (2.5 ml). The reaction mixture was then heated to reflux and allowed to stir for 18 h. The mixture was then concentrated *in vacuo* and the products were isolated by column chromatography (0-2.5% Et_2O in hexane) to furnish **55**/**56** (0.060 g, 80%, 18:82 (*E*:*Z*)).

Following *General Procedure F*, results are reported as a) amount of phenylacetylene **3**, b) amount of catalyst, c) amount of tribenzylphosphine **54**, d) solvent, e) reaction time, f) temperature, g) product yield, h) product selectivity (*E*:*Z*), and i) cyclotrimerization product yield.

Table 13, Entry 1

a) 0.100 g, 0.97 mmol, b) complex **44**, 0.017 g, 0.017 mmol, 1.7 mol%, c) 0.090 g, 0.30 mmol, d) toluene, 1.6 ml, e) 18 hours, f) 25˚C, g) 0.0 g, 0%, h) N/A, and i) N/A.

Table 13, Entry 2

a) 0.100 g, 0.97 mmol, b) complex **44**, 0.017 g, 0.017 mmol, 1.7 mol%, c) 0.090 g, 0.30 mmol, d) toluene, 1.6 ml, e) 18 hours, f) 50˚C, g) 0.0 g, 0%, h) N/A, and i) N/A.

Table 13, Entry 3

a) 0.100 g, 0.97 mmol, b) complex **44**, 0.017 g, 0.017 mmol, 1.7 mol%, c) 0.090 g, 0.30 mmol, d) toluene, 1.6 ml, e) 18 hours, f) 60˚C, g) 0.0 g, 0%, h) N/A, and i) N/A.

Table 13, Entry 4

a) 0.100 g, 0.97 mmol, b) complex **44**, 0.017 g, 0.017 mmol, 1.7 mol%, c) 0.090 g, 0.30 mmol, d) toluene, 1.6 ml, e) 18 hours, f) 70˚C, g) 0.0 g, 0%, h) N/A, and i) N/A.

Table 13, Entry 5

a) 0.100 g, 0.97 mmol, b) complex **44**, 0.017 g, 0.017 mmol, 1.7 mol%, c) 0.090 g, 0.30 mmol, d) toluene, 1.6 ml, e) 18 hours, f) 75˚C, g) 0.045 g, 45%, h) 46:54, and i) 0.008 g, 8%.

Table 13, Entry 6

a) 0.100 g, 0.97 mmol, b) complex **44**, 0.017 g, 0.017 mmol, 1.7 mol%, c) 0.090 g, 0.30 mmol, d) toluene, 1.6 ml, e) 18 hours, f) 85˚C, g) 0.042 g, 42%, h) 42:58, and i) 0.007 g, 7%.

Table 13, Entry 7

a) 0.100 g, 0.97 mmol, b) complex **44**, 0.017 g, 0.017 mmol, 1.7 mol%, c) 0.090 g, 0.30 mmol, d) toluene, 1.6 ml, e) 18 hours, f) 110˚C, g) 0.080 g, 80%, h) 19:81, and i) 0.010 g, 10%.

Following *General Procedure F*, results are reported as a) amount of phenylacetylene **3**, b) amount of catalyst, c) amount of tribenzylphosphine **54**, d) solvent, e) reaction time, f) product yield, g) product selectivity (*E*:*Z*), and h) cyclotrimerization yield.

Table 14, Entry 1

a) 0.100 g, 0.97 mmol, b) complex **44**, 0.017 g, 0.017 mmol, 1.7 mol%, c) 0.090 g, 0.30 mmol, d) toluene, 1.6 ml, e) 2.5 hours, f) 0.080 g, 80%, g) 13:87, and h) 0.013 g, 13%.

Table 14, Entry 2

a) 0.100 g, 0.97 mmol, b) complex **44**, 0.017 g, 0.017 mmol, 1.7 mol%, c) 0.090 g, 0.30 mmol, d) toluene, 1.6 ml, e) 18 hours, f) 0.081 g, 81%, g) 11:89, and h) 0.009 g, 9%.

Following *General Procedure F*, results are reported as a) amount of phenylacetylene **3**, b) amount of catalyst, c) amount of phosphine, d) solvent, e) reaction time, f) product yield, g) product selectivity (*E*:*Z*), and h) cyclotrimerization yield.

Table 15, Entry 1

a) 0.100 g, 0.97 mmol, b) complex **44**, 0.017 g, 0.017 mmol, 1.7 mol%, c) PBu_3, 0.060 g, 0.30 mmol, d) toluene, 1.6 ml, e) 18 hours, f) 0.038 g, 38%, g) 66:34, and h) 0.012 g, 12%.

Table 15, Entry 2

a) 0.100 g, 0.97 mmol, b) complex **44**, 0.017 g, 0.017 mmol, 1.7 mol%, c) dppb, 0.072 g, 0.17 mmol, d) toluene, 1.6 ml, e) 18 hours, f) 0 g, 0%, g) N/A, and h) N/A.

Table 15, Entry 3

a) 0.100 g, 0.97 mmol, b) complex **44**, 0.017 g, 0.017 mmol, 1.7 mol%, c) dppb, 0.142 g, 0.33 mmol, d) toluene, 1.6 ml, e) 18 hours, f) 0 g, 0%, g) N/A, and h) N/A.

Following *General Procedure G*, results are reported as a) amount of phenylacetylene **3**, b) amount of catalyst, c) amount of tribenzylphosphine **54**, d) solvent, e) reaction time, f) temperature, g) product yield, h) product selectivity (*E*:*Z*), and i) cyclotrimerization yield.

Table 16, Entry 1

a) 0.100 g, 0.97 mmol, b) complex **44**, 0.017 g, 0.017 mmol, 1.7 mol%, c) 0.090 g, 0.3 mmol, d) toluene, 1.6 ml, e) 1 hour, f) 110˚C, g) 0.071 g, 71%, h) 21:79, and i) 0.012 g, 12%.

Table 16, Entry 2

a) 0.100 g, 0.97 mmol, b) complex **44**, 0.017 g, 0.017 mmol, 1.7 mol%, c) 0.0 g, 0.0 mmol, d) toluene, 1.6 ml, e) 1 hour, f) 110˚C, g) 0.016 g, 16%, h) 44:56, and i) 0.034 g, 34%.

Table 16, Entry 3

a) 0.100 g, 0.97 mmol, b) complex **44**, 0.017 g, 0.017 mmol, 1.7 mol%, c) 0.297 g, 0.97 mmol, d) toluene, 1.6 ml, e) 1 hour, f) 110˚C, g) 0.045 g, 45%, h) 22:78, and i) 0.017 g, 17%.

Scheme 44

a) 0.100 g, 0.97 mmol, b) complex **44**, 0.017 g, 0.017 mmol, 1.7 mol%, c) 0.090 g, 0.3 mmol, d) *p*-xylene, 1.6 ml, e) 1 hour, f) 130˚C, g) 0.064 g, 64%, h) 18:82, and i) 0.013 g, 13%.

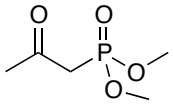
Scheme 46

A round bottom flask, fitted with a reflux condenser was flame-dried under vacuum and allowed to cool under nitrogen prior to being charged with complex **44** (0.013 g, 0.012 mmol) and dry toluene (1.2 ml). The system was evacuated and purged with argon several times before being placed under an atmosphere of hydrogen. The solution was allowed to stir for 20 minutes, and a colour change from red to yellow was observed. It is important to note that, at this point, the catalyst seemed relatively insoluble. The hydrogen was removed and the system purged with argon. In a separate flask was stirred phenylacetylene **3** (0.075 g, 0.73 mmol) and tribenzylphosphine **54** (0.070 g, 0.23 mmol) in dry toluene (1.3 ml), which was subsequently added in one portion, *via* a syringe, to the hydrogenated catalyst. The resulting mixture was heated to reflux and allowed to stir for 18 hours. The mixture was then concentrated *in vacuo* and the products were isolated by column chromatography (2.5% Et_2O in hexane). The purified material was analysed by ^1H NMR, and GC-MS, which indicated the formation of enyne **55**/**56**, (0.021 g, 28%, 34:66 (*E*:*Z*)) and the cyclotrimerization product (0.007 g, 9%).

Scheme 47

A round bottom flask, fitted with a reflux condenser, was flame-dried under vacuum and allowed to cool under nitrogen prior to being charged with complex **44** (0.013 g, 0.012 mmol) and dry toluene (1.2 ml). The system was evacuated and purged with argon several times before being placed under an atmosphere of hydrogen. The solution was allowed to stir for 20 minutes, and a colour change from red to yellow observed. It is important to note that, at this point, the catalyst seemed relatively insoluble. The hydrogen was removed and the system purged with argon. In a separate flask was stirred phenylacetylene **3** (0.075 g, 0.73 mmol) in dry toluene (1.3 ml), which was subsequently added in one portion, *via* a syringe, to the hydrogenated catalyst. The resulting mixture was heated to reflux and allowed to stir for 18 hours. The mixture was then concentrated *in vacuo* and the products were isolated by column chromatography (2.5% Et_2O in hexane). The purified material was analysed by ^1H NMR, and GC-MS, which indicated the formation of enyne **55**/**56**, (0.011 g, 14%, 18:82 (*E*:*Z*)) and the cyclotrimerization product (0.028 g, 37%).

Dimethyl 2-oxopropylphosphonate, ***66***[61]



Scheme 49

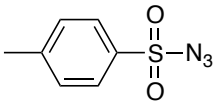
A previously flame-dried, round bottom flask, was charged with a solution of α-chloroacetone **64** (55.42 g, 602 mmol) and trimethylphosphite **65** (74.70 g, 602 mmol) in acetone (166 ml) and acetonitrile (137 ml). To the stirred reaction mixture was added potassium iodide (100 g, 602 mmol) cautiously. After 4.5 hours at room temperature, the mixture was heated at 50˚C for a further 4 hours before cooling to room temperature. The solids were then removed by filtration and the residue purified by distillation (93-97˚C, 0.02 mmHg) to give the desired product **66** as a clear liquid (51.99 g, 52%).

IR (DCM): 3475, 2956, 1714, 1255 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.79 (d, J = 11.0 Hz, 6H, OCH_3), 3.11 (d, ^{2}J = 22.8 Hz, 2H, CH_2), 2.33 ppm (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 198.7 (d, ^{2}J = 3.0 Hz), 53.1 (d, ^{2}J = 6.2 Hz), 42.8 (d, ^{1}J = 127.1 Hz), 31.4 ppm.

para-Toluenesulfonyl azide, ***68***[61]



Scheme 50

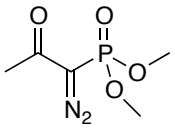
To a stirred solution of tosyl chloride **67** (30 g, 157 mmol) in acetone (180 ml) and water (125 ml) was added sodium azide (13.5 g, 207 mmol) in one portion. The mixture was heated to reflux, and allowed to stir for 5 hours. Water was then added (200 ml) and the mixture diluted with DCM (250 ml). The combined organic extracts were then dried over sodium sulfate and concentrated *in vacuo* to afford compound **68** (28.73 g, 93%) as a colourless oil, which solidified on storage at -18˚C.

IR (DCM): 2999, 2129, 1596 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, J = 8.2 Hz, 2H, ArH), 7.41 (d, J = 8.2 Hz, 2H, ArH), 2.48 ppm (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.3, 135.5, 130.3, 127.5, 21.7 ppm.

Dimethyl 1-diazo-2-oxopropylphosphonate, ***69***[61]



Scheme 51

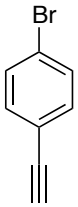
To a previously flame dried round bottom flask charged with a stirred solution of dimethyl 2-oxopropylphosphonate **66** (6.7 g, 40 mmol) in toluene (120 ml) and THF (20 ml) at 0˚C was added sodium hydride (1.07 g, 42 mmol, dry 95%) portionwise. After stirring 1 hour, *para*-toluenesulfonyl azide **68** (7.95 g, 40 mmol) was added as a solution in toluene (40 ml). The solution was then allowed to warm to room temperature and stirred for a further 18 hours. The solvent was then removed *in vacuo* and the crude residue purified by column chromatography (eluent: 0-60% Et_2O in EtOAc) to yield the title compound **69** as a yellow oil (6.27 g, 81%).

IR (DCM): 3494, 2956, 2853, 2128, 1655 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 3.84 (d, J = 12.0 Hz, 6H, OCH_3), 2.26 ppm (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 189.9 (d, ^2J = 13.1 Hz), 63.4 (d, ^1J = 218.5 Hz), 53.6 (d, ^2J = 5.6 Hz), 27.1 ppm.

p-*Bromophenylacetylene*, ***77***[62]



Following *General Procedure H*, results are reported as a) amount of *para*-substituted benzaldehyde, b) amount of Ohira-Bestmann reagent, c) amount of K_2CO_3, d) volume of MeOH, and e) yield of product.

Table 17, Entry 1

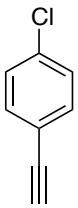
a) **71**, 0.25 g, 1.35 mmol, b) 0.31 g, 1.62 mmol, c) 0.37 g, 2.70 mmol, d) 15 ml, and e) **77**, 0.203 g, 83%.

IR (DCM): 3267, 2976, 1902 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.5 Hz, 2H, ArH), 7.33 (d, *J* = 8.5 Hz, 2H, ArH), 3.11 ppm (s, 1H, alkyne CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 133.6, 131.6, 123.2, 121.1, 82.6, 78.4 ppm.

p-*Chlorophenylacetylene*, ***78***[63]



Following *General Procedure H*, results are reported as a) amount of *para*-substituted benzaldehyde, b) amount of Ohira-Bestmann reagent, c) amount of K_2CO_3, d) volume of MeOH, and e) yield of product.

Table 17, Entry 2

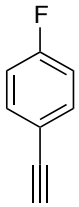
a) **72**, 0.25 g, 1.78 mmol, b) 0.34 g, 2.12 mmol, c) 0.49 g, 3.55 mmol, d) 15 ml, and e) **78**, 0.200 g, 82%.

IR (DCM): 3269, 2111 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, 2H, *J* = 8.9 Hz, ArH), 7.31 (d, 2H, *J* = 8.9 Hz, ArH), 3.11 ppm (s, 1H, alkyne CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 133.4, 130.9, 129.5, 120.6, 82.5, 78.1 ppm.

p-*Fluorophenylacetylene*, ***79***[64]



Following *General Procedure H*, results are reported as a) amount of *para*-substituted benzaldehyde, b) amount of Ohira-Bestmann reagent, c) amount of K_2CO_3, d) volume of MeOH, and e) yield of product.

Table 17, Entry 3

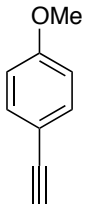
a) **73**, 0.25 g, 2.01 mmol, b) 0.46 g, 2.4 mmol, c) 0.56 g, 4.02 mmol, d) 20 ml, and e) **79**, 0.211 g, 88%.

IR (DCM): 3295, 1938 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.37 (m, 2H, ArH), 7.15-7.10 (m, 2H, ArH), 3.04 ppm (s, 1H, alkyne CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.7 (d, $^{1}J_{C\text{-}F}$ = 995 Hz), 134.1, 118.2, 115.6 (d, $^{2}J_{C\text{-}F}$ = 89 Hz), 82.6, 76.9 ppm.

p-M*ethoxyphenylacetylene,* ***80***[65]



Following *General Procedure H*, results are reported as a) amount of *para*-substituted benzaldehyde, b) amount of Ohira-Bestmann reagent, c) amount of K_2CO_3, d) volume of MeOH, and e) yield of product.

Table 17, Entry 4

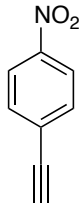
a) **74**, 0.25 g, 1.84 mmol, b) 0.35 g, 2.20 mmol, c) 0.51 g, 3.67 mmol, d) 15 ml, and e) **80**, 0.180 g, 74%.

IR (DCM): 3252, 2009 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, 2H, *J* = 8.6 Hz, ArH), 7.30 (d, 2H, *J* = 8.6 Hz, ArH), 3.49 (s, 3H, OMe), 3.11 ppm (s, 1H, alkyne CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 133.4, 130.9, 128.7, 120.6, 82.5, 78.1, 50.9 ppm.

p-*Nitrophenylacetylene,* ***81***[66]



Following *General Procedure H*, results are reported as a) amount of *para*-substituted benzaldehyde, b) amount of Ohira-Bestmann reagent, c) amount of K_2CO_3, d) volume of MeOH, and e) yield of product.

Table 17, Entry 5

a) **75**, 0.19 g, 1.26 mmol, b) 0.25 g, 1.56 mmol, c) 0.36 g, 2.60 mmol, d) 15 ml, and e) **81**, 0.137 g, 72%.

IR (DCM): 3260, 2012 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, 2H, *J* = 9.0 Hz, ArH), 7.66 (d, 2H, *J* = 9.0 Hz, ArH), 3.38 ppm (s, 1H, alkyne CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.0, 132.5, 129.4, 123.1, 81.8, 81.1 ppm.

Attempted Preparation of p-*Triflurormethylphenylacetylene,* ***82***[67]

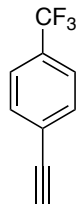
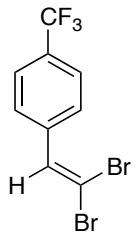


Table 17, Entry 6

A round bottom flask was flame dried under vacuum and allowed to cool under nitrogen prior to being charged with aldehyde **76** (0.287 g, 1.65 mmol), potassium carbonate (0.483 g, 3.50 mmol), and dry methanol (25 ml). The slurry was stirred for 30 min prior to the addition of Ohira-Bestmann reagent **69 (**0.380 g, 1.97 mmol), the resulting mixture was stirred at room temperature for 18 h. After this time, the mixture was diluted with ether and washed with saturated sodium bicarbonate. The organics were then pooled, dried over Na_2SO_4, concentrated *in vacuo*, and then purified by column chromatography (0-10% diethyl ether in petrol). The material decomposed during purification and a complex mixture of products was obtained.

1-(2,2-Dibromovinyl)-4-(trifluoromethyl)benzene, ***85***[68]



Scheme 54

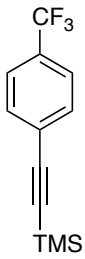
To a previously flame dried round bottom flask charged with a stirred solution of carbon tetrabromide (1.98 g, 6.0 mmol) and triphenylphosphine (3.15 g, 12.0 mmol) in DCM (10 ml) at 0˚C was added 4-(trifluoromethyl)benzaldehyde **83** (1.00 g, 5.7 mmol) dissolved in DCM (8 ml). The resulting reaction mixture was stirred at 0˚C for 3 hours, before being diluted with a saturated aqueous solution of NH_4Cl and extracted with DCM. The combined organic layers were dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (eluent: 0-5% EtOAc in petrol) to give the dibromoolefin **85** (1.89 g, 95% yield) as a clear yellow oil.

IR (DCM): 2130, 1618, 1302 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (s, 4H, ArH), 7.53 ppm (s, 1H, olefinic CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.8, 135.6, 131.4 (q, $^{2}J_{C\text{-}F}$ = 29 Hz), 128.7, 125.4, 120.5 (q, ^{1}J = 268 Hz), 92.2 ppm.

4-(Trifluoromethyl)phenyl(trimethylsilyl)acetylene, ***84***[69]



Scheme 55

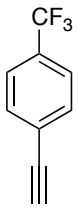
To a previously flame dried round bottom flask charged with a stirred solution of dibromo olefin **85** (0.80 g, 2.4 mmol) in THF (8 ml). The mixture was cooled to -78˚C followed by the dropwise addition of *n*-BuLi (2.5 ml, 2.1 M in hexanes, 5.3 mmol). The yellow solution was allowed to stir at -78˚C for 15 minutes before being warmed to 0˚C. After 30 minutes at 0˚C, the reaction was cooled to -78˚C and chlorotrimethylsilane (1.32 g, 12.1 mmol) was added. The mixture was slowly warmed to room temperature and allowed to stir for 16 hours. The resulting clear orange/brown solution was diluted with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The organic portion was dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was then isolated by column chromatography (eluent: 0-5% EtOAc in petrol) to give the protected alkyne **84** (0.48 g, 82% yield) as a pale yellow oil.

IR (DCM): 3049, 2165 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (s, 4H, ArH), 0.27 ppm (s, 9H, $SiCH_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 131.7, 129.5 (q, $^{2}J_{C\text{-}F}$ = 31 Hz), 126.5, 124.7, 122.0 (q, $^{1}J_{C\text{-}F}$ = 268 Hz), 102.9, 96.7, -0.71 ppm.

4-(Trifluoromethyl)phenylacetylene, ***82***[67]



Scheme 56

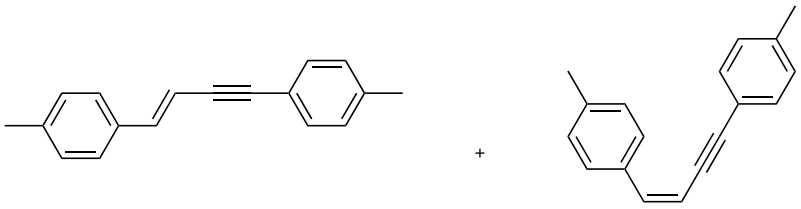
To a previously flame dried round bottom flask charged with a stirred solution of alkyne **84**, (0.15 g, 0.62 mmol) in dry MeOH (6 ml) was added potassium carbonate (0.085 g, 0.62 mmol). The resulting mixture was stirred for 16 hours, before being diluted with EtOAc and washed with water and brine. The organic layers were combined and dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield alkyne **82** (0.076 g, 72%) as a pale yellow oil.

IR (DCM): 3290, 2082 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (s, 4H, ArH), 3.22 ppm (s, 1H, alkyne CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 132.4, 130.6 (q, $^{2}J_{C\text{-}F}$ = 31 Hz), 125.9, 125.3, 123.8 (q, $^{1}J_{C\text{-}F}$ = 273 Hz), 82.2, 79.6 ppm.

(E)-1,4-Di-p-tolyl-1-buten-3-yne ***87***[60] *and (Z)-1,4-Di-p-tolyl-1-buten-3-yne* ***88***[60]



Following *General Procedure E*, results are reported as a) amount of alkyne, b) amount of catalyst, c) amount of phosphine, d) solvent, e) reaction time, f) product yield, and g) product selectivity (*E*:*Z*).

Scheme 57

a) 4-Ethynyltoluene **86**, 0.075 g, 0.65 mmol, b) complex **44**, 0.012 g, 0.011 mmol, 1.7 mol%, c) PBn_3 **54**, 0.065 g, 0.21 mmol, d) toluene, 1.4 ml, e) 18 hours, f) 0.053 g, 71%, and g) 19:81.

The product of alkyne dimerization was isolated as a mixture of (*E*)- and (*Z*)-enynes with the ratio being determined by comparison to the published ^{1}H NMR data.

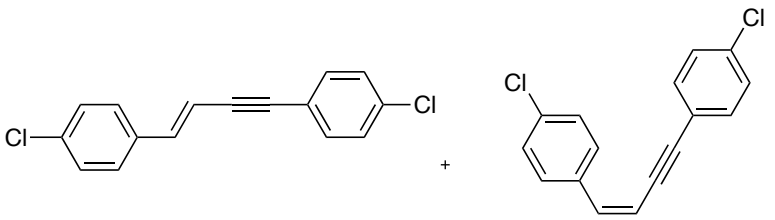
The following data is based on a 19:81 (*E*:*Z*) mixture:

IR (DCM): 2926, 2360 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.2 Hz, 0.81H, ArH) 7.43-7.18 (m, 7.19H, ArH), 7.03 (d, *J* = 16.2 Hz, 0.19H, *E*-olefin CH), 6.98 (d, *J* = 11.9 Hz, 0.81H, *Z*-olefin CH), 6.35 (d, *J* = 16.2 Hz, 0.19H, *E*-olefin CH), 5.89 (d, *J* = 11.9 Hz, 0.81H, *Z*-olefin CH), 2.40 ppm (bs, 6H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.4, 138.0, 137.9, 137.8, 137.5, 133.54, 133.49, 130.9, 130.8, 128.8, 128.6, 128.5, 128.22, 128.20, 125.7, 120.1, 120.0, 106.7, 106.1, 95.4, 95.4, 87.4, 87.4, 21.1, 21.0, 20.9 ppm.

(E)-1,4-Di-p-chlorophenyl-1-buten-3-yne ***89***[70] *and (Z)-1,4-Di-p-chlorophenyl-1-buten-3-yne* ***90***[71]



Following *General Procedure E*, results are reported as a) amount of alkyne, b) amount of catalyst, c) amount of phosphine, d) solvent, e) reaction time, f) product yield, and g) product selectivity (*E*:*Z*).

Scheme 58

a) 1-Chloro-4-ethynylbenzene **78**, 0.075 g, 0.55 mmol, b) complex **44**, 0.010 g, 0.009 mmol, 1.7 mol%, c) PBn_3 **54**, 0.050 g, 0.17 mmol, d) toluene, 1.2 ml, e) 18 hours, f) 0.036 g, 48%, and g) 24:76.

Scheme 59

a) 1-Chloro-4-ethynylbenzene **78**, 0.075 g, 0.55 mmol, b) complex **44**, 0.014 g, 0.013 mmol, 2.4 mol%, c) PBn_3 **54**, 0.050 g, 0.17 mmol, d) toluene, 1.2 ml, e) 18 hours, f) 0.056 g, 74%, and g) 23:77.

The product of alkyne dimerization was isolated as a mixture of (*E*)- and (*Z*)-enynes with the ratio being determined by comparison to the published ^{1}H NMR data.

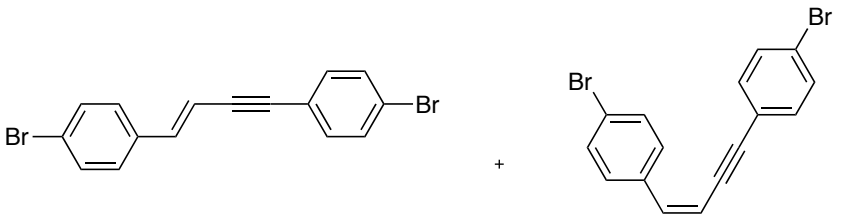
The following data is based on a 23:77 (*E*:*Z*) mixture:

IR (DCM): 3049, 2950, 1640 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.2 Hz, 0.77H, ArH), 7.41-7.32 (m, 7.23H, ArH), 6.98 (d, *J* = 16.3 Hz, 0.23H, *E*-olefin CH), 6.67 (d, *J* = 11.9 Hz, 0.77H, *Z*-olefin CH), 6.33 (d, *J* = 16.3 Hz, 0.23H, *E*-olefin CH), 5.92 ppm (d, *J* = 11.9 Hz, 0.77H, *Z*-olefin CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.5, 137.6, 134.92, 134.88, 134.7, 134.62, 134.57, 134.2, 133.0, 132.6, 129.9, 129.2, 129.0, 128.8, 128.5, 127.7, 122.0, 121.6, 108.7, 107.7, 95.2, 91.4, 89.8, 88.8 ppm.

(E)-1,4-Di-p-bromophenyl-1-buten-3-yne ***91***[60] *and (Z)-1,4-Di-p-bromoophenyl-1-buten-3-yne* ***92***[60]



Following *General Procedure E*, results are reported as a) amount of alkyne, b) amount of catalyst, c) amount of phosphine, d) solvent, e) reaction time, f) product yield, and g) product selectivity (*E*:*Z*).

Scheme 60

a) 1-Bromo-4-ethynylbenzene **77**, 0.075 g, 0.41 mmol, b) complex **44**, 0.011 g, 0.010 mmol, 2.4 mol%, c) PBn_3 **54**, 0.044 g, 0.14 mmol, d) toluene, 1.1 ml, e) 18 hours, f) 0.059 g, 79%, and g) 15:85.

The product of alkyne dimerization was isolated as a mixture of (*E*)- and (*Z*)-enynes with the ratio being determined by comparison to the published ^{1}H NMR data.

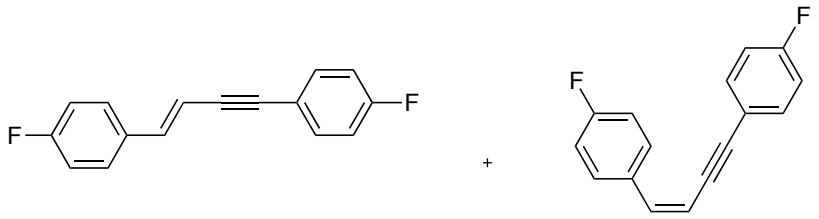
The following data is based on a 15:85 (*E*:*Z*) mixture:

IR (DCM): 2922, 2851, 2333 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.5 Hz, 1.70H, ArH), 7.52 - 7.50 (m, 3.40H, ArH), 7.48-7.33 (m, 1.20H, ArH), 7.28 (d, *J* = 8.4 Hz, 1.70H, ArH), 6.97 (d, *J* = 16.3 Hz, 0.15H *E*-olefin CH), 6.66 (d, *J* = 11.9 Hz, 0.85H, *Z*-olefin CH) 6.33 (d, *J* = 16.3 Hz, 0.15H, *E*-olefin CH) 5.91 ppm (d, *J* = 11.9 Hz, 0.85H, *Z*-olefin CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.2, 137.7, 135.3, 135.0, 132.8, 132.7, 131.8, 131.7, 131.6, 131.4, 130.1, 127.7, 122.8, 122.6, 122.5, 122.4, 122.1, 122.0, 108.5, 107.8, 95.3, 91.1, 89.6, 88.8 ppm.

(E)-1,4-Di-p-fluorophenyl-1-buten-3-yne ***93***[60] *and (Z)-1,4-Di-p-fluorophenyl-1-buten-3-yne* ***94***[60]



Following *General Procedure E*, results are reported as a) amount of alkyne, b) amount of catalyst, c) amount of phosphine, d) solvent, e) reaction time, f) product yield, and g) product selectivity (*E*:*Z*).

Scheme 61

a) 1-Fluoro-4-ethynylbenzene **79**, 0.075 g, 0.62 mmol, b) complex **44**, 0.016 g, 0.015 mmol, 2.4 mol%, c) PBn_3 **54**, 0.057 g, 0.19 mmol, d) toluene, 1.3 ml, e) 18 hours, f) 0.062 g, 82%, and g) 15:85.

The product of alkyne dimerization was isolated as a mixture of (*E*)- and (*Z*)-enynes with the ratio being determined by comparison to the published ^{1}H NMR data.

The following data is based on a 15:85 (*E*:*Z*) mixture:

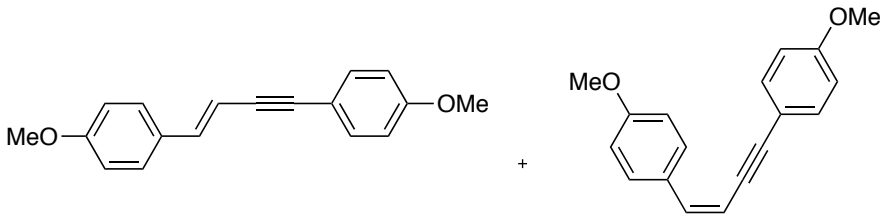
IR (DCM): 2928, 2855, 1598 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91-7.87 (m, 1.70H, ArH), 7.48-7.37 (m, 2.30H, ArH), 7.09-6.97 (m, 4.15H, ArH & olefin CH), 6.66 (d, *J* = 11.9 Hz, 0.85H, *Z*-olefin CH) 6.27 ppm (d, *J* = 16.2 Hz, 0.15H, *E*-olefin CH) 5.88 ppm (d, *J* = 11.9 Hz, 0.85H, *Z*-olefin CH).

The ^{13}C NMR was complicated by overlapping multiplet splitting patterns, as a result, in order to further verify the formation of the desired product(s) an ESI-MS was obtained.

ESI-MS: calculated for $C_{16}H_{11}F_2$ [M^++ H]: 241.0829; found: 241.0889.

(E)-1,4-Di-p-methoxyphenyl-1-buten-3-yne ***95***[60] *and (Z)-1,4-Di-p-methoxyphenyl-1-buten-3-yne* ***96***[60]



Following *General Procedure E*, results are reported as a) amount of alkyne, b) amount of catalyst, c) amount of phosphine, d) solvent, e) reaction time, f) product yield, and g) product selectivity (*E*:*Z*).

Scheme 62

a) 1-Ethynyl-4-methoxybenzene **80**, 0.075 g, 0.57 mmol, b) complex **44**, 0.014 g, 0.012 mmol, 2.4 mol%, c) PBn_3 **54**, 0.051 g, 0.17 mmol, d) toluene, 1.0 ml, e) 120 hours, f) 0.012 g, 16%, and g) 45:55.

The product of alkyne dimerization was isolated as a mixture of (*E*)- and (*Z*)-enynes with the ratio being determined by comparison to the published ^{1}H NMR data.

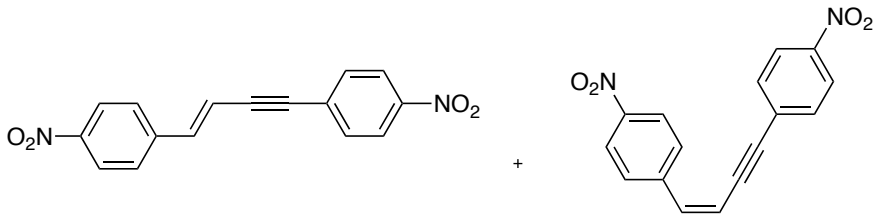
The following data is based on a 45:55 (*E*:*Z*) mixture:

IR (DCM): 2931, 2344, 1253 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.9 Hz, 1.10H, ArH), 7.45-6.85 (m, 7.35H, ArH & olefin CH), 6.62 (d, *J* = 12.0 Hz, 0.55H, olefin CH), 6.23 (d, *J* = 16.2 Hz, 0.45H, olefin CH), 5.80 (d, *J* = 12.0 Hz, 0.55H, olefin CH), 3.86 (s, 1.65H, OCH_3), 3.85 (s, 3H, OCH_3) 3.84 ppm (s, 1.35H, OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 159.5, 159.4, 159.3, 139.9, 137.2, 132.7, 132.6, 130.0, 129.6, 129.2, 127.3, 127.2, 115.7, 115.6, 113.8, 113.5, 105.8, 105.0, 95.2, 90.8, 87.7, 87.2, 55.12, 55.10, 55.03, 54.09 ppm.

*(E)-1,4-Di-p-nitrophenyl-1-buten-3-yne **97** and (Z)-1,4-Di-p-nitrophenyl-1-buten-3-yne **98***

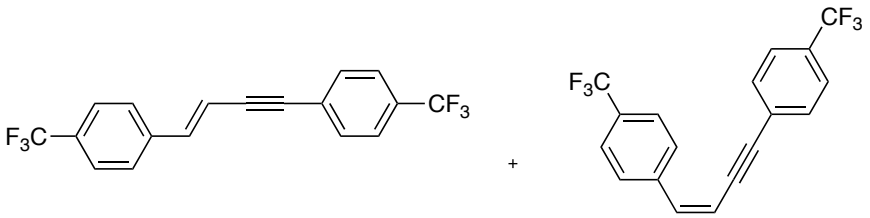


Following *General Procedure E*, results are reported as a) amount of alkyne, b) amount of catalyst, c) amount of phosphine, d) solvent, e) reaction time, f) product yield, and g) product selectivity (*E*:*Z*).

Scheme 63

a) 1-Ethynyl-4-nitrobenzene **81**, 0.075 g, 0.51 mmol, b) complex **44**, 0.013 g, 0.012 mmol, 2.4 mol %, c) PBn_3 **54**, 0.046 g, 0.15 mmol, d) toluene, 1.0 ml, e) 18 hours, f) 0.0 g, 0%, and g) N/A.

(E)-1,4-Di-p-trifluoromethylphenyl-1-buten-3-yne ***99***[60] *and (Z)-1,4-Di-p-ltrifluoromethyphenyl-1-buten-3-yne* ***100***[60]



Following *General Procedure E*, results are reported as a) amount of alkyne, b) amount of catalyst, c) amount of phosphine d) solvent, e) reaction time, f) product yield, and g) product selectivity (*E*:*Z*)

Scheme 64

a) 1-Ethynyl-4-(trifluoromethyl)benzene **82**, 0.065 g, 0.44 mmol, b) complex **44**, 0.008 g, 0.008 mmol, 2.4 mol%, c) PBn_3 **54**, 0.041 g, 0.13 mmol, d) toluene, 0.8 ml, e) 18 hours, f) 0.049 g, 75%, and g) 23:77.

The product of alkyne dimerization was isolated as a mixture of (*E*)- and (*Z*)-enynes with the ratio being determined by comparison to the published ^{1}H NMR data.

The following data is based on a 23:77 (*E*:*Z*) mixture:

IR (DCM): 3390, 2853, 2364 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.2 Hz, 1.54H, ArH), 7.69-7.54 (m, 6.46H, ArH), 7.13 (d, *J* = 16.3 Hz, 0.23H, *E*-olefin CH), 6.81 (d, *J* = 11.9 Hz, 0.77H, *Z*-olefin CH), 6.49 (d, *J* = 16.3 Hz, 0.23H, *E*-olefin CH), 6.07 ppm (d, *J* = 11.9 Hz, 0.77H, *Z*-olefin CH).

The ^{13}C NMR was complicated by overlapping multiplet splitting patterns, as a result, in order to further verify the formation of the desired product(s) an ESI-MS was obtained.

ESI-MS: calculated for $C_{18}H_{10}F_6Na$ [M^++ Na]: 363.0584; found: 362.9548.

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Chapter 2

Development of Novel α-Helix Mimetics for Screening within Fragment-Based Drug Discovery

Contents

1.	**Introduction**	128
	1.1 3D Consortium and Programme Aims	128
	1.2 Drug Discovery in the Twentieth and Twenty-First Centuries	130
	1.2.1 Generation of a Lead Compound from a Natural Product	131
	1.2.2 High-Throughput Screening	134
	1.3 Fragment-Based Drug Discovery	135
	1.3.1 Overview of Fragment-Based Drug Discovery	135
	1.3.2 Ligand Efficiency and Fragment Optimisation	137
	1.3.3 Fragment Based Drug Discovery – Case Study	138
	1.4 3D Molecules	139
	1.5 Targeting Protein-Protein Interactions	141
2.	**Previous and Proposed Work**	143
3.	**Results and Discussion**	146
	3.1 Retrosynthetic Analysis of Novel Pyridyl Scaffolds	146
	3.2 Towards the Preparation of Compound **13** – Route 1	148
	3.3 Towards the Preparation of Compound **13** – Route 2	151
	3.3.1 Retrosynthetic Analysis of Compound **13** – Route 2	151
	3.3.2 Synthesis of Compound **13** – Route 2	152
	3.4 Towards the Preparation of Compound **13** – Route 3	155
	3.4.1 Retrosynthetic Analysis of Compound **13** – Route 3	155
	3.4.2 Synthesis of Compound **13** – Route 3	156
	3.5 Towards the Preparation of Compound **13** – Route 4	159
	3.5.1 Retrosynthetic Analysis of Compound **13** – Route 4	159
	3.5.2 Synthesis of Compound **13** – Route 4	160
	3.6 Towards the Preparation of Compound **13** – Route 5	163
	3.6.1 Retrosynthetic Analysis of Compound **13** – Route 5	163

3.6.2 Synthesis of Compound **13** – Route 5 164
3.7 Synthesis of Novel 3D Fragments 165

4. Conclusion 169

5. Future Work 172

6. Experimental 174
6.1 General 174
6.2 Synthetic Substrates and Procedures 176

7. References 196

Appendix 199

1 Introduction

Interactions between proteins are a fundamental aspect of the biological signalling pathway. Indeed, many integral biological functions are mediated by protein-protein interactions (PPI). In addition, undesired protein-protein interactions are responsible for a range of diseases and this has led to PPI being a target within drug discovery programmes.[1] However, identifying a small molecule that successfully binds to a specific target protein is a challenging task. This common issue is, in part, attributable to the lack of obvious binding sites on protein surfaces.[2] Having stated this, a range of drug development technologies, such as high-throughput screening (HTS), have been employed with respect to identifying a suitable drug candidate. Traditionally, many of the molecules utilised in the drug development have been sp^2-rich aromatic compunds. In relation to this, it is believed that expanding the range of molecules to include more sp^3-rich compounds, which possess a more three-dimensional (3D) conformation, will allow a greater area of chemical space to be investigated with respect to identifying a lead compound.

1.1 3D Consortium and Programme Aims

The twentieth century witnessed many breakthroughs within the realm of drug discovery, resulting in the development of a range of medicines that have vastly improved the quality of human life across the globe. A plethora of diseases are now readily treatable and some debalitating conditions, such as smallpox, have been eliminated entirely. The eradication of smallpox, through a collaborative effort by scientists and medics, represents a major milestone for humanity.[3] This achievement showcased that seemingly insurmountable obstacles can be overcome through the concerted efforts of scientists.

Moving into the present era, there is now a need to further push the boundaries of chemistry and biology, in order to identify new drugs to combat the conditions which continue to cause

suffering. New target classes may prove key in this respect. However many of these classes have proven difficult to identify high quality hits for, such as those relating to protein-protein interactions. In order to combat this issue, academic and industrial researchers across a range of discliplines have united in an effort to generate libraries of compounds which possess an explicit 3D conformation. Indeed, it is the ultimate goal of the 3D consortium to screen the developed 3D fragments against a broad range of target classes in order to identify high quality hits for drug development. It is envisaged that this collaborative approach will bring together expertise across a range of chemistry and biology, in order to facilitate the development of potential therapeutic compounds. Current members of the consortium include:

- University of Cambridge;
- University College London;
- University of Dundee Drug Discovery Unit (DDU);
- The Beatson Institute for Cancer Research Drug Discovery Program (DDP);
- The Paterson Institute for Cancer Research;
- The Institute for Cancer Research;
- Cancer Research Technology; and
- Medical Research Council Technology (MRCT) Centre.

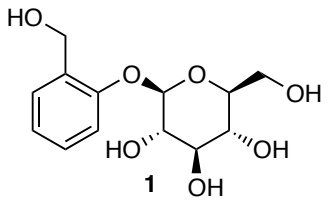
The immediate goal of the research programme associated with the Beatson Research Institute is the development of novel 3D molecules to target protein-protein interactions. More specifically, the novel compounds will be screened *via* a range of biophysical and biochemical techniques against known cancer drug targets. A background to the proposed research programme is detailed herein.

1.2 Drug Discovery in the Twentieth and Twenty-First Centuries

It is no secret that the discovery of new drugs is beleaguered by high attrition rates throughout all stages of research and development. Whilst, quantifying the cost of bringing a drug to market is subject to many variables, economists at the United States Federal Trade Commission suggest that $1 billion is a realistic figure to ascribe to the cost of the development of a single drug.[4] These high costs are, in part, attributable to the quality of the initial compounds investigated. In recent times, the general mode of drug discovery has focused on the elaboration of a molecule which has proven effective in a biological assay against a targeted mechanism. This approach sounds simple in theory, but a range of chemical, physical, and biological properties need to be considered in order to ensure that the drug exhibits the desired therapeutic effect. Intense studies surrounding the absorption, distribution, metabolism, and excretion (ADME) profiles of potential drugs are therefore a vital part of the drug discovery process. The quality of a chemical lead is not solely dependent on its initial performance in biological assays but through further elaboration of the drug's pharmacological properties. Frustratingly, the optimisation of these attributes is generally considered more difficult than inducing the biological effect of interest. Indeed, the chemical technologies employed within the field of drug discovery over the last fifty years have changed dramatically. There are several commonly used methods of generating a chemical lead, each with their own merits and drawbacks.

1.2.1 Generation of a Lead Compound from a Natural Product

Perhaps the most obvious method of creating a new drug is to investigate the properties of naturally occurring compounds. Nature has offered a plethora of compounds which have been utilised by people for millennia. Consider, for example, Salicin **1**, (**Figure 1**) which is obtained from the bark of Willow trees. This natural product has been used in various crude forms throughout the ages as an analgesic and antipyretic. Indeed, subsequent studies identified a derivative of this species, acetylsalicylic acid **2** which is a more potent analogue of the natural analgesic.[5]

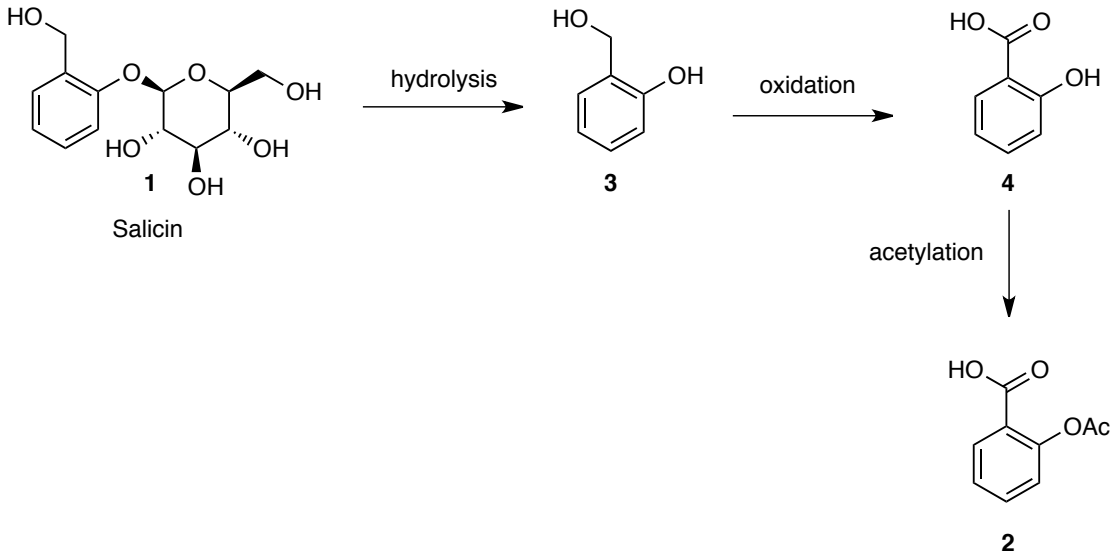


1

Salicin

Figure 1

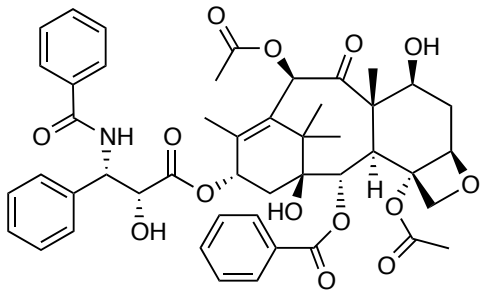
The first reported synthesis of pure acetylsalicylic acid, Aspirin **2**, in 1897 by Felix Hoffman and Arthur Eichengrun represents one of the most important syntheses in organic chemistry.[6] The preparative pathway begins with hydrolysis of the salicin natural product, **1**, following this an oxidation and acetylation protocol furnishes the target compound, **2** (**Scheme 1**). The synthesis of the target compound may look trivial by today's standards but the impact that this small molecule has had on shaping the landscape of drug discovery cannot be overstated.



Scheme 1

Aspirin production, and indeed consumption, has continued to rise over the last century with an estimated 40,000 tons consumed globally each year.[7] The American plants owned by Bayer were acquired by various parties as a result of reparations exacted from Germany at the end of the First World War. Indeed, the patent for Aspirin was eventually held by Smith Kline-Beecham, who sold the business back to Bayer for the unprecedented sum of $1 billion.[8] The landscape of drug discovery was forever altered through the synthesis and purification of such a simple small molecule, which is responsible, in part, for launching the billion dollar pharmaceutical industry that we recognise today.

Incredible scientific progress has been made since the initial synthesis of Aspirin was first reported, with the isolation and characterisation of complex molecules occurring at a fervent pace throughout the twentieth century. One of the most intricate and important natural products employed in cancer chemotherapy, Taxol (**Figure 2**), was first extracted from the bark of the Pacific Yew tree in the 1960's and went on to have an enormous impact in both clinical care and synthetic chemistry.[9]

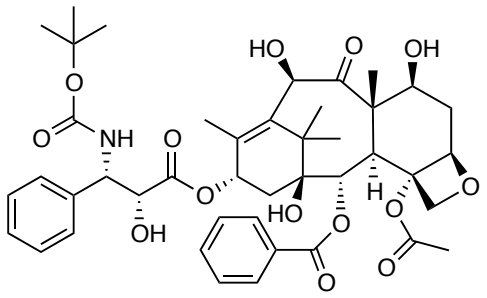


5
Taxol

Figure 2

From a synthetic chemistry perspective, the tetracyclic heptadecane skeleton and eleven stereocentres illustrate the challenges that are faced in synthesising this elaborate compound. Taxol has therefore attracted considerable interest from numerous academic research groups across the globe. However, the complexity of Taxol is not to be underestimated with only six total syntheses being reported to date.[10]

As highlighted above, the impact of natural products on drug discovery has been sustained over the course of the last century. An additional factor that is readily employed in this approach to drug discovery is the ability to create even more potent analogues of natural products through simple, or indeed more complex, manipulations of key functionality. In fact, one of the initial synthetic analogues of Taxol, Taxotere (**Figure 3**), has proven a highly successful anticancer drug in its own right.[11] The changes are relatively subtle: substitution of the benzoyl group for that of a *tert*-butoxycarbonyl group on the nitrogen, as well as replacment of the acetoxy group with a free hydroxyl unit. As such, these modifications have resulted in Taxotere, **6**, possessing an improved pharmacological profile and indeed enhanced therapeutic ability, in some cancers, in relation to its parent compound.



6
Taxotere

Figure 3

In recent years, this approach to drug discovery has been utilised much more sparingly. This is attributable to difficulties involved in extracting large quantities of the desired compounds. As such, complementary methods of drug discovery have evolved to take precedent over the previously employed natural product approach.[12]

1.2.2 High-Throughput Screening

High-throughput screening (HTS) has been the most prevalent form of drug discovery since the early 1990's.[13] This approach entails screening a vast number of compounds (of the order of 1,000-1,000,000) against a target of interest. In relation to this, the majority of first generation compound libraries contained compounds that possessed undesired molecular complexity.[14] Accordingly, subsequent research has employed libraries featuring compounds which possessed more 'drug-like' properties. The compounds that produce promising results within these studies are identified, with subsequent modifications delivering chemical leads.

In relation to assessing the drug-like attributes of a species, a set of guidelines, proposed by Lipinski, have become an industry standard in terms of acting as a blueprint for the synthesis of new chemical leads.[15] The criteria described encompasses the molecular weight and considers hydrogen-bonding interactions present in the compounds. With these parameters set, this approach allows for the rapid synthesis of 'drug-like' compounds and, indeed, many

successful drugs fall within the parameters set by Lipinski and co-workers. Examples of important drugs that have been discovered as a result of HTS include Imatinib (marketed as Gleevec), which has revolutionised cancer treatment in recent years.[16] Having stated this, in comparison to the vast number of compounds investigated, a relatively small number of drugs have reached the marketplace. Indeed, the low return against significant investment in HTS has led to the pharmaceutical industry exploring alternative methods of drug discovery. It could be envisaged that a more rational, and iterative, approach to drug discovery would cut costs and attrition rates.

1.3 Fragment-Based Drug Discovery

1.3.1 Overview of Fragment-Based Drug Discovery

Fragment-based drug discovery (FBDD) has recently emerged as a proficient alternative to the previously utilised method of high-throughput screening. FBDD is relatively simple in terms of the rationale involved. In essence, approximately 1,000 fragments are screened, against a target of interest, using biophysical techniques. The fragments themselves are mostly between 150-250 MW. In addition the amassed libraries generally contain a wide breadth of chemical scaffolds and functionalities.[17]

The key to FBDD is the manner in which initial fragment hits, which have low potency attributable to their size, form high-quality interactions with the molecular target. These hit fragments, which can be detected in a more facile manner due to advances made in biophysical chemistry in recent years, can then be further optimised into potent lead compounds. Indeed, this process can involve linking fragments which bind at proximal sites within the target, or growing into unexplored potential binding sites. An overview of the underlying principles of FBDD is illustrated in **Figure 4**.[18]

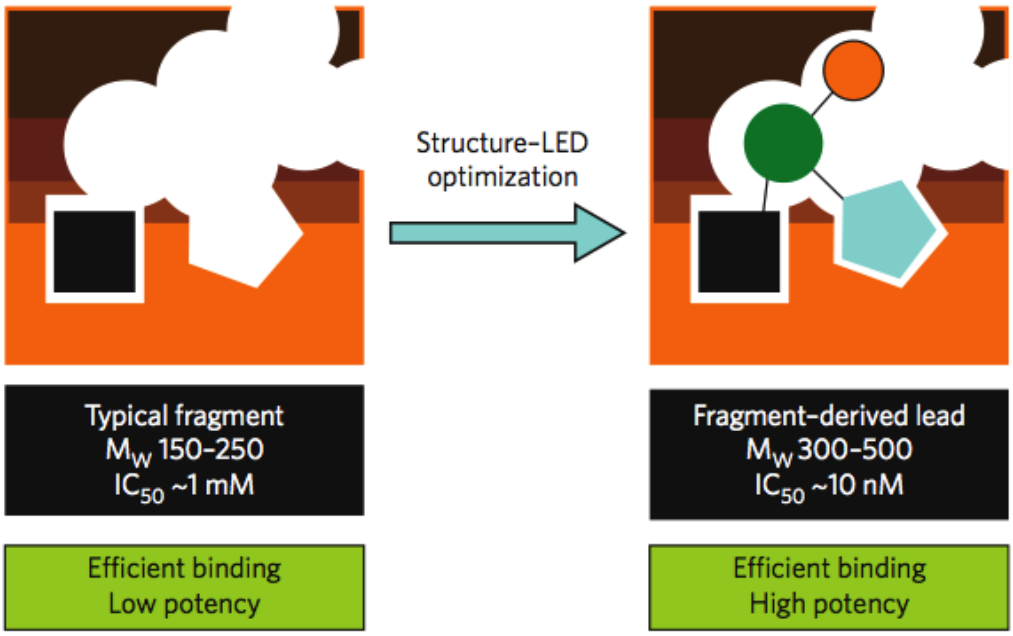


Figure 4[18]

In recent years it has been suggested that there is a decrease in the average molecular weight and lipophilicity of potential drugs as they pass from phase 1 trials to approved drugs. This implies that high molecular weight and high lipophilicity are major drivers for attrition through their impact on ADME properties.[19] As a result, pharmaceutical companies are monitoring these physical properties more closely during lead identification/optimisation and reducing the molecular weight and lipophilicity of their screening collections accordingly. An important attribute of FBDD is that the optimisation process begins with relatively small fragments (MW approximately 150). This allows for careful control of the size and complexity of potential leads, as opposed to the higher-affinity starting points in HTS, which are generally higher in weight (MW approximately 400). In relation to this, a novel method of monitoring the development of fragments has been developed. This protocol, known as ligand effiency, represents an efficient manner by which to track the development of potential drug fragments. [20]

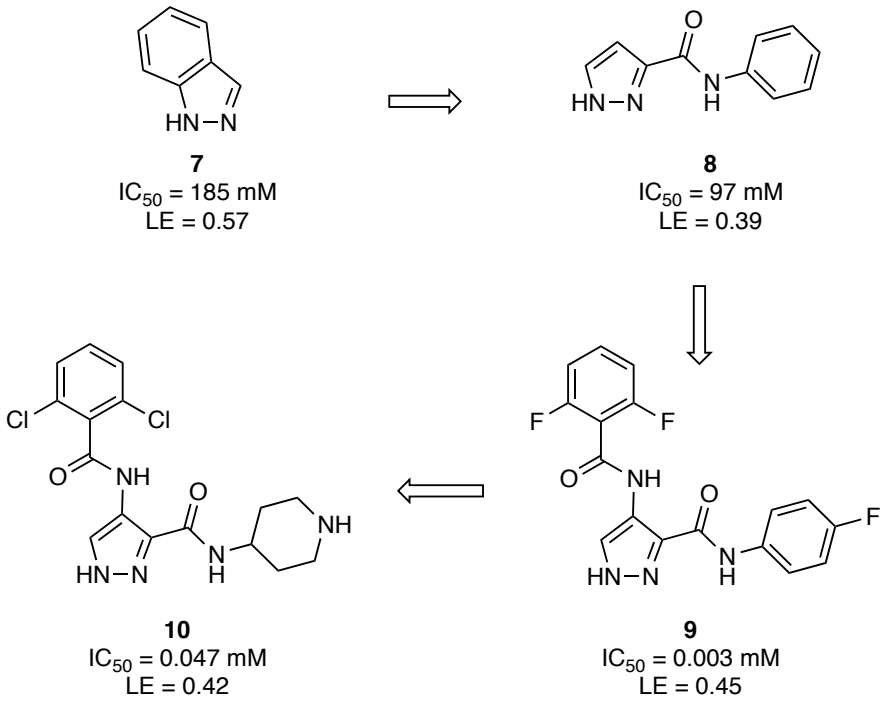
1.3.2 Ligand Efficiency and Fragment Optimisation

Ligand efficiency (LE) has recently emerged as a reliable method to judge the relative optimisability of different potential drug molecules. More specifically, LE involves taking the concentration of an inhibitor that is required for 50% inhibition of an enzyme *in vitro* (IC_{50}) and dividing this by the number of heavy atoms (*N*) present in the fragment (LE = IC_{50}/N).[18] This allows for an uncomplex and more appropriate comparison of differently sized fragments than affinity alone. Indeed, it has been proposed that fragments possessing a ligand efficiency of greater than 0.3 are the optimum fragments for development. In this regard, it is desirable to maintain as high a ligand efficiency as possible throughout the optimsation process. Moreover, a complementary 'rule of three' approach is commonly employed to assess the physiochemical properties of fragments.[21] The properties associated with this approach are: maintaining a molecular weight of under 300, minimising the number of hydrogen bond donors to less than 3, and maintaing a partition coefficient (clog P) under 3.

As stated previously, the ethos of FBDD is grounded in the identification of high-quality, but potentially low-affinity, interactions. The affinity range of 10 mM to 100 μM is much weaker than that identified traditionally in HTS through enzyme or receptor bioassay screens. Accordingly, more advanced and sensitive techniques must be employed to identify fragments of interest. As discussed previously, biophysical techniques such as NMR spectroscopy, X-ray diffraction, surface plasmon resonance, and mass spectrometry are key in establishing fragments with potential for optimisation.[22] However, these advanced techniques all require specific hardware, trained personnel, and a well-grounded infrastructure. This is a definite obstacle to overcome in terms of facilitating widespread use of FBDD as an efficient and widely employed method of drug discovery.

1.3.3 Fragment Based Drug Discovery – Case Study

The effectiveness and applicability of FBDD is illustrated through the case history of a cyclin dependent kinase (CDK) inhibitor developed by Astex.[23] Cyclin dependent kinases are involved in the cell cycle and cell replication, and are routinely found in both solid tumours and lymphomas.[18] A library consisting of approximately 1,000 fragments were screened against the kinase of interest, with X-ray screening identifying the most promising molecule. This molecule was subsequently optimised into a drug candidate and progressed into phase 1 trials (**Scheme 2**).[23] More specifically, with respect to the optimisation process, fragment **7** was identified as binding to the hinge region of the kinase, therefore, amide functionality was introduced to reinforce the hydrogen-bonding interactions, shown in compound **8**. The fragment was further elaborated through exploiting a di-*ortho*substituted aryl group to induce a twist in the conformation of the molecule and expansion into a proximal binding pocket, to yield compound **9**, which was taken forward as the lead molecule. A few subtle modifications led to the improved solubility of compound **10**, which was subsequently investigated in clinical trials. This example adheres to the philosophy of maintaining LE values throughout the optimisation process and highlights the potential of FBDD as a method by which to develop new therapeutic agents.



Scheme 2

1.4 3D Molecules

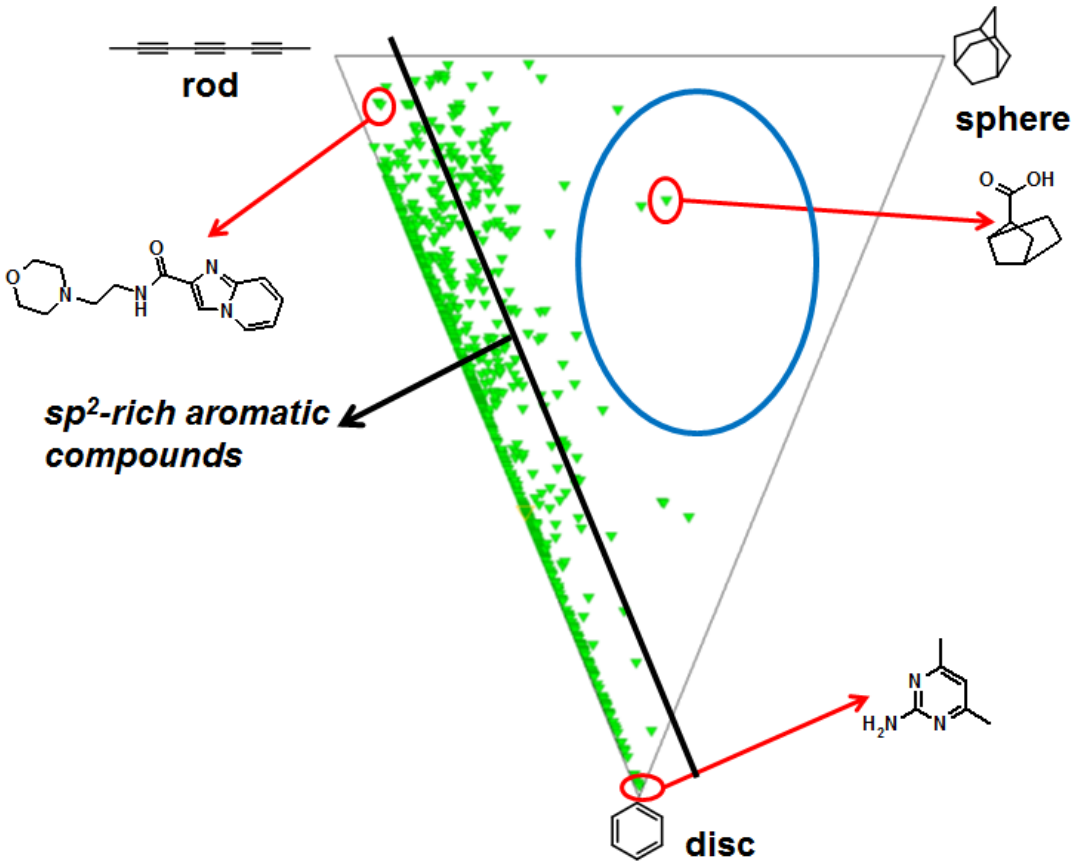
As previously discussed, Lipinkski's guidelines have functioned as a somewhat rough blueprint for drug discovery. However, one attribute that has been consistently overlooked is the complexity of potential drug molecules. It has been shown that the rise of parallel synthesis leads to predominantly achiral, aromatic/heteroaromatic compounds.[24] This most likely arises due to the ease of preparation of these compounds, through metal-mediated coupling reactions and amide bond forming reactions, resulting in an sp^2-rich library.

In an effort to address this issue there have been a number of attempts to synthesise a range of more complex compounds, commonly referred to as 'diversity orientated synthesis'.[25] It is envisaged that compounds accessed *via* this approach will be comparable to natural products. However, the complexity of these compounds has led to numerous issues in terms of their synthesis. In contrast, this in turn presents an opportunity for organic chemists to

create new methods and reactions, which will facilitate their synthesis in a rapid and efficient manner.

With regards to diversity orientated synthesis, the degree of saturation present has emerged as a key component. This can be probed by investigating complex, sp^3-rich, compounds with the tetrahedral carbon units forcing the compounds into a nonplanar conformation. This gives rise to complex molecules whilst simuateously minimising the molecular weight. It has been suggested that an increase in the sp^3 character of a molecule follows a linear relationship with increasing success in clinical studies.[24] The increased 3D shape lends itself to more selective target/receptor interactions, leading to greater specificity. The study concluded that there was a "significant correlation between both increasing saturation and increasing chiral centres as compounds progress through clinical testing".[24]

To illustrate the ubiquity of flat aromatic compounds, a molecular shape analysis was carried out on the compound collection possessed by the Beatson Institute (**Graph 1**). Each corner of the graph represents a different attribute. The top left corner represents compounds which can be described as rod like, with a linear type structure. The bottom corner represents disc like compounds, which are planar in conformation. The top right corner represents compounds of a sphere like conformation, which are non-planar and have predominantly sp^3 character. Representative compounds of each area are illustrated above. From the graph, it is clear that the vast majority of compounds within the library are planar, aromatic, and generally sp^2-rich. This is also the case for many industrial compound libraries. It is envisaged that populating the under developed area of chemical space (blue circle), through diversity orientated synthesis, will lead to promising new drugs.



Graph 1[26]

1.5 Targeting Protein-Protein Interactions

An ever-present need for new therapeutic agents has led to intense research surrounding the development of compounds targeting protein-protein interactions (PPI).[1] As stated previously, a vast array of cellular functions including cell growth and DNA replication are controlled by these interactions. Breakthroughs within the realm of protein biology/chemistry have allowed for specific proteins to be targeted in order to induce a desired biological effect, for example restricting cell growth of a rapidly metastasising tumour.[27]

It has recently been established that loss, or over-expression, of a specific interaction at an inappropriate time and/or location can lead to various diseases.[28] As a result, PPI's have attracted considerable interest from the research community as targets for novel therapeutic agents. Having stated this, the most obvious difficulty associated with targeting the interactions is overcoming problems encountered as a result of the complex conformational issues associated with proteins.[29] It is important to appreciate that proteins feature a large surface area, however, in order to elicit a desired effect a small molecule may only need to interact with a handful of amino acid residues.[30]

The development of small molecules that can disrupt protein-protein interactions is a primary objective in treating an array of diseases. One method that has attracted considerable interest is the synthesis of small molecules that can mimic the α-helix structure found in numerous proteins.[31] Indeed, the α-helix structure is an integral form of recognition for a range of proteins and, thus, is widely is responsible for mediating various PPI's. Accordingly, it follows that mimicking this structural recognition feature of proteins, using specifically designed synthetic scaffolds that replicate structural features of the proteins secondary structure, could lead to the development of novel therapeutic agents.

2 Previous and Proposed Work

As stated previously, the majority of compounds present in the screening libraries of pharmaceutical companies are chiefly composed of planar sp^2-rich moities. Based on this, compounds possessing a more 3D conformation are underrepresented in the compound collections. As such, it is anticipated that the development of novel moieties possessing this attribute will lead to a greater area of chemical space being investigated. Indeed, it is envisaged that this approach will identify a range of lead compounds for development within respective drug development programmes.

In relation to the above, it is proposed that the novel scaffolds, **11** and **12**, will facilitate access to a range of compounds possessing an inherent 3D nature (Figure 5). Indeed, the cyclopropyl functionality present in both compounds is integral to imparting a 3D conformation.

Figure 5

As previously discussed, mimicking the secondary structure of proteins represents an efficient manner by which to interfere with protein-protein interactions. In relation to this, it has been reported that *ortho*-substituted biphenyl unit compounds are potential mimics of the α-helix structure.[32] Based on this, it follows that compounds exhibiting this skeletal composition could potentially disrupt protein-protein interactions. Further still, it has been disclosed that the α-substituted aryl cyclopropyl framework, found in compounds **11** and **12**, is a bioisostere of *ortho*-substituted biphenyl units.[33] This relationship can be clearly inferred from a visual overlay of the two units: the *ortho*-substituted biphenyl unit (yellow)

superimposes over the α-substituted aryl cyclopropyl framework (green) in an efficient manner (**Figure 6**). As such, the α-substituted aryl cyclopropyl framework could potentially function as an α-helix mimietics and form the basis for new therapeutic agents.

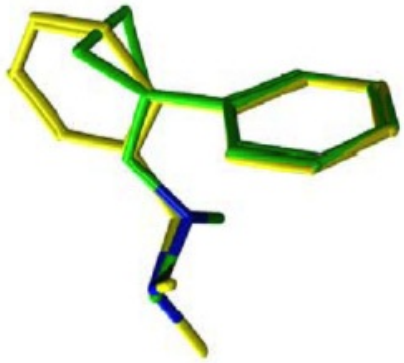


Figure 6[34]

Through the initiation of collaborations with the Beatson Institute (and as part of the 3D consortium), the primary aim of the project was to design a scalable synthetic route towards such α-cyclopropyl pyridyl scaffolds. As *gem*-substituted cyclopropyl-pyridyl compounds are commericially unavailable the developed route had to install the key cyclopropyl functionality in an efficient manner, as well as allow for late stage diversification of the scaffold. With these clear goals identified, it was decided to investigate the synthesis of late stage intermediate **13**, which would satisfy both demands. For example, with respect to further elaboration of the molecular framework, it can be envisaged that the pyridyl chloride functionality could facilitate nucleophilic aromatic substitution or, indeed, a plethora of palladium-mediated coupling transformations to yield **14**. In addition, the ester functionality could be saponified to the acid functionality which could, in turn, allow access to a range of amide species, **15** (**Figure 7**). Indeed, with respect to further synthetic manipulations, the above suggestions are by no means exhaustive and there is the potential to access an array of interesting moieties based on the cyclopropyl pyridyl scaffold.

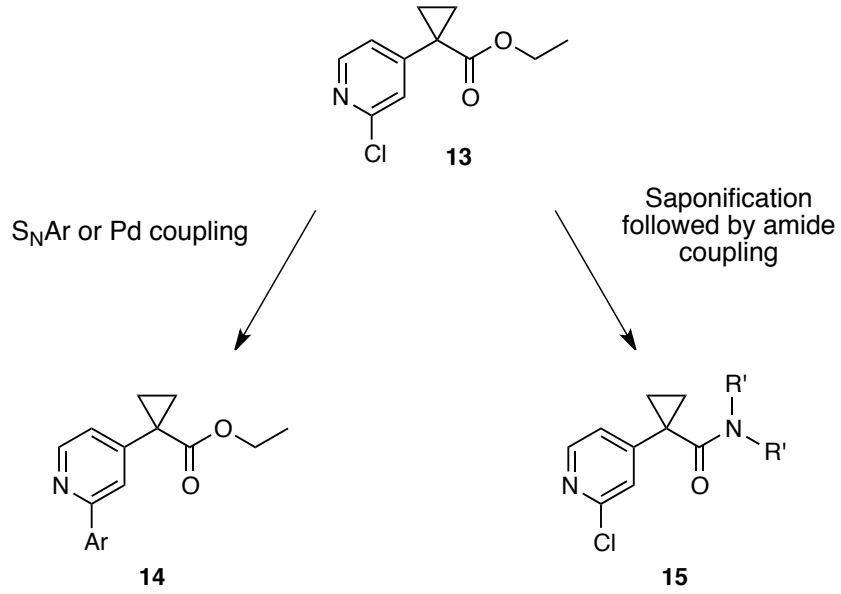


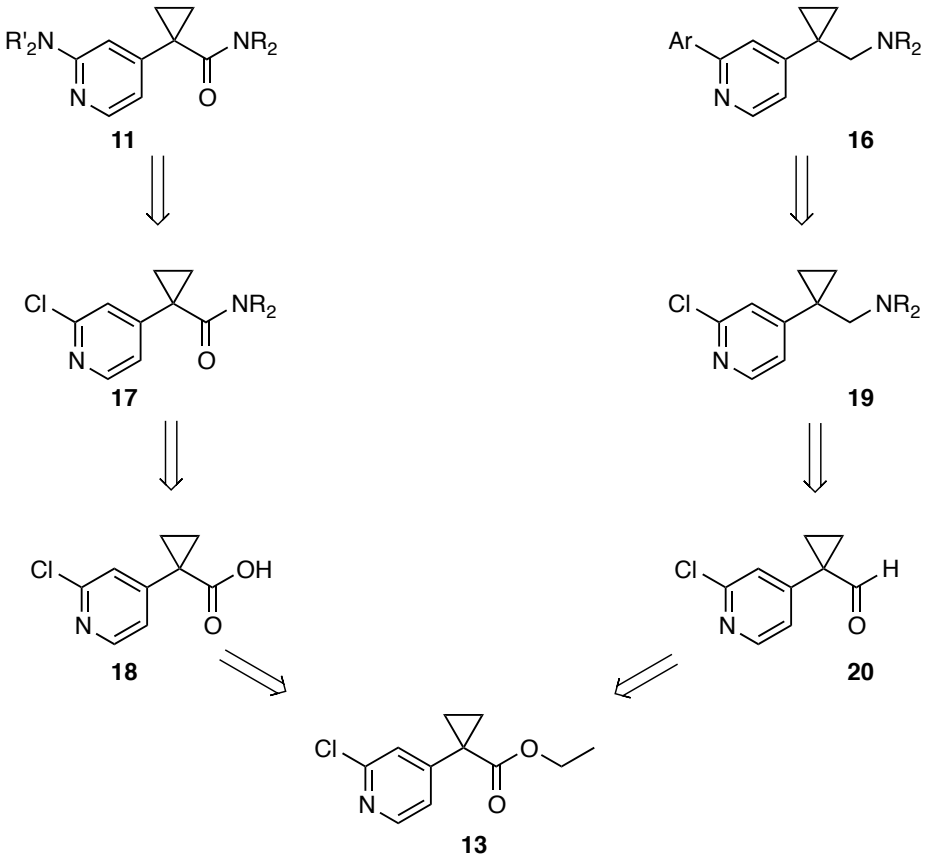
Figure 7

In summary, the immediate aim of the project is to develop a scalable synthetic route towards compound **13**. Upon completion of this objective, attention will turn to the embellishment of the novel scaffold. It is envisaged that an analogue of compound **11** could be accessed from **13** which would provide an excellent proof-of-concept with respect to the proposed preparative strategy.

3 Results and Discussion

3.1 Retrosynthetic Analysis of Novel Pyridyl Scaffolds

As discussed above, the ultimate focus of the project was the development of an efficient preparative approach towards compounds of the type **11** and **12**. Based on this, a retrosynthetic analysis was undertaken which highlighted that compound **13** could be considered a common intermediate with respect to the synthesis of species analogous to both **11** and **16** (**Scheme 3**). More specifically, the synthesis of compounds of type **11** could be achieved *via* the employment of an S_NAr reaction of chloride derivative **17**. In turn, the amide functionality present in compound **17**, could be constructed using standard amide coupling techniques.[35] As such, the carboxylic acid coupling partner **18** could feasibly be accessed *via* hydrolysis of compound **13**. Similarly, compounds of type **16** could be accessed through Suzuki coupling chemistry (or analogous organometallic coupling methods), with the amine portion of compound **19** being introduced from the reductive amination of compound **20**. The employment of a DIBAL-H-mediated reduction would install the aldehyde portion of compound **20** from the common intermediate, compound **13**.

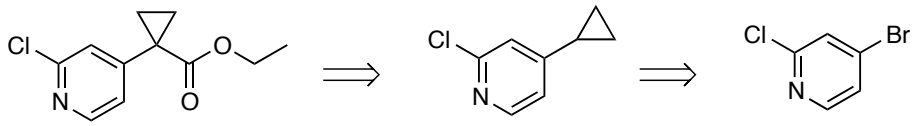


Scheme 3

With compound **13**, identified as a common late stage intermediate which would allow scope for diversification, initial efforts were focused on determining a robust and efficient pathway for its synthetic preparation.

3.2 Towards the Preparation of Compound 13 – Route 1

At the outset, it was envisaged that the most conceptually straightforward manner of accessing compound **13** was *via* deprotonation, at the benzylic position, of compound **21**, followed by quenching with a suitable electrophile such as ethyl chloroformate (**Scheme 4**). Accordingly, the installation of the cyclopropyl unit could be achieved through a palladium-mediated coupling reaction employing the commercially avaliable halogenated pyridine species **22**.



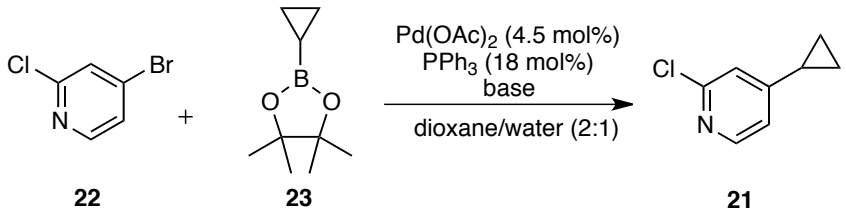
13 **21** **22**

Scheme 4

With the above pathway in mind, attention was turned to the palladium-mediated Suzuki coupling to afford **21**. The Suzuki coupling is one of the most powerful methods of carbon-carbon bond formation and is a precedented method of introducing the desired cyclopropyl moiety.[36] The only obvious potential for difficulty arises from the fact that the bromochloropyridine starting material is polyhalogenated. Having stated this, it is sensible to assume that the palladium will insert into the weaker carbon-bromine bond in a much more facile manner than that of the, relatively stronger, carbon-chlorine bond.[37]

With the above in mind, it was envisaged that the Suzuki reaction, illustrated in **Scheme 5**, would proceed in a chemoselective manner. Accordingly, an optimisation study was initiated (**Table 1**). The method of promotion was investigated with initial efforts employing microwave irradiation. The bases trialled, potassium carbonate and cesium carbonate, gave varying results with potassium carbonate facilitating the reaction in a disappointing 26% yield (**Entry 1**). In contrast, cesium carbonate gave a more acceptable 54% yield (**Entry 2**). Attention turned to thermal promotion as it was reasoned that the complex mixture of

byproducts observed (under microwave irradation) might be attributable to the relatively harsh reaction conditions. Pleasingly, in both cases, an increase in yield was observed, with compound **21** ultimately being isolated in an excellent 94% yield using cesium carbonate as the base (**Entry 4**).



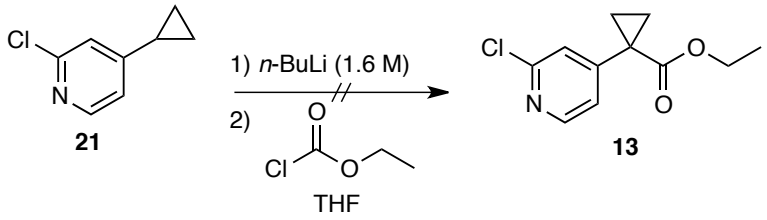
22 **23** **21**

Scheme 5

Entry	*Conditions*	*Temperature*	*Time*	*Base*	*Yield*
1	MWI	120°C	20 min	K_2CO_3	26%
2	MWI	120°C	20 min	Cs_2CO_3	54%
3	Thermal	100°C	16 h	K_2CO_3	33%
4	Thermal	100°C	16 h	Cs_2CO_3	94%

Table 1

With compound **21** in hand, attention turned to the introduction of the ester moiety present in intermediate **13**. It was envisaged that the tertiary carbon bearing the cyclopropyl ring should prove moderately acidic. However, with no literature precedent for a similar reaction on a substrate of this nature, coupled with the potential for a competing S_NAr displacement, the deprotonation attempts were fraught with potential obstacles. Nonetheless, it was rationalised that compound **21** could be treated with *n*-butyllithium (*n*-BuLi) and quenched with ethyl chloroformate (**Scheme 6**).



Scheme 6

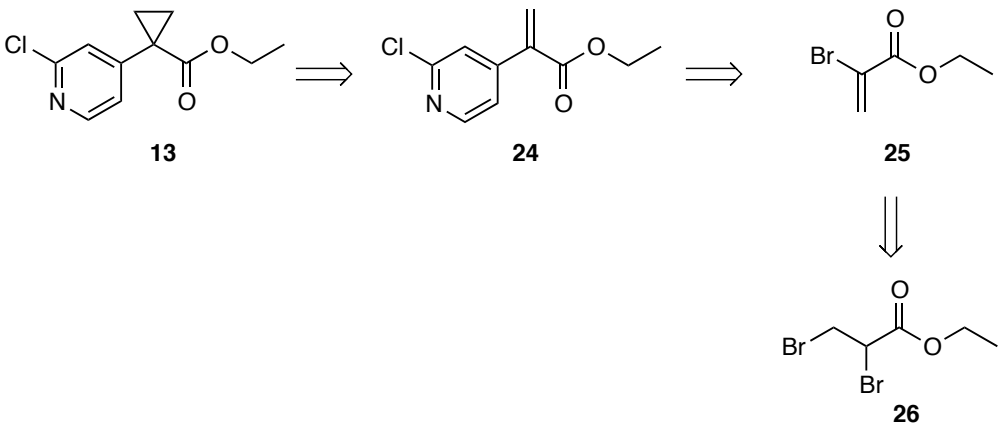
The initial attempt involved cooling the reaction to -78°C and adding *n*-BuLi in a dropwise fashion. Upon complete addition, the solution was allowed to warm to -40°C before being cooled to -78°C and quenched with ethyl chloroformate. After warming to room temperature, the mixture was stirred for 16 hours. After this time complete consumption of the starting material was observed, however, disappointingly, the desired product had not formed and the reaction mixture contained an unidentifiable range of products. With this result in hand, the reaction was repeated employing a similar approach as before. However upon addition of *n*-BuLi the reaction was kept at -78°C for 1.5 hours before ethyl chloroformate was introduced. It was envisaged that the sustained lower temperature would limit by-product formation. The remainder of the process was, as before, with room temperature reactions for 16 hours. Unfortunately, the reaction failed to yield the desired product and a complex mixture of products was, again, observed.

It was surprising to encounter such a complex reaction profile as it was originally conceived that performing the reaction at low temperatures would minimise potential S_NAr reactions, as well as any undesired lithium-halogen exchange processes. The chances of such an exchange occurring on a 2-halopyridine substrate, such as **21**, are generally considered unlikely, as the lithiated species would encounter considerable lone-pair repulsion from the nitrogen of the pyridine. Indeed, the formation of the complex mixture is most likely attributable to the strained cyclopropyl moiety undergoing a homolytic degradation pathway. Whilst a potential solution to this may have been the introduction of radical scavengers, this was not a particularly attractive method of generating the desired intermediate in large quantities, and an alternative route was devised.

3.3 Towards the Preparation of Compound 13 – Route 2

3.3.1 Retrosynthetic Analysis of Compound 13 – Route 2

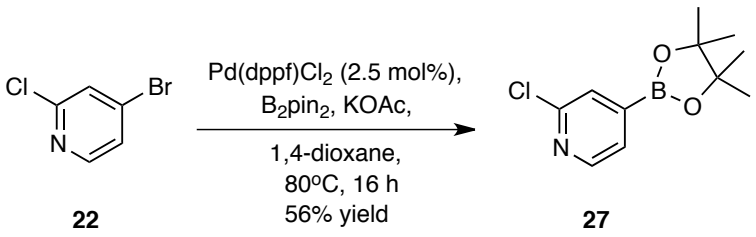
At this juncture, it was reasoned that an α,β-unsaturated ester, **24**, would serve as a good functional handle for late stage introduction of the cyclopropane ring. Accordingly, an alternative synthetic route to compound **13** was devised (**Scheme 7**). It was envisaged that employment of either a Corey-Chaykovsky reaction or a Simmons-Smith reaction of compound **24** would deliver the cyclopropyl moiety of compound **13**. A Suzuki coupling of the α-halo ester, compound **25**, with a suitably substituted borylated pyridine unit would form compound **24**. Ultimately, the α-haloenone would be synthesised from the commercially available ethyl 2,3-dibromopropanoate, compound **26**.



Scheme 7

3.3.2 Synthesis of Compound 13 – Route 2

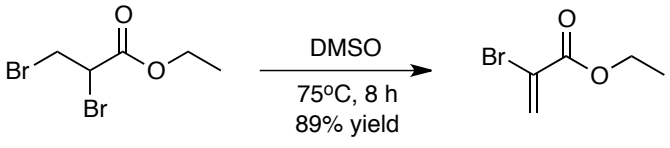
This synthetic approach began with the formation of the appropriate coupling partners for the Suzuki reaction. The aryl boronic ester, compound **27**, was produced from the corresponding halogenated species, compound **22**, through employment of a Miyaura borylation (**Scheme 8**).[38] The reaction proceeded with 56% yield, and complete consumption of the starting material was observed. Pleasingly, appreciable quantities of the boronic ester were obtained and attention turned to the synthesis of the desired vinyl halide coupling partner, compound **25**.



22 **27**

Scheme 8

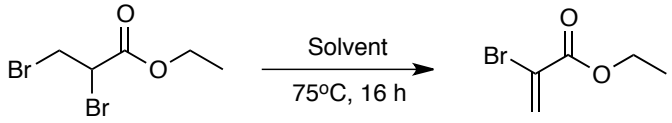
There was surprisingly little by way of literature precedent for the synthesis of the desired α-halo ester **25**, although Li and coworkers recently disclosed an expedientsynthetic strategy.[39] It was reported that simply heating ethyl 2,3-dibromopropanoate in DMSO led to the formation of the desired α-haloenone in good yield (**Scheme 9**).



26 **25**

Scheme 9

Accordingly, the synthetic approach detailed by Li *et al.* was investigated, however, disappointingly, the desried α-halo ester **25** failed to form after a series of attempts (**Scheme 10, Table 2**). The initial attempt employed the exact conditions reported by Li, however the starting material failed to react at all (**Entry 1**). It was reasoned that adventitious water may aid the reaction and this was probed accordingly (**Entries 2 & 3**). In a similar manner, the starting material failed to react and, therefore, an alternative approach was devised.



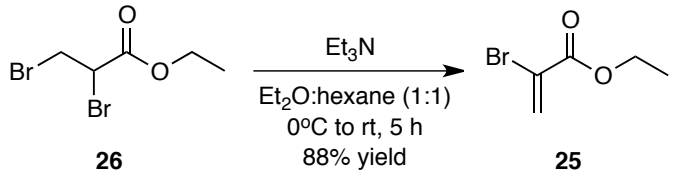
26 **25**

Scheme 10

Entry	*Solvent*	*Yield*
1	DMSO	-
2	DMSO (1% H_2O)	-
3	DMSO (5% H_2O)	-

Table 2

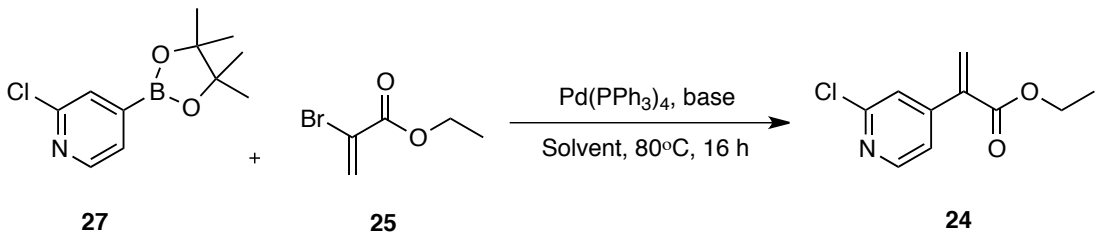
Undeterred, it was envisaged that treating ethyl 2,3-dibromopropionate, **26**, with a base, would facilitate an elimination reaction to form the desired compound **25**. As highlighted in **Scheme 11**, treatment of **26** with triethylamine led to the formation of the desired α-haloenone, compound **25**, in good yield.



26 **25**

Scheme 11

With both coupling partners in hand, attention turned to the Suzuki reaction as a means by which to access compound **24** (**Scheme 12, Table 3**). Two sets of robust and transferable reaction conditions were investigated simultaneously. Initially, palladium tetrakis(triphenylphosphine) was employed alongside cesium carbonate and a 2:1 mixture of dioxane and water; the resulting suspension was heated to 80°C and stirred for 16 hours (**Entry 1**). Frustratingly, the desired compound, **24**, failed to form and a complex mixture of products was observed. Indeed, employing palladium tetrakis(triphenylphosphine) alongside potassium carbonate and a 3:1 mixture of dimethylformamide (DMF) and water resulted in a similar reaction outcome (**Entry 2**). Upon analysing the respective reaction mixtures *via* liquid-chromatography mass spectrometry (LC-MS) it was confirmed that the desired α,β-unsaturated ester, compound **24**, had failed to form. Interestingly, thin-layer chromatography (TLC) analysis of the α-haloenone starting material, **25**, produced a startling result; the previously pure α-haloenone had degraded to produce a complex mixture of products. Subsequent ^{1}H NMR confirmed the degradation, with multiple new indistinct peaks in the aliphatic region. It would appear that the reason for the commercial unavailability of this compound was due to its unstable nature. As a potential method of overcoming this difficulty, it was decided to purify the starting material *via* repeat flash column chromatography. The freshly isolated material was utilised immediately in the Suzuki coupling, under the previously employed conditions (**Entries 3 & 4**). However, this approach was proved ineffective as the α-haloenone, **25**, underwent degradation at the elevated temperatures routinely employed in the Suzuki reaction resulting in, again, a complex mixture of byproducts and none of the desired material being observed. Accordingly, an alternative approach to the cyclopropyl scaffold, **13**, was devised.



27 **25** **24**

Scheme 12

Entry	*Base*	*Solvent*	*Yield*
1	Cs_2CO_3	dioxane/H_2O (2:1)	-
2	K_2CO_3	DMF/H_2O (3:1)	-
3*	Cs_2CO_3	dioxane/H_2O (2:1)	-
4*	K_2CO_3	DMF/H_2O (3:1)	-

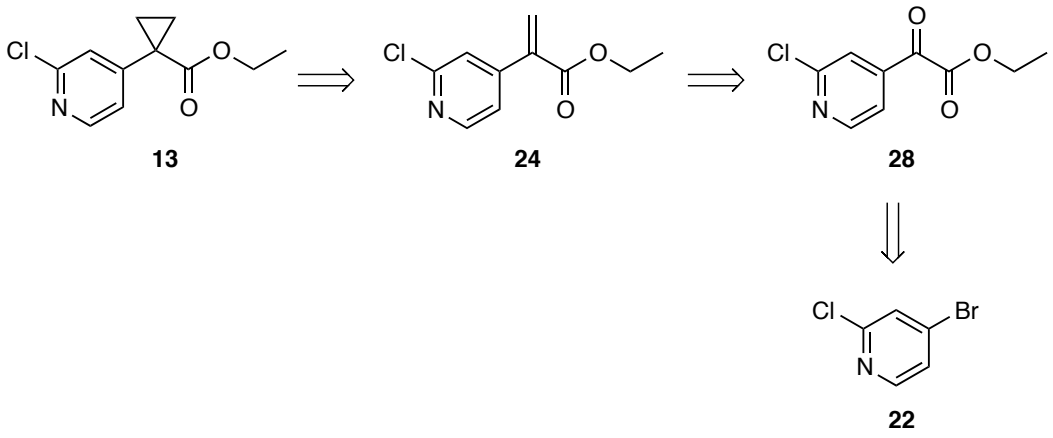
* Compound **25** purified immediately before use.

Table 3

3.4 Towards the Preparation of Compound 13 – Route 3

3.4.1 Retrosynthetic Analysis of Compound 13 – Route 3

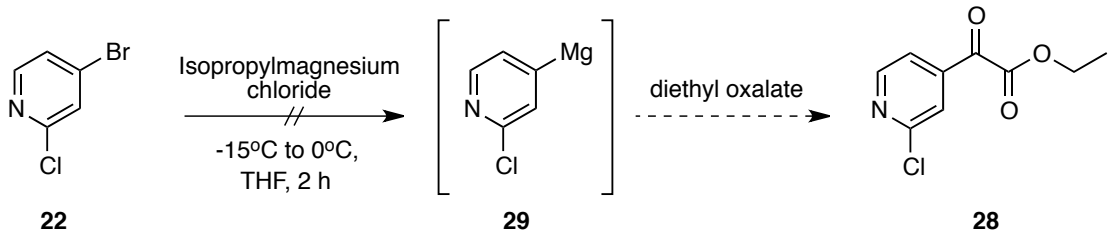
With the above results in mind, it was envisaged that a less direct method of forming the desired α,β-unsaturated ester, **24**, might be required (**Scheme 13**). As such, methylenation of the corresponding α-keto ester, **28**, would provide the desired Corey-Chaykovsky precursor, compound **24**. The α-keto ester could conceivably be formed *via* a Grignard reaction from the aforementioned bromochloropyridine, compound **22**.



Scheme 13

3.4.2 Synthesis of Compound 13 – Route 3

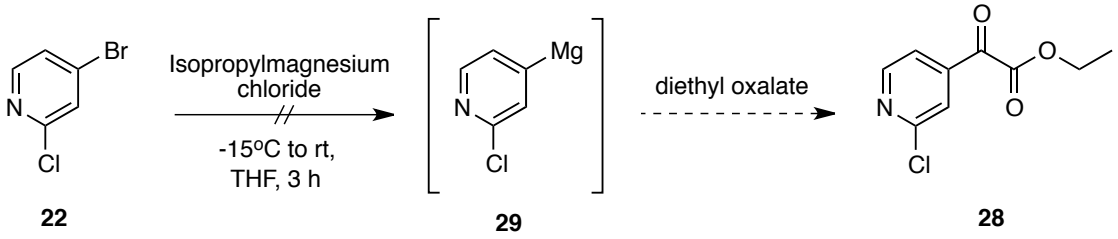
As such, attention turned to the formation of keto ester **28**. In this regard, initial investigations were concerned with the formation of the Grignard reagent **29**, with an ultimate aim of reacting this with a suitable electrophile. As shown in **Scheme 14** compound **22** was reacted with isoproylmagnesium chloride at -15°C before warming to 0°C. After a period of 2 hours at 0°C an aliquot of the reaction mixture was quenched with acetone and the resulting species analysed by LC-MS. Disappointingly, the desired organomagnesium species had failed to form and the reaction was abandoned.



Scheme 14

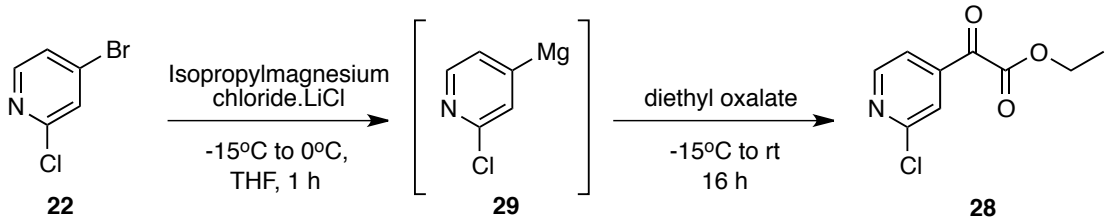
It was reasoned that the low temperatures maintained in the above reaction were perhaps too low to facilitate the Grignard formation. As a result, the subsequent reaction was allowed to warm to room temperature and stirred for three hours following the addition of isopropyl

magnesium chloride (**Scheme 15**). Disappointingly, in a similar manner to that observed previously, LC-MS analysis indicated that the Grignard reagent failed to form despite these comparatively elevated temperatures.



Scheme 15

To overcome the difficulties associated with forming the desired Grignard reagent, an alternative magnesium source was sought. Knochel *et al.* have showcased that the addition of lithium chloride can increase the reactivity of organomagnesium reagents.[40] This is believed to arise through the disruption of polymeric aggregates by LiCl, which leads to enhanced performance. Based on this, Knochel's procedure was adopted in an attempt to generate the desired organomagnesium species, **29**. The reaction was performed as before, but utilising an isopropylmagnesium chloride – lithium chloride solution in place of the original organomagnesium compound (**Scheme 16**, **Table 4**). Pleasingly, a colour change from pale yellow to ruby red was observed, subsequent LC-MS analysis of the reaction mixture confirmed the formation of the desired organomagnesium species, **29**. Following this, the organometallic species was quenched with diethyl oxalate to furnish ketoester **28** in a 55% yield (**Entry 1**). Indeed, the chemical yields were reproducible over a range of reaction scales (**Entries 2** & **3**). Despite the successful access to **28** as detailed above, it was decided to investigate the utility of an alternative electrophile in the hope that an improved yield could be obtained.

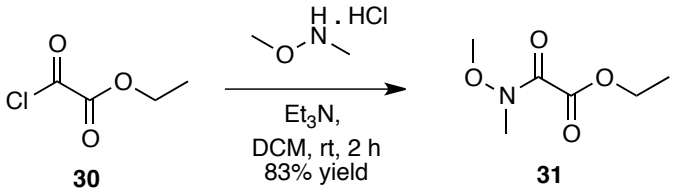


Scheme 16

Entry	*Yield*
1	55%
2	62%
3	65%

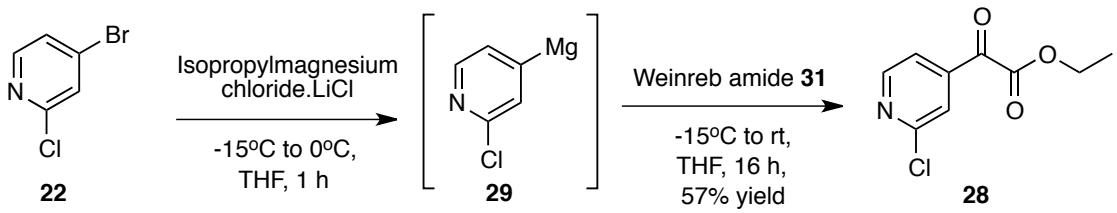
Table 4

Accordingly, the Weinreb amide of the α-keto ester was synthesised for employment as the electrophile in the above Grignard reaction (**Scheme 17**). Pleasingly, the formation of Weinreb amide **31**, proceeded without incident in a yield of 83%.



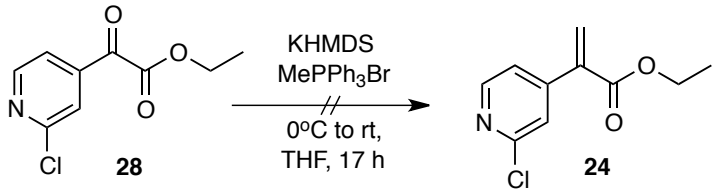
Scheme 17

With this reagent in hand, the Grignard reaction was then attempted under the previously employed conditions (**Scheme 18**). Unfortunately, this alternative electrophile failed to prove an advantage over the previously employed diethyl oxalate with only 57% of the desired α-keto ester, **28**, being isolated.



Scheme 18

With the α-keto ester in hand, attention turned to the methylenation of the ketone portion of the molecule. It was envisaged that a Wittig reaction would introduce this functionality, providing a good handle for subsequent cyclopropanation attempts. With this in mind, the α-keto ester was subjected to methylenation conditions shown below (**Scheme 19**). Disappointingly, the reaction failed to deliver the desired product. Fortunately, simultaneous to this experiment, a new and potentially more efficient synthetic pathway had been considered.



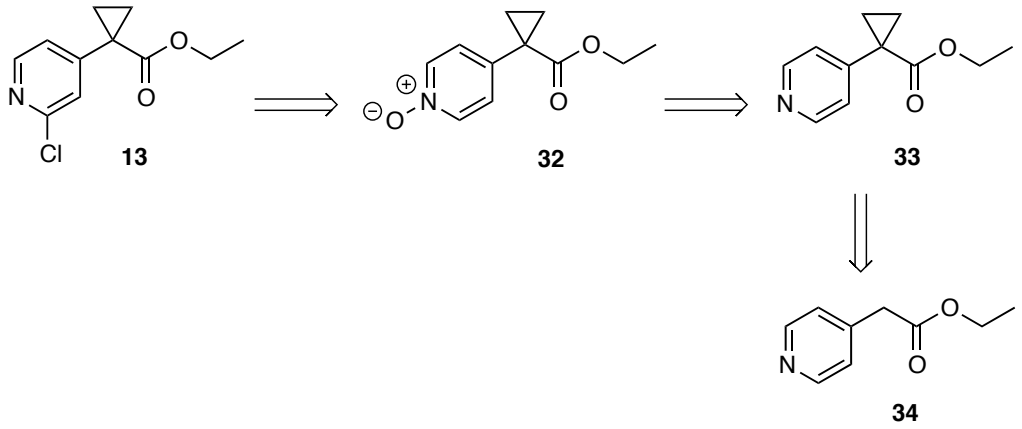
Scheme 19

3.5 Towards the Preparation of Compound 13 – Route 4

3.5.1 Retrosynthetic Analysis of Compound 13 – Route 4

As discussed previously, the installation of the requisite cyclopropyl functionality represents an integral aspect of the research programme. Based on the disappointing results obtained previously with respect to the synthesis of compound **13**, it was decided to investigate an alternative synthetic approach that would focus on the early installation of the cyclopropyl unit. As such, in contrast to the previous synthetic efforts, the fourth route was devised with

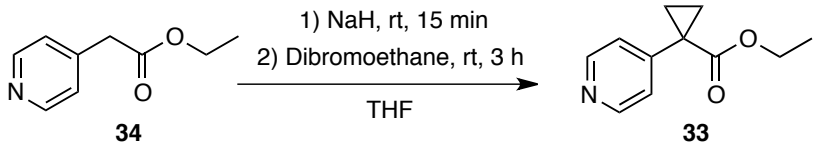
halogenation of the heteroaryl ring being the final step in the synthesis of the key intermediate, compound **13**. As illustrated in **Scheme 20**, the preparation of compound **13** is potentially achieved through introduction of the chloro substituent from the corresponding *N*-oxide species, compound **32**. This can feasibly be prepared from oxidation of the pyridine moiety of compound **33**, which can in turn be prepared from the commerically available heteroaryl species, **34**.



Scheme 20

3.5.2 Synthesis of Compound 13 – Route 4

It was envisaged that the acidic methylene protons of compound **34** could be exploited in order to install the cyclopropyl unit. With this in mind, the commerically available pyridyl ester, **34**, was treated with sodium hydride before introducing dibromoethane in an effort to construct the three membered ring (**Scheme 21**, **Table 5**). Gratifyingly, this approach proved successful and the cyclopropyl functionality was installed in a pleasing 66% yield (**Entry 1**). In addition, the reaction protocol was found to be reproducible (**Entry 2**) and amenable to gram scale reaction (**Entries 3** & **4**). As such, this represented a significant milestone within the research programme as the installation of this integral unit had previously proven elusive.

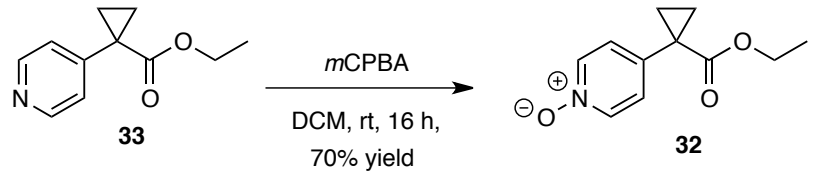


Scheme 21

Entry	*Yield*
1	66%
2	72%
3	65%
4	73%

Table 5

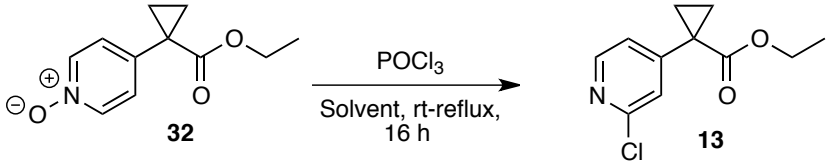
Following the formation of **33**, attention was now focused on the formation of the *N*-oxide derivative, **32**. It was envisaged that this unit would provide a suitable functional handle for introducing the requisite chloro substituent of **13**. As such, the oxidation of **33** was attempted with *meta*-chloroperoxybenzoic acid (*m*CPBA) (**Scheme 22**). Pleasingly, the desired product was isolated in a satisfying 70% yield.



Scheme 22

With *N*-oxide, **32**, in hand, attention turned to embellishment of the heteroaromatic ring *via* the strategic employment of a chlorinating agent. Based on this, compound **32** was treated with phosphoryl chloride with the aim of introducing the requisite chloro substituent (**Scheme 23, Table 6**). Pleasingly, performing the reaction in refluxing 1,4-dioxane resulted in the desired product, **13**, being obtained in a 47% yield (**Entry 1**). Further still, upon

moving to refluxing toluene an improved yield of 55% was obtained (**Entry 2**). It was especially gratifying to acceess intermediate **13**, as this moiety underpinned the synthetic approach towards compounds of the type **11** and **16**, respectively.



Scheme 23

Entry	*Solvent*	*Yield*
1	1,4-Dioxane	47%
2	Toluene	55%

Table 6

In an effort to improve the chemical yield of **13**, it was envisaged that microwave promotion may improve the efficiency of the reaction. Accordingly, the reaction was subjected to microwave irradiation (MWI) with the results illustrated below (**Scheme 24, Table 7**). Despite further quantities of **13** being obtained, the chemical yields achieved under MWI were comparable to that of the thermally-promoted reactions (**Entries 1** & **2**).

Scheme 24

Entry	*Solvent*	*Yield*
1	Toluene	52%
2	1,4-Dioxane	51%

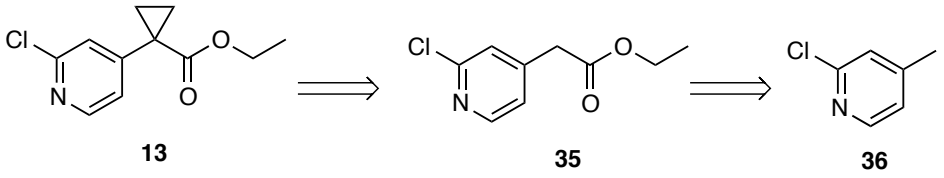
Table 7

To summarise, the novel key intermediate, **13**, which would allow for subsequent diversification, had been isolated following a 3-step synthesis. This was an important achievement in the context of the project. The route described is scalable and allows for a plethora of further organic transformations centred around the previously inaccessible pyridyl cyclopropane scaffold. Without detracting from the overall synthetic route, there are certain time constraints associated with the current route. The key intermediate can be accessed in approximately 4 days from the commercially available starting material. As the importance of compound **13** cannot be overstated, a fifth and final synthetic route was devised with the aim of generating the desired scaffold in an exceptionally short time-frame.

3.6 Towards the Preparation of Compound 13 – Route 5

3.6.1 Retrosynthetic Analysis of Compound 13 – Route 5

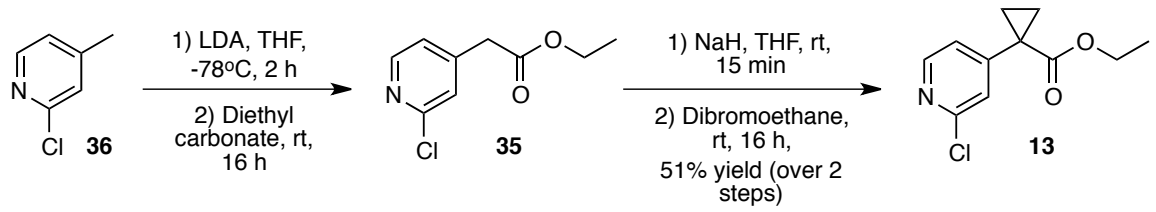
It was hypothesised that the rapid construction of the key intermediate was feasible through a similar synthetic strategy to that employed in route 4 and, more specifically, following the pathway illustrated below (**Scheme 25**). Accordingly, the cyclopropane moiety could be installed, as before, through employment of sodium hydride and dibromoethane. It was reasoned that employing a starting material with the chloro functionality present could streamline the preparative process towards **13**. Based on this it was envisaged that ester **35** could be accessed from the relatively inexpensive and readily available substituted picoline species, **36**. As such, this amended synthetic strategy would hopefully facilitate the preparation of **13** in a reduced number of synthetic steps and an enhanced chemical yield.



Scheme 25

3.6.2 Synthesis of Compound 13 – Route 5

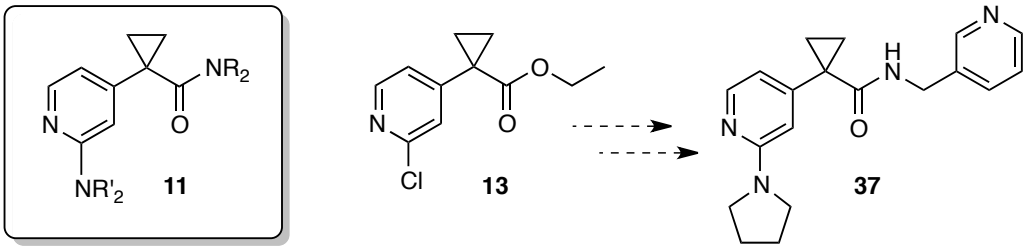
The synthesis began with the deprotonation of commercially available compound **36**, which was then quenched with diethyl carbonate acting as the electrophile (**Scheme 26**). The reaction proceeded in an efficient manner with compound **35** being identified as the main product by LC-MS analysis. Following a similar synthetic pathway from route 4, compound **35** was deprotonated with sodium hydride followed by quenching with dibromoethane. The unoptimized reaction proceeded in a good yield leading to the isolation of the key intermediate, **13**, in a 51% yield (based over 2 steps). Accordingly, this amended approach facilitated access to compound **3** in an expedient fashion.



Scheme 26

3.7 Synthesis of Novel 3D Fragments

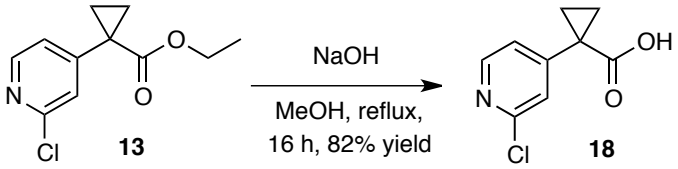
As discussed previously, the overall aim of the research is to synthesise novel fragments for screening within a fragment based drug discovery programme. Based on this, compounds of the type **11** were selected as high priority targets based on their aforementioned potential capacity to function as α-helix mimetics. In this regard, it was envisaged that a range of compounds could be accessed through manipulation of the key intermediate, compound **13**. As such, based on the readily available reagents required, it was reasoned that compound **37** would serve as a proof of concept with respect to a synthetic approach towards compounds based on **11** (**Scheme 27**).



Scheme 27

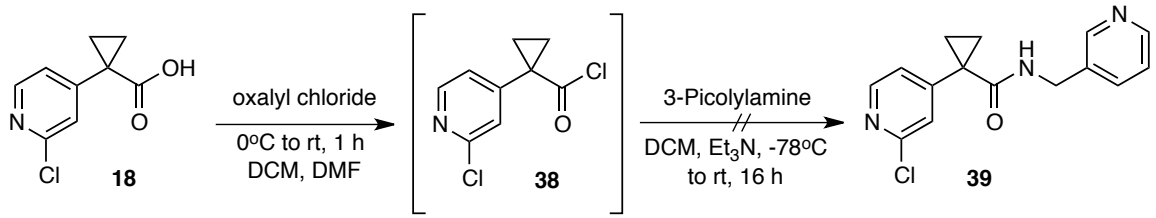
The primary objective was to install the amide functionality, with a brief comparison of coupling methods being carried out in order to identify the most promising agent. Upon completion of this study, the pyrrolidine moiety would be introduced and would complete the synthesis of compound **37**. The synthetic strategy developed would serve as a blueprint for subsequent syntheses of fragments centered around the scaffold of compound **13**.

As such, the synthesis began with the hydrolysis of the key intermediate, compound **13** (**Scheme 28**). The reaction proceeded as expected with the key carboxylic acid, **18**, isolated in an encouraging 82% yield.



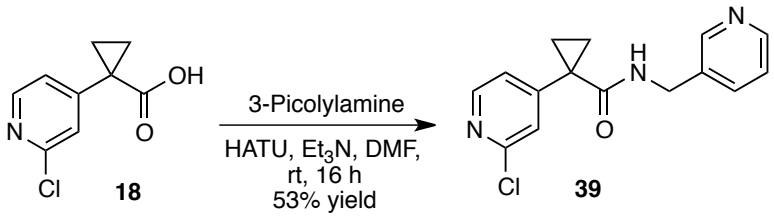
Scheme 28

With acid **18** in hand, installation of the amide moiety was investigated using two alternative reaction protocols. Firstly, the *in-situ* synthesis of the acyl chloride, followed by coupling, proved unsuccessful (**Scheme 29**). Although the acyl chloride formed, as detected by LC-MS, the subsequent amide coupling failed to occur.



Scheme 29

Given there is a plethora of available coupling methods, devising an alternative approach was relatively facile. HATU was the first reagent to be trialled (**Scheme 30**). Gratifyingly, the employment of this coupling reagent led to the isolation of the desired amide, **39**, in an acceptable yield.



Scheme 30

With the desired amide functionality in place it seemed logical to obtain an X-ray crystal structure of fragment **39**, in order to fully appreciate the conformation of the compound. As

is depicted, the cyclopropane sits perpendicular to the pyridine unit, as was anticipated (**Figure 9**). This is key to employment of fragments of this type being employed in '3D fragment based screening', as it prevents the molecule from adopting a planar conformation.

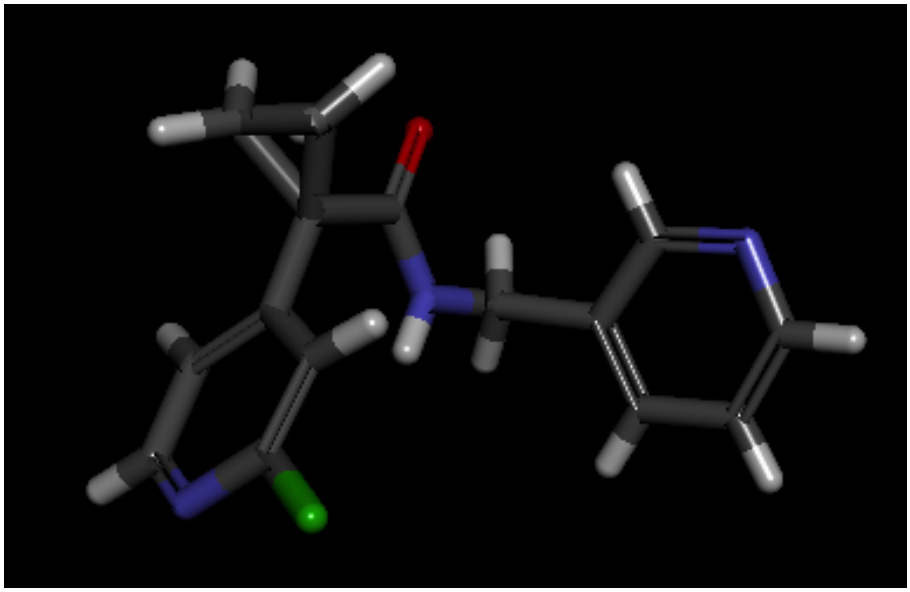
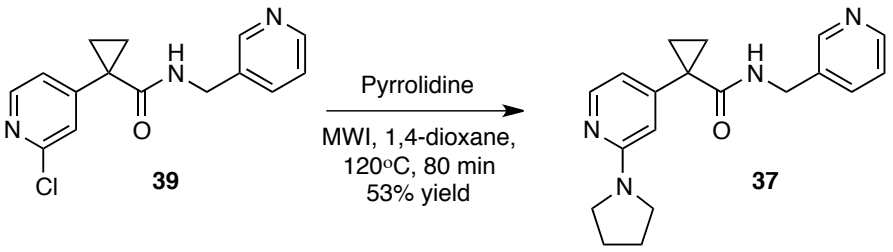


Figure 9

Delighted with the progress made, the final step was initiated in order to introduce the pyrrolidine unit and complete the synthesis. It was envisaged that the pyrrolidine could be introduced by exploitation of the compound's ability to undergo nucleophilic aromatic substitution. This approach is relatively simple in concept and, indeed, execution. Pyrrolidine was simply stirred with compound **39** in 1,4-dioxane, with the reaction being promoted by microwave irraditation (**Scheme 31**). Gratifyingly, compound **37** was isolated in a good yield, after only 80 minutes, completing the synthesis of the novel target.

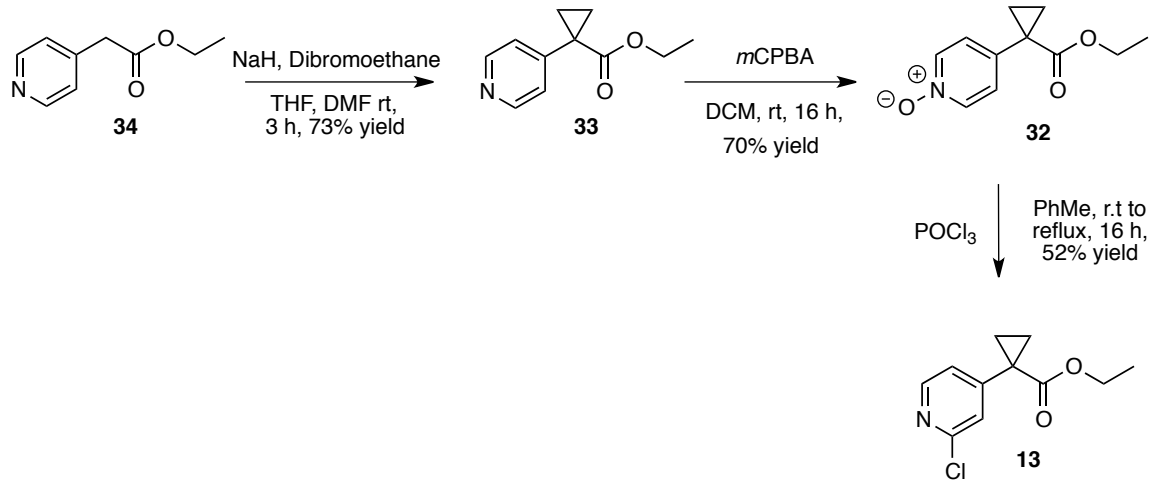


Scheme 31

The reaction detailed above represents a significant achievement within the research programme. Indeed, the primary aim of the project was to design a suitable synthetic pathway to compounds of this type. As such, there was now a suitable preparative approach in hand. The following sections of the report encompass the overall conclusions and future work associated with the preliminary collaborative research programme with the Beatson Institute.

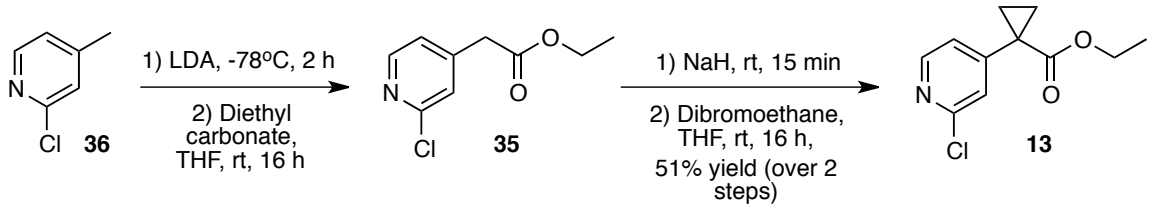
4 Conclusion

At the outset of the project, the initial goal was the synthesis of the previously inaccessible pyridyl cyclopropane scaffold **13**. In this regard, several preparative routes were designed and investigated. Following an appreciable synthetic effort, route 4 facilitated the formation of the desired intermediate, **13** (**Scheme 32**). This was achieved by treating **34** with sodium hydride and dibromoethane to install the cyclopropyl unit of **33**. Subsequent formation of the *N*-oxide analogue, **32**, *via* an *m*CPBA-mediated oxidation installed a suitable funtional handle for the ultimate introduction of the chloro substituent. This was achieved by treating **32** with $POCl_3$, which furnished the desired intermediate **13**. This result was incredibly satisfying as accessing compound **13** was deemed integral to the ultimate aim of the project. Further, it was reasoned that subtle amendments to the synthetic protocol could facilitate the formation of **13** in a more expedient fashion.



Scheme 32

Based on the desire to improve the preparative approach, route 5 was developed with the intention of circumventing the two-step protocol which was key to the introduction of the chloro substituent. As such picoline **36**, was homologated to the pyridyl species **35**, before treatment with sodium hydride and dibromoethane (**Scheme 33**). Pleasingly, this approach delivered intermediate **13** in an excellent 51% yield, over two steps. In addition, this strategy circumvented the requirement to employ a chlorinating agent.



Scheme 33

With two scalable synthetic approaches to the **13** in hand, attention turned to further elaboration of the novel scaffold. Based on this, the formation of a substituted amide motif illustrated the potential developments that could be introduced. More specifically, a pyrrolidine substituent was introduced to the heteroaromatic ring system in order to demonstrate the facile nature of further elaboration of the molecular framework. Pleasingly, compound **37** was accessed in an appreciable yield and aptly functions as a synthetic blueprint towards compounds of this type (**Figure 10**).

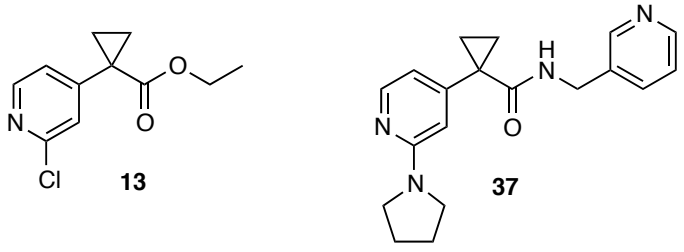
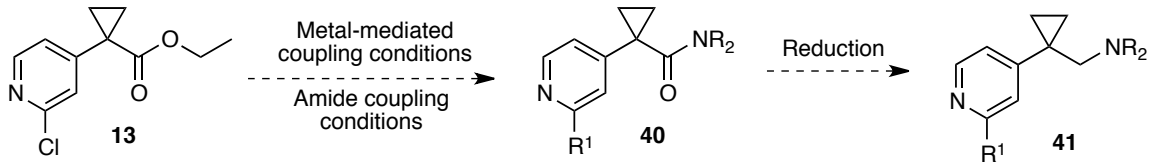


Figure 10

In summary, the above results are particularly pleasing as the project described herein was limited to a 16-week period. Indeed, the developments made within this collaborative research programme will allow for a vast array of fragments to be synthesised in a rapid fashion. In this regard, the potential alpha-helix mimetics synthesised as a result of the strategy developed throughout the course of this project will be screened against key cancer drug targets in a range of biophysical & biochemical assays in the Drug Discovery Laboratory at the Beatson Institute, Glasgow.

5 Future Work

The most obvious area for future work is the development of a suite of compounds based on the pyridyl cyclopropyl framework at the heart of intermediate **13**. Based on this, it can be reasoned that an expansive array of fragments, possessing this scaffold, could be accessed in an expedient fashion. As such, it follows that a comprehensve investigation into the applicability of compound **13** within the realms of metal-mediated transformations, such as the Suzuki and Buchwald-Hartwig reactions, would serve to enhance the range of compounds obtainable (**Scheme 34**). In addition, it follows that compounds of the type **40** could undergo a reduction protocol to offer access to a range of amine analogues. Indeed, these approaches perhaps represent the logical progression of the project.



Scheme 34

Having said this, it follows that the development of a range of novel scaffolds would allow a greater area of chemical space to be probed. As such, substituting the cyclopropyl moiety for that of an oxetane, **42**, or azetidine, **43**, based species would allow an even greater range of chemical entities to be accessed (**Figure 11**). It is envisaged that the chemistry developed within this programme could feasibly be transferred to the scaffolds illustrated below, further showcasing the wide applicability of the synthetic protocols discussed.

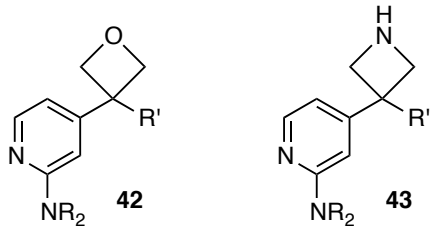


Figure 11

As discussed previously, the establishment of the 3D consortium represents a significant effort on the part of British-based researchers to embrace fragment based drug discovery as a potential means of discovering new therapeutic agents. In relation to this, there are a plethora of options available with respect to furthering the development of novel fragments. More specifically however, the developments suggested above represent worthwhile avenues of investigation with respect to immediate future research.

6 Experimental

6.1 General

All reagents were obtained from commercial suppliers (Aldrich, Alfa Aesar or Strem) and used without further purification, unless otherwise stated. All reactions were carried out under an inert, dry nitrogen atmosphere, unless otherwise stated. In cases where degassed solvent was employed: nitrogen was bubbled through the appropriate solvent for 5 minutes.

Thin Layer Chromatography was carried out using Camlab silica plates coated with fluorescent indicator UV254. These were then analysed using a Mineralight UVGL-25 lamp and developed using vanillin or potassium permanganate solutions.

Flash Column Chromatography was carried out using a Biotage Isolera Four, fitted with Biotage SNAP cartridges.

Liquid Chromatography – Mass Spectrometry was carried out using an Acquity Ultra Performance Liquid Chromatography system, fitted with a BEH C18 1.7 μm 2.1 x 50 mm column. Employing either a basic gradient of 5-95% 0.1% ammonium hydroxide in MeCN : 0.1% ammonium hydroxide in 10 mM aqueous ammonium bicarbonate solution or an acidic gradient of 5-95% 0.1% Formic Acid in MeCN : 0.1% formic acid in H_2O. Unless otherwise stated, formation of organometallics was monitored by quenching a small aliquot of the reaction mixture with acetone and conducting LC-MS analysis on the resulting alcohol.

Preparative High Performance Liquid Chromatography was carried out using a Waters High-Performance Liquid Chromatography (HPLC) system, fitted with an XBridge Prep C18 5 μm OBD 19 x 100 mm column. Employing a basic gradient of 5-95% 0.1% ammonium hydroxide in MeCN : 0.1% ammonium hydroxide in 10 mM aqueous ammonium bicarbonate solution.

IR spectra were obtained on a Perkin Elmer Spectrum 1 machine.

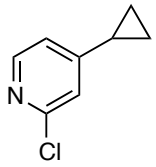
^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer at 400 MHz and 100 MHz, respectively, or a Bruker DRX 500 spectrometer at 500 MHz and 125 MHz, respectively. Chemical shifts are reported in ppm. Coupling constants are reported in Hz and refer to $^{3}J_{H\text{-}H}$ interections, unless otherwise stated. Note: $CDCl_3$ solvent signals were used as internal reference points at δ 7.26 and 77.16 ppm for ^{1}H and ^{13}C NMR respectively.

Reactions performed under microwave irradiation were carried out in a CEM Discover instrument using sealed glass tubes.

High resolution mass spectra were recorded on a Finnigan MAT 90XLT instrument at the EPSRC Mass Spectrometry facility at Swansea University, Wales.

6.2 Synthetic Substrates and Procedures

Preparation of 2-chloro-4-cyclopropylpyridine, ***21***[41]



General Procedure A

A microwave vial, fitted with a magnetic stirrer bar, was charged with palladium acetate and triphenylphosphine. The mixture was solubilised in a previously degassed mixture of 1,4-dioxane (2 ml) and water (1 ml). This suspension was stirred for 10 minutes followed by the addition of 4-bromo-2-chloropyridine, cyclopropyl boronic acid pinacol ester, and base. The resulting mixture was heated under microwave irradiation at 120°C for 20 minutes. Following this, the sample was concentrated *in vacuo* and the resulting oil was solubilised in Et_2O and washed with water. The aqueous portion was further washed with Et_2O. The combined organics were washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography (eluent: DCM to 2.5% MeOH in DCM) to furnish the desired product, **21**, as a colourless oil.

Following the *General Procedure A*, data are presented as (a) amount of $Pd(OAc)_2$, (b) amount of phosphine, (c) amount of 4-bromo-2-chloropyridine, (d) amount of cyclopropyl boronic acid pinacol ester, (e) base, and (f) product **21**.

Table 1, Entry 1

(a) 7 mg, 0.03 mmol, (b) 32 mg, 0.12 mmol, (c) 136 mg, 0.71 mmol, (d) 100 mg, 0.60 mmol, (e) K_2CO_3, 170 mg, 1.27 mmol, and (f) 20 mg, 26% yield.

Table 1, Entry 2

(a) 7 mg, 0.03 mmol, (b) 32 mg, 0.12 mmol, (c) 136 mg, 0.71 mmol, (d) 100 mg, 0.60 mmol, (e) Cs_2CO_3, 416 mg, 1.27 mmol, and (f) 49 mg, 54% yield.

General Procedure B

A round-bottom flask fitted with a reflux condensor and magnetic stirrer bar was charged with palladium acetate and triphenylphosphine. The mixture was solubilised in a previously degassed mixture of 1,4-dioxane (2 ml) and water (1 ml). This suspension was stirred at room temperature for 16 hours followed by the addition of 4-bromo-2-chloropyridine, cyclopropyl boronic acid pinacol ester, and base. The mixture was then heated to reflux and allowed to stir for 16 hours. After this time, the sample was concentrated *in vacuo*. The resulting oil was solubilised in Et_2O and washed with water. The aqueous portion was washed with a further quantity of Et_2O. The combined organics were given a brine wash, dried over magnesium sulfate, filtered, and concentrated in vacuo. The resulting oil was purified by flash column chromatography (0 to 2.5% MeOH in DCM) to furnish the desired product, **21**, as a clear oil.

Following the *General Procedure B*, data are presented as (a) amount of $Pd(OAc)_2$, (b) amount of phosphine, (c) amount of 4-bromo-2-chloropyridine, (d) amount of cyclopropyl boronic acid pinacol ester, (e) base, and (f) product **21**.

Table 1, Entry 3

(a) 7 mg, 0.03 mmol, (b) 32 mg, 0.12 mmol, (c) 136 mg, 0.71 mmol, (d) 100 mg, 0.60 mmol, (e) K_2CO_3, 170 mg, 1.27 mmol, and (f) 30 mg, 33% yield.

Table 1, Entry 4

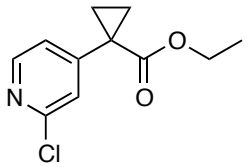
(a) 7 mg, 0.03 mmol, (b) 32 mg, 0.12 mmol, (c) 136 mg, 0.71 mmol, (d) 100 mg, 0.60 mmol, (e) Cs_2CO_3, 416 mg, 1.27 mmol, and (f) 86 mg, 94% yield.

IR (DCM): 1372, 895 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 8.21 (d, 1H, *J* = 5.2 Hz, ArH), 7.00 (s, 1H, ArH), 6.87 (d, 1H, *J* = 5.2 Hz ArH), 1.89-1.85 (m, 1H, cyclopropyl CH), 1.16-1.11 (m, 2H, cyclopropyl CH_2), 0.86-0.82 ppm (m, 2H, cyclopropyl CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): 156.9, 151.1, 148.7, 120.5, 119.0, 14.4, 10.3 ppm.

Attempted preparation of ethyl-1-(2-chloropyridin-4-yl)cyclopropanecarboxylate, ***13***



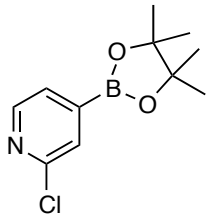
Scheme 6

To a 3-necked round-bottom flask fitted with a magnetic stirrer bar, low temperature thermometer, and nitrogen inlet was added 2-chloro-4-cyclopropylpyridine (80 mg, 0.52 mmol) and THF (5 ml). The reaction mixture was cooled to -78°C with the aid of an acetone/dry ice bath, prior to the dropwise addition of *n*-BuLi (0.36 ml, 1.6 M in THF, 0.57 mmol), care was taken to ensure the internal temperature remained below -55°C. The reaction mixture was allowed to warm to -40°C over 1.5 hours before cooling to -78°C, followed by the dropwise addition of ethyl chloroformate (59 mg, 0.55 mmol). The reaction mixture was allowed to warm to 0°C over 2 hours and stirred for a further hour. The mixture was then allowed to warm to room temperature and stirred for 16 hours. Whilst LC-MS analysis revealed complete consumption of starting material the desired product failed to form. This was confirmed by ^{1}H NMR analysis.

To a 3-necked round-bottom flask fitted with a magnetic stirrer bar, low temperature thermometer, and nitrogen inlet was added 2-chloro-4-cyclopropylpyridine (80 mg, 0.52 mmol) and THF (5 ml). The reaction mixture was cooled to -78°C with the aid of an acetone/dry ice bath, prior to the dropwise addition of *n*-BuLi (0.36 ml, 1.6 M in THF, 0.57

mmol), care was taken to ensure the internal temperature remained below -60°C. The reaction mixture was allowed to stir at -78°C for 1.5 hours, followed by the dropwise addition of ethyl chloroformate (59 mg, 0.55 mmol). The reaction mixture was allowed to warm to 0°C over 2 hours and stirred for a further hour. The mixture was then allowed to warm to room temperature and stirred for 16 hours. Whilst LC-MS analysis revealed complete consumption of starting material, the desired product failed to form. This was confirmed by ^{1}H NMR analysis.

Preparation of 2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine, ***27***[42]



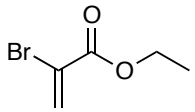
Scheme 8

A round-bottom flask, fitted with a reflux condenser and magnetic stirrer bar, was charged with a solution of 4-bromo-2-chloropyridine (500 mg, 2.60 mmol) in 1,4-dioxane (5 ml). The mixture was degassed (argon bubbled through for 20 minutes) before the addition of bis(pinacolato)diboron (857 mg, 3.38 mmol), potassium acetate (510 mg, 5.20 mmol) and $PdCl_2$(dppf) (53 mg, 0.07 mmol). The resulting suspension was allowed to stir at 80°C for 16 hours. The mixture was allowed to cool and filtered over celite. The celite was washed through with EtOAc, and the resulting organic solution was washed sequentially with water and brine. The aqueous phase was washed with EtOAc and the organic layers were combined before being dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography (0 to 5% MeOH in DCM), resulting in the isolation of **27** as a colourless oil (282 mg, 56% yield).

IR (DCM): 2938, 1372, 1141 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 8.42 (d, 1H, J = 4.7 Hz, ArH), 7.70 (s, 1H, ArH), 7.55 (d, 1H, J = 4.7 Hz, ArH) 1.37 ppm (s, 12H, CH_3).
^{13}C NMR (100 MHz, $CDCl_3$): 152.4, 148.8, 142.1, 129.1, 126.6, 84.4, 24.3 ppm.

Preparation of ethyl 2-bromoacrylate, ***25***[39]



Scheme 10, Table 2

Entry 1

To a round-bottom flask fitted with a magnetic stirrer bar and reflux condensor was added ethyl 2,3-dibromopropionate (750 mg, 2.89 mmol), and DMSO (9 ml). The resulting mixture was heated to 75°C and allowed to stir for 16 hours. Both LC-MS and ^{1}H NMR analysis indicated that only starting material was present.

Entry 2

To a round-bottom flask fitted with a magnetic stirrer bar and reflux condensor was added ethyl 2,3-dibromopropionate (750 mg, 2.89 mmol), DMSO (9 ml), and water (0.09 ml). The resulting mixture was heated to 75°C and allowed to stir for 16 hours. Both LC-MS and ^{1}H NMR analysis indicated that only starting material was present.

Entry 3

To a round-bottom flask fitted with a magnetic stirrer bar and reflux condensor was added ethyl 2,3-dibromopropionate (750 mg, 2.89 mmol), DMSO (9 ml), and water (0.45 ml). The reaction mixture was heated to 75°C and allowed to stir for 16 hours. Both LC-MS and ^{1}H NMR analysis indicated that only starting material was present.

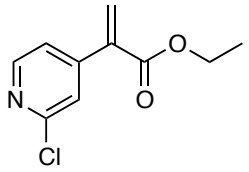
Scheme 11

To a round-bottom flask fitted with a magnetic stirrer bar and internal low temperature thermometer was added ethyl 2,3-dibromopropionate (1500 mg, 5.77 mmol), diethyl ether (5 ml), and hexane (5 ml). The resulting mixture was cooled to 0°C prior to the dropwise addition of triethylamine (842 ml, 6.05 mmol). Upon addition of the base a white precipitate crashed out of solution. The slurry was warmed to room temperature and stirred for 5 hours. Following this, the white precipitate was filtered and washed with hexane. The organic phase was washed sequentially with water and brine. The aqueous layers were combined and extracted with diethyl ether. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield ethyl 2-bromoprop-2-enoate, **25**, (866 mg, 3.484 mmol, 88 % yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): 6.95 (d, 1H, J = 1.6 Hz, olefinic CH), 6.26 (d, 1H, J = 1.6 Hz, olefinic CH), 4.29 (q, 2H, J = 7.1 Hz, CH_2), 1.34 ppm (t, 3H, J = 7.1 Hz, CH_3).
^{13}C NMR (100 MHz, $CDCl_3$): 162.1, 132.4, 121.0, 63.1, 14.4 ppm.

Due to the unstable nature of the compound an IR spectrum was not obtained.

Attempted Preparation of ethyl-2-(2-chloropyridin-4-yl)acrylate, ***24***



General Procedure

To a round bottom flask fitted with a magnetic stirrer bar and reflux condensor was added **27** and degassed solvent. To this mixture was added ethyl 2-bromoprop-2-enoate, tetrakistriphenylphosphine palladium, and base. The resulting suspension was stirred at 80°C for 16 hours. The crude residue was analysed by LC-MS and ^{1}H NMR analysis.

Following the *General Procedure*, data are presented as (a) amount of **27**, (b) volume of solvent, (c) amount of 2-bromoprop-2-enoate, (d) amount of tetrakistriphenylphosphine palladium, (e) amount of base, and (f) outcome.

Table 3,

Entry 1

(a) 90 mg, 0.38 mmol, (b) 1,4-dioxane (2 ml) and water (1 ml), (c) 80 mg, 0.45 mmol, (d) 11 mg, 0.01 mmol, (e) Cs_2CO_3, 159 mg, 0.49 mmol, and (f) desired product failed to form.

Entry 2

(a) 90 mg, 0.38 mmol, (b) 1,4-dioxane (2 ml) and water (1 ml), (c) 80 mg, 0.45 mmol, (d) 11 mg, 0.01 mmol, (e) K_2CO_3, 83 mg, 0.60 mmol, and (f) desired product failed to form.

For the following two reaction attempts, the ester substrate, ***25****, was purified by flash column chromatography immediately prior to use.*

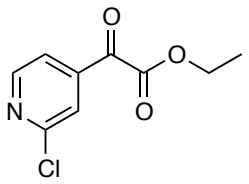
Entry 3

(a) 90 mg, 0.38 mmol, (b) 1,4-dioxane (2 ml) and water (1 ml), (c) 80 mg, 0.45 mmol, (d) 11 mg, 0.01 mmol, (e) Cs_2CO_3, 159 mg, 0.49 mmol, and (f) desired product failed to form.

Entry 4

(a) 90 mg, 0.38 mmol, (b) 1,4-dioxane (2 ml) and water (1 ml), (c) 80 mg, 0.45 mmol, (d) 11 mg, 0.01 mmol, (e) K_2CO_3, 83 mg, 0.60 mmol, and (f) desired product failed to form.

Preparation of ethyl 2-(2-chloropyridin-4-yl)-2-oxoacetate, ***28***



Preliminary experiments are detailed under Scheme 14 and Scheme 15, below.

Scheme 14

To a previously oven dried 3-necked round-bottom flask fitted with a magnetic stirrer bar, nitrogen inlet and low temperature internal thermometer was added 4-bromo-2-chloropyridine (190 mg, 0.99 mmol) and THF (4 ml). The solution was cooled to -15°C followed by dropwise addition of isopropylmagnesium chloride (0.75 ml, 1.3 M in THF, 0.99 mmol). The mixture was allowed to warm to 0^{o}C over 2 hours. LC-MS analysis indicated that the desired Grignard reagent failed to form.

Scheme 15

To a previously oven dried 3-necked round-bottom flask fitted with a magnetic stirrer bar, nitrogen inlet and low temperature internal thermometer was added 4-bromo-2-chloropyridine (190 mg, 0.99 mmol) and THF (4 ml). The solution was cooled to -15°C followed by dropwise addition of isopropylmagnesium chloride (0.75 ml, 1.3 M in THF, 0.99 mmol). The mixture was allowed to warm to room temperature over 3 hours. LC-MS analysis indicated that the desired Grignard reagent failed to form.

Scheme 16, Table 6 - General Procedure

To a previously oven dried 3-necked round-bottom flask fitted with a magnetic stirrer bar, nitrogen inlet, and internal low temperature thermometer was added 4-bromo-2-chloropyridine and THF. The resulting mixture was cooled to -15°C, followed by the

dropwise addition of isopropylmagnesium chloride lithium chloride complex (1.3 M in THF). The mixture was allowed to warm to 0°C, over 1 h, at which point the pale yellow solution became a dark red/purple and the mixture was analysed by LC-MS. The solution was cooled to -15°C and diethyl oxalate was added. The solution was allowed to warm to room temperature and stirred for 16 hours. The reaction was queched with aqueous ammonium chloride and diluted with diethyl ether. The organic phase was washed with water and then brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The resulting crude oil was purified by flash column chromatography (0 to 7.5% MeOH in DCM) to yield **28** as a colourless oil.

Following the *General Procedure*, data are presented as (a) amount of 4-bromo-2-chloropyridine, (b) volume of THF (c) amount of isopropylmagnesium chloride lithium chloride complex, (d) amount of diethyl oxalate, (e) product **28**.

Entry 1

(a) 190 mg, 0.99 mmol, (b) 4 ml, (c) 0.75 ml, 1.3 M in THF, 0.99 mmol, (d) 159 mg, 1.09 mmol, (e) 130 mg, 55% yield.

Entry 2

(a) 1000 mg, 5.20 mmol, (b) 12 ml, (c) 4.00 ml, 1.3 M in THF, 5.20 mmol, (d) 763 mg, 5.31 mmol, (e) 680 mg, 62% yield.

Entry 3

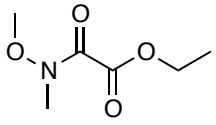
(a) 190 mg, 0.99 mmol, (b) 4 ml, (c) 0.75 ml, 1.3 M in THF, 0.99 mmol, (d) 159 mg, 1.09 mmol, (e) 153 mg, 65% yield.

IR (DCM): 3264, 2243, 1786, 1656 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): 8.65 (d, 1H, J = 5.1 Hz, ArH), 7.94 (s, 1H, ArH), 7.82 (d, 1H, J = 5.1 Hz), 4.50 (q, 2H, J = 7.2 Hz, CH_2), 1.46 ppm (t, 3H, J = 7.2 Hz, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): 180.4, 161.7, 153.5, 151.8, 150.5, 123.5, 120.7, 62.8, 13.5 ppm.

HRMS *m/z* (ESI) Calc. for $C_9H_9ClNO_3$ (M^++H): 214.0265. Found: 214.0264.

Preparation of ethyl-2-(methoxy(methyl)amino)-2-oxoacetate ***31***[43]



Scheme 17

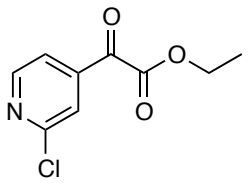
To a round bottom flask fitted with magnetic stirrer bar was added *N*,*O*-dimethylhydroxylamine hydrochloride (714 mg, 7.32 mmol) in DCM (12 ml). To the resulting slurry was added triethylamine (740 mg, 7.32 mmol) followed by dropwise addition of ethyl chlorooxoacetate (1000 mg, 7.32 mmol). The reaction was allowed to stir for 2 hours and then quenched with a saturated aqueous sodium hydrogen carbonate solution. The organic phase was then washed sequentially with dilute hydrochloric acid (12 ml), water, and brine. The aqueous phase were back washed with DCM. The organics were pooled, dried over $MgSO_4$, and concentrated *in vacuo* to yield **31** (1026 mg, 83% yield) as a colourless oil.

IR (DCM): 2985, 2941, 1749, 1683 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 4.36 (q, 2H, *J* = 6.8 Hz, OCH_2) 3.77 (s, 3H, OCH_3) 3.25 (s, 3H, NCH_3) 1.38 ppm (t, 3H, *J* = 6.8 Hz, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): 161.9, 161.6, 61.7, 61.5, 30.9, 13.4 ppm.

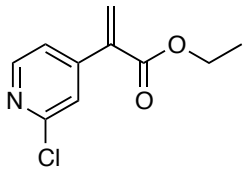
Preparation of ethyl 2-(2-chloropyridin-4-yl)-2-oxoacetate, ***28***



Scheme 18

To an oven-dried 3 necked round bottom flask fitted with a magnetic stirrer bar, nitrogen inlet, and internal low temperature thermometer was 4-bromo-2-chloropyridine (269 mg, 1.40 mmol) and THF (4 ml). The mixture was cooled to -15°C and isopropylmagnesium chloride lithium chloride complex solution (1.08 ml, 1.3 M in THF, 1.40 mmol). added. After warming to 0°C over 1 hour, the mixture was cooled to -15°C and **31** (251 mg, 1.56 mmol) was added. The mixture was allowed to stir for 16 hours at room temperature. After this time the reaction was quenched with a saturated aqueous ammonium chloride solution and extracted into diethyl ether. The organic phase was then washed sequentially with a saturated aqueous sodium hydrogen carbonate solution, water, and brine. The organic phase was then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting crude oil was purified by flash column chromatography (0 to 5% MeOH in DCM) to yield **28** (158 mg, 57% yield) as a colourless oil.

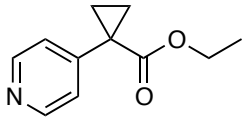
Attempted Preparation of ethyl 2-(2-chloropyridin-4-yl)acrylate, ***24***



Scheme 19

A round bottom flask fitted with a magnetic stirrer bar and nitrogen inlet was charged with a suspension of methyltriphenylphosphonium bromide (441 mg, 1.24 mmol) in THF (5 ml). The mixture was cooled to 0°C and a solution of potassium bis(trimethylsilyl)amide (246 mg, 1.24 mmol) was added dropwise. This mixture was stirred at 0°C for 15 min before being warmed to room temperature and stirred for a further 45 min. After this time the reaction mixture was cooled to 0°C, followed by the addition of a solution of **28** (220 mg, 1.03 mmol) in the minimum volume of THF. The reaction mixture was warmed to room temperature and stirred for 16 hours. Following this, the reaction was quenched by addition of a saturated aqueous ammonium chloride solution. The products were extracted into DCM, and washed sequentially with water and brine. The organics were then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (0 to 10% MeOH in DCM). LC-MS and TLC analysis of the isolated fractions indicated that the desired product had failed to form.

Preparation of ethyl 1-(pyridin-4-yl)cyclopropanecarboxylate, ***33***



Scheme 21*, *Table 5* - *General Procedure

To a round bottom flask fitted with a magnetic stirrer bar and nitrogen inlet was added **34** in THF, followed by the portionwise addition of sodium hydride. The resulting suspension was stirred at room temperature for 15 min, followed by the dropwise addition of 1,2-dibromoethane. The solution was allowed to stir for 3 hours, prior to dilution with a saturated aqueous sodium hydrogen carbonate solution. The mixture was extracted into

DCM, washed with water, and brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The material was then purified by flash column chromatography (0 to 10% MeOH in DCM) to yield **33** as a yellow oil.

Following the *General Procedure*, data are presented as (a) amount of **34**, (b) volume of THF (c) amount of sodium hydride, (d) amount of dibromoethane, (e) product **33**.

Entry 1

(a) 250 mg, 1.51 mmol, (b) 4.5 ml, (c) 180 mg, 7.50 mmol, (d) 845 mg, 4.50 mmol, (e) 190 mg, 66% yield.

Entry 2

(a) 250 mg, 1.51 mmol, (b) 4.5 ml, (c) 180 mg, 7.50 mmol, (d) 845 mg, 4.50 mmol, (e) 208 mg, 72% yield.

Entry 3

(a) 1,000 mg, 6.05 mmol, (b) 14 ml, (c) 800 mg, 33.35 mmol, (d) 3,400 mg, 18.10 mmol, (e) 1,136 mg, 65% yield.

Entry 4

(a) 1,000 mg, 6.05 mmol, (b) 14 ml, (c) 800 mg, 33.35 mmol, (d) 3,400 mg, 18.10 mmol, (e) 1,276 mg, 73% yield.

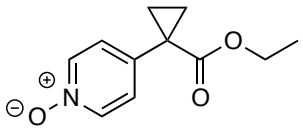
IR (DCM): 2993, 2255, 1792, 1285 cm^{-1}.

^1H NMR (400 MHz, d^6-DMSO): 8.56 (d, 2H, J = 6.0 Hz, ArH), 7.26 (d, 2H, J = 6.0 Hz, ArH), 4.14 (q, 2H, J = 7.2 Hz, OCH_2), 1.69 - 1.66 (m, 2H, cyclopropyl CH_2), 1.24 - 1.21 (m, 2H, cyclopropyl CH_2), 1.19 ppm (t, 3H, J = 7.2 Hz).

^{13}C NMR (100 MHz, d^6-DMSO): 173.0, 149.6, 148.4, 125.2, 122.0, 61.3, 28.4, 15.4 ppm.

HRMS *m/z* (ESI) Calc. for $C_{11}H_{14}NO_2$ (M^++H): 192.1019. Found: 192.1018.

Preparation of 4-(1-(ethoxycarbonyl)cyclopropyl)pyridine 1-oxide, ***32***



Scheme 22

To a round-bottom flask fitted with a magnetic stirrer bar and nitrogen inlet was added ethyl 1-(4-pyridyl)cyclopropanecarboxylate (1,100 mg, 5.75 mmol) and DCM (22 ml), with the resulting solution being allowed to stir for 5 minutes before the addition of *m*-CPBA (1,390 mg, 8.05 mmol). The mixture was then allowed to stir for 16 hours at room temperature and then quenched with a saturated aqueous solution of sodium sulfite and extracted with DCM. The organics were then further washed with a saturated aqueous solution of $NaHCO_3$, water, and brine. The organics were pooled, dried over $MgSO_4$, filtered, and then concentrated *in vacuo*. The crude mixture was then purified by flash column chromatography (0 to 5% MeOH in DCM) to yield **32** (834 mg, 70 % yield) as a white powder.

Melting Point: 104-106°C.

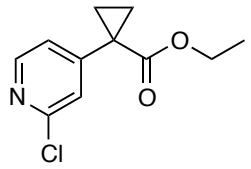
IR (DCM): 3568, 2255, 1292 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): 8.17 (d, 2H, J = 7.3 Hz, ArH), 7.25 (d, 2H, J = 7.3 Hz, ArH), 4.14 (q, 2H, J = 7.0 Hz, $COCH_2$), 1.73 – 1.70 (m, 2H, cyclopropane CH_2), 1.21 (t, 3H, J = 7.0 Hz, CH_2CH_3) 1.19-1.16 ppm (m, 2H, cyclopropane CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): 164.7, 143.2, 138.7, 127.7, 61.6, 26.9, 16.7, 14.1 ppm.

HRMS *m/z* (ESI) Calc. for $C_{11}H_{14}NO_2$ (M^++H): 208.0968. Found: 208.0969.

*Preparation of ethyl 1-(2-chloropyridin-4-yl)cyclopropanecarboxylate **13***



Scheme 23, Table 6 - General Procedure

To a 3-necked round bottom flask fitted with a magnetic stirrer bar and reflux condenser was added **32** and the appropriate solvent. To this stirred solution was added dropwise phosphorus oxychloride and the mixture allowed to stir for 30 minutes before being heated to reflux for 16 hours. The mixture was cooled to room temperature and the excess $POCl_3$ was removed by evaporation. The resulting oil was solubilised in DCM and washed sequentially with a saturated aqueous sodium hydrogen carbonate solution, water, and brine. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The material was then purified by flash column chromatography (0 to 5% MeOH in DCM) to give to yield **13** as a yellow/brown oil.

Following the *General Procedure*, data are presented as (a) amount of **32**, (b) volume of solvent, (c) amount of $POCl_3$, (d) product **13**.

Entry 1

(a) 120 mg, 0.58 mmol, (b) 1,4-dioxane, 4 ml, (c) 222 mg, 1.45 mmol, (d) 62 mg, 47% yield.

Entry 2

(a) 120 mg, 0.58 mmol, (b) PhMe, 4 ml, (c) 222 mg, 1.45 mmol, (d) 72 mg, 55% yield.

***Scheme 24*, *Table 7* - General Procedure**

To a microwave vial fitted with a magnetic stirrer bar, was added **32** and the appropriate solvent. To this solution was added phosphorus oxychloride and the mixture was heated to 120°C under microwave irradiation for 20 min. The mixture was cooled to room temperature and the excess $POCl_3$ was removed by evaporation. The resulting oil was solubilised in DCM and washed sequentially with a saturated aqueous solution of sodium hydrogen carbonate, water, and brine. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The material was then purified by flash column chromatography (0 to 5% MeOH in DCM) to give to yield **13** as a yellow/brown oil.

Following the *General Procedure*, data are presented as (a) amount of **32**, (b) volume of solvent, (c) amount of $POCl_3$, (d) outcome.

Entry 1

(a) 120 mg, 0.58 mmol, (b) PhMe, 2 ml, (c) 222 mg, 1.45 mmol, (d) 68 mg, 52% yield.

Entry 2

(a) 120 mg, 0.58 mmol, (b) 1,4-dioxane, 2 ml, (c) 222 mg, 1.45 mmol, (d) 66 mg, 51% yield.

Scheme 26

To a round bottom flask fitted with a magnetic stirrer bar was added 2-chloro-4-methylpyridine (250 mg, 1.96 mmol) and THF (8 ml). The mixture was cooled to -78°C and LDA (1.09 ml, 1.8 M in THF/hexane, 1.96 mmol) was added dropwise over 15 min. The mixture was allowed to stir for 2 hours, followed by the dropwise addition of diethyl carbonate (266 mg, 2.25 mmol). The reaction was allowed to warm to room temperature and stirred for 16 hours. After this time, the reaction was quenched with a saturated aqueous solution of ammonium chloride, extracted into ethyl acetate, and concentrated *in vacuo*. LC-MS analysis of the reaction mixture indicated the formation of the crude material, **35**. The

material was solubilised in THF (12 ml), followed by the portionwise addition of sodium hydride (235 mg, 9.80 mmol). The suspension was allowed to stir for 15 minutes before the dropwise addition of dibromoethane (1,104 mg, 5.88 mmol). The mixture was stirred for 16 hours, before being quenched with a saturated aqueous solution of sodium hydrogen carbonate and diluted with ethyl acetate. The organic phase was washed sequentially with water and brine, then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The material was then purified by flash column chromatography (0 to 5% MeOH in DCM) to give to yield **13** (225 mg, 51% yield over 2 steps) as a yellow/brown oil.

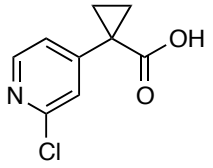
IR (DCM): 3061, 2937, 1716 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): 8.34 (d, 1H, J = 5.1 Hz, ArH), 7.31 (s, 1H, ArH), 7.21 (d, 1H, J = 5.1 Hz, ArH), 4.15 (q, 2H, J = 7.2 Hz, OCH_2), 1.69 (t, 3H, J = 7.2 Hz, CH_3), 1.29 – 1.27 (m, 2H, cyclopropane CH_2) 1.24 – 1.22 ppm (m, 2H, cyclopropane CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): 166.8, 162.5, 149.0, 132.4, 125.3, 123.7, 52.2, 28.2, 16.1, 13.6 ppm.

HRMS *m/z* (ESI) Calc. for $C_{11}H_{13}ClNO_2$ (M^++H): 226.0629. Found: 226.0631.

Preparation of 1-(2-chloropyridin-4-yl)cyclopropanecarboxylic acid, ***18***



Scheme 28

To a 3-necked round bottom-flask fitted with a magnetic stirrer bar, nitrogen inlet, and reflux condensor was added ethyl 1-(2-chloro-4-pyridyl)cyclopropanecarboxylate (240 mg, 1.06 mmol) and methanol (5 ml). To this stirred solution was added sodium hydroxide (2 M aq. soln 2 ml) and the resulting mixture heated to reflux and allowed to stir for 16 hours. The mixture was then allowed to cool to room temperature and acidified with aqueous citric acid

(4 ml). Following extraction with ethyl acetate, the mixture was washed with water, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 1-(2-chloro-4-pyridyl)cyclopropanecarboxylic acid, **18**, (185 mg, 82 % yield) as a white solid.

Melting Point: 120 - 122°C

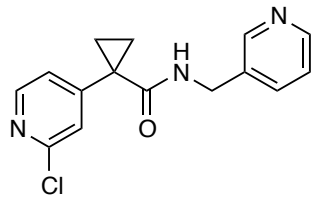
IR (DCM): 2738, 1770 cm^{-1}.

^1H NMR (400 MHz, d^6-DMSO): 8.19 (d, 1H, J = 5.1 Hz, ArH), 7.41 (s, 1H, ArH), 7.26 (d, 1H J = 5.1 Hz, ArH), 1.29 - 1.26 (m, 2H, cyclopropyl CH_2), 0.87 – 0.84 ppm (m, 2H, cyclopropyl CH_2).

^{13}C NMR (100 MHz, d^6-DMSO): 173.4, 159.2, 149.9, 148.5, 125.1, 124.2, 29.7, 14.7 ppm.

HRMS *m/z* (ESI) Calc. for $C_9H_9ClNO_2$ (M^++H^+): 198.0316. Found: 198.0315.

Preparation of 1-(2-chloropyridin-4-yl)-N-(pyridin-2-ylmethyl)cyclopropanecarboxamide, ***39***



Scheme 29

To a round-bottom flask equipped with magnetic stirrer bar and nitrogen inlet was added **18** (15 mg, 0.08 mmol) in a solution of DMF (0.01 ml) and DCM (2 ml). The resulting mixture was cooled to 0°C and oxalyl chloride (19 mg, 0.15 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and was stirred for 1 hour. LC-MS analysis indicated the formation of the desired acid chloride. The solution was concentrated *in vacuo* and twice azeotroped with DCM (10 ml). The solid acid chloride was solubilised in DCM (2 ml) and added dropwise to a stirred solution of 3-picolylamine (0.01 ml, 0.08 mmol), triethylamine (0.02 ml, 0.15 mmol), and DCM (2 ml) at -78°C. The mixture

was allowed to warm to room temperature and was stirred for 16 hours. LC-MS and ^{1}H NMR analysis confirmed that the desired product had failed to form.

Scheme 30

To a solution of **18** (20 mg, 0.10 mmol) stirring in DMF (1 ml) was added HATU (47 mg, 0.12 mmol), triethylamine (21 mg, 0.20 mmol), and 3-picolylamine (11 mg, 0.10 mmol). The reaction mixture was then allowed to stir at room temperature for 16 hours before concentrating *in vacuo* to yield a crude yellow oil. The oil was solubilised in methanol (0.5 ml) before purifying by preparative HPLC to yield **39** (17 mg, 53 % yield) as a white solid.

Melting Point: 112 - 114°C.

IR (DCM): 3436, 2254, 1677 cm^{-1}.

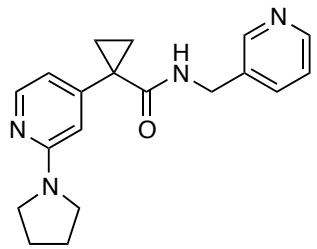
^{1}H NMR (400 MHz, $CDCl_3$): 8.54 (bs, 1H, ArH), 8.49 (bs, 1H, ArH), 8.38 (d, 1H, J = 5.1 Hz, ArH), 7.60 – 7.57 (m, 1H, ArH), 7.39 – 7.36 (m, 1H, ArH), 7.26 – 7.20 (m, 2H, ArH), 4.44 (d, 2H, J = 6.6 Hz, CH_2Ar), 1.72 – 1.69 (m, 2H, cyclopropyl CH_2), 1.13 – 1.10 ppm (m, 2H, cyclopropyl CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): 176.6, 154.7, 151.8, 150.4, 150.1, 149.4, 149.0, 135.4, 126.2, 124.5, 123.8, 41.7, 39.8, 15.7 ppm.

HRMS *m/z* (ESI) Calc. for $C_{15}H_{15}ClN_3O$ (M^++H): 288.0898. Found: 288.0895.

X-Ray analysis was conducted on this species, full X-ray data can be found in the appendix.

Preparation of N-(pyridin-2-ylmethyl)-1-(2-(pyrrolidin-1-yl)pyridin-4-yl)cyclopropanecarboxamide, ***37***



Scheme 31

To a microwave vial equipped with a stirrer bar was added pyrrolidine (0.03 ml, 0.350 mmol), **39** (50 mg, 0.17 mmol) and 1,4-dioxane (0.5 ml). The mixture was heated in the microwave at 120°C for 40 minutes. Incomplete conversion of the starting material was observed by LC-MS analysis, and so the mixture was irradiated for a further 40 minutes at 120°C. The resulting mixture was concentrated *in vacuo*, diluted with DCM, and washed sequentially with a saturated aqueous sodium hydrogen carbonate solution, water, and brine. The organic phase was then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude oil was then purified by preperative HPLC to yield **37** (28 mg, 53 % yield) as a white solid.

Melting Point: 122 - 124°C.

IR (DCM): 3691, 3433, 1654 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): 8.53- 8.51 (m, 1H, ArH), 8.49 – 8.46 (m, 1H, ArH), 7.68 – 7.66 (m, 1H, ArH), 7.60 – 7.57 (m, 1H, ArH), 7.26 – 7.24 (m, 1H, ArH), 6.60 – 6.58 (m, 1H, ArH), 6.43 – 6.40 (m, 1H, ArH), 4.42 (d, 2H, J = 6.1 Hz, CH_2Ar), 3.49 – 3.46 (m, 4H, NCH_2CH_2), 2.04 – 2.01 (m, 4H, NCH_2CH_2), 1.64 – 1.62 (m, 2H, cyclopropyl CH_2), 1.10 – 1.07 ppm (m, 2H, cyclopropyl CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): 172.8, 149.5, 148.9, 148.8, 148.5, 135.3, 134.0, 123.5, 113.0, 108.3, 47.0, 46.9, 41.5, 30.3, 25.5, 15.45 ppm.

HRMS *m/z* (ESI) Calc. for $C_{19}H_{23}N_4O$ (M^++H): 323.1866. Found: 323.1870.

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Appendix

1. Crystal Data for **39**

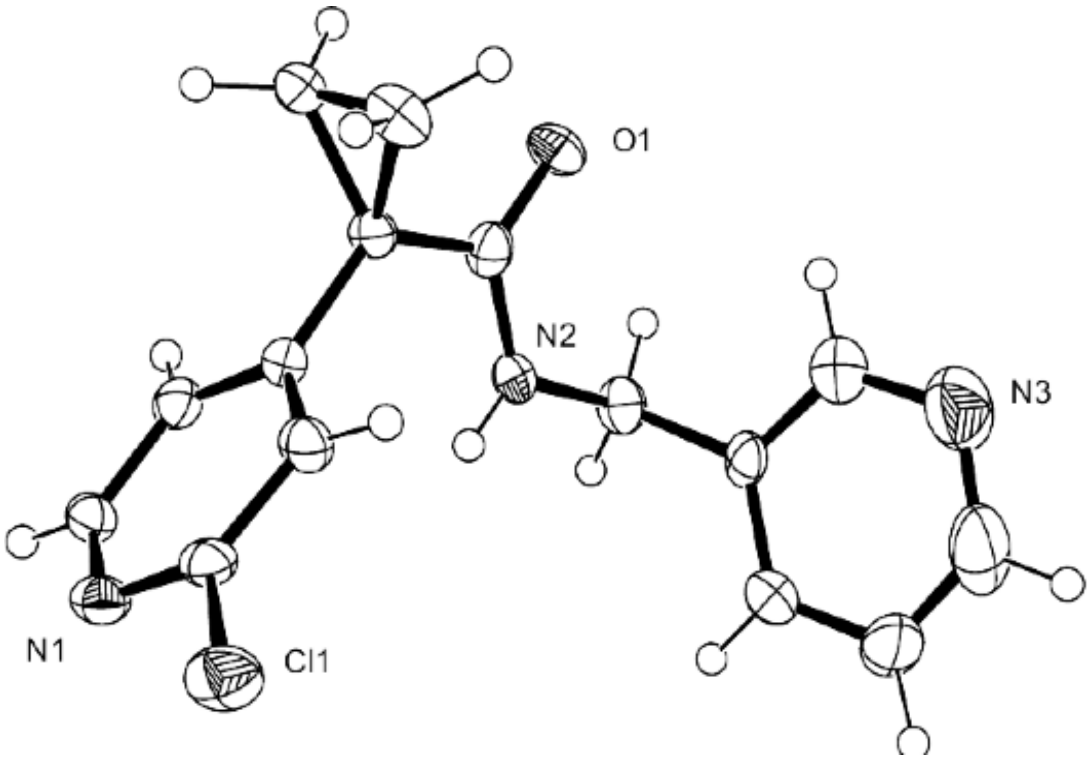


Table 1. Crystal data and structure refinement for p21kerr062011.

Identification code	p21kerr062011	
Empirical formula	C15 H14 Cl1 N3 O1	
Formula weight	287.74	
Temperature	123(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 9.5350(8) Å	⟨= 90°.
	b = 10.2195(9) Å	®= 101.360(9)°.

	c = 14.4426(13) Å © = 90°.
Volume	1379.8(2) $Å^3$
Z	4
Density (calculated)	1.385 Mg/m^3
Absorption coefficient	0.276 mm^{-1}
F(000)	600
Crystal size	0.4 x 0.15 x 0.08 mm^3
Theta range for data collection	2.88 to 26.00°.
Index ranges	-10<=h<=11, -12<=k<=12, -17<=l<=17
Reflections collected	11915
Independent reflections	5431 [R(int) = 0.0546]
Completeness to theta = 26.00°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.58757
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5431 / 1 / 370
Goodness-of-fit on F^2	1.034
Final R indices [I>2sigma(I)]	R1 = 0.0589, wR2 = 0.1162
R indices (all data)	R1 = 0.1054, wR2 = 0.1446
Absolute structure parameter	0.40(10)
Largest diff. peak and hole	0.276 and -0.343 $e.Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for p21kerr062011. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1)	5588(1)	5550(1)	1738(1)	39(1)
Cl(2)	10491(1)	-796(1)	1605(1)	36(1)
O(1)	12930(3)	3278(4)	2807(2)	33(1)
O(2)	17903(3)	1374(4)	2673(2)	32(1)
N(1)	6341(4)	3768(4)	649(3)	28(1)

N(2)	10817(5)	2292(5)	2847(3)	26(1)
N(3)	11988(6)	3260(5)	5885(3)	65(2)
N(4)	11296(4)	963(4)	526(3)	27(1)
N(5)	15833(5)	2302(5)	2853(3)	27(1)
N(6)	16156(4)	3543(4)	6134(3)	36(1)
C(1)	6855(6)	4573(5)	1354(3)	26(1)
C(3)	7310(5)	3023(6)	337(3)	27(1)
C(4)	8763(5)	3088(6)	700(3)	28(1)
C(5)	9266(5)	3970(5)	1424(3)	23(1)
C(6)	8270(5)	4728(5)	1778(3)	27(1)
C(7)	10842(5)	4123(5)	1792(3)	23(1)
C(8)	11626(6)	3191(5)	2517(3)	27(1)
C(9)	11420(5)	1372(5)	3597(3)	29(1)
C(10)	11205(5)	1833(6)	4549(3)	27(1)
C(11)	10065(6)	1426(7)	4928(4)	55(2)
C(12)	9891(6)	1944(8)	5794(4)	66(2)
C(13)	10860(7)	2818(9)	6218(4)	71(3)
C(15)	12125(6)	2738(6)	5050(3)	49(2)
C(16)	11438(6)	5503(6)	1885(3)	34(1)
C(17)	11730(6)	4663(5)	1114(3)	32(1)
C(21)	11777(5)	197(5)	1236(3)	26(1)
C(23)	12294(5)	1707(5)	233(3)	28(1)
C(24)	13734(5)	1628(5)	608(3)	24(1)
C(25)	14214(5)	755(5)	1337(3)	23(1)
C(26)	13200(6)	50(5)	1681(3)	25(1)
C(27)	15779(5)	537(6)	1714(3)	23(1)
C(28)	16593(5)	1439(5)	2446(3)	24(1)
C(29)	16502(5)	3164(6)	3594(3)	30(1)
C(30)	16290(5)	2785(6)	4565(3)	26(1)
C(31)	16340(5)	3746(5)	5244(3)	29(1)
C(33)	15950(6)	2292(6)	6356(3)	37(1)
C(34)	15943(5)	1268(5)	5749(3)	35(1)
C(35)	16111(5)	1506(5)	4832(3)	33(1)
C(36)	16634(6)	-15(5)	1022(3)	31(1)
C(37)	16297(6)	-865(6)	1792(3)	35(1)

Table 3. Bond lengths [Å] and angles [°] for p21kerr062011.

Cl(1)-C(1)	1.740(5)
Cl(2)-C(21)	1.754(5)
O(1)-C(8)	1.234(6)
O(2)-C(28)	1.229(5)
N(1)-C(1)	1.326(6)
N(1)-C(3)	1.342(6)
N(2)-C(8)	1.346(6)
N(2)-C(9)	1.463(6)
N(2)-H(1N)	0.83(5)
N(3)-C(13)	1.340(8)
N(3)-C(15)	1.348(6)
N(4)-C(21)	1.300(6)
N(4)-C(23)	1.350(6)
N(5)-C(28)	1.348(6)
N(5)-C(29)	1.434(6)
N(5)-H(2N)	0.84(5)
N(6)-C(33)	1.342(7)
N(6)-C(31)	1.347(5)
C(1)-C(6)	1.377(6)
C(3)-C(4)	1.382(6)
C(3)-H(3)	0.9500
C(4)-C(5)	1.392(6)
C(4)-H(4)	0.9500
C(5)-C(6)	1.399(6)
C(5)-C(7)	1.500(6)
C(6)-H(6)	0.9500
C(7)-C(8)	1.501(7)
C(7)-C(16)	1.517(8)
C(7)-C(17)	1.518(6)
C(9)-C(10)	1.505(6)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900

C(10)-C(11)	1.374(7)
C(10)-C(15)	1.378(7)
C(11)-C(12)	1.398(8)
C(11)-H(11)	0.9500
C(12)-C(13)	1.343(9)
C(12)-H(12)	0.9500
C(13)-H(13)	0.9500
C(15)-H(15)	0.9500
C(16)-C(17)	1.476(7)
C(16)-H(16A)	0.9900
C(16)-H(16B)	0.9900
C(17)-H(17A)	0.9900
C(17)-H(17B)	0.9900
C(21)-C(26)	1.390(7)
C(23)-C(24)	1.376(6)
C(23)-H(23)	0.9500
C(24)-C(25)	1.387(6)
C(24)-H(24)	0.9500
C(25)-C(26)	1.375(6)
C(25)-C(27)	1.501(6)
C(26)-H(26)	0.9500
C(27)-C(28)	1.499(7)
C(27)-C(37)	1.512(7)
C(27)-C(36)	1.518(6)
C(29)-C(30)	1.506(6)
C(29)-H(29A)	0.9900
C(29)-H(29B)	0.9900
C(30)-C(31)	1.382(7)
C(30)-C(35)	1.383(7)
C(31)-H(31)	0.9500
C(33)-C(34)	1.364(7)
C(33)-H(33)	0.9500
C(34)-C(35)	1.386(6)
C(34)-H(34)	0.9500
C(35)-H(35)	0.9500

C(36)-C(37)	1.495(7)
C(36)-H(36A)	0.9900
C(36)-H(36B)	0.9900
C(37)-H(37A)	0.9900
C(37)-H(37B)	0.9900

C(1)-N(1)-C(3)	115.8(4)
C(8)-N(2)-C(9)	122.1(4)
C(8)-N(2)-H(1N)	121(3)
C(9)-N(2)-H(1N)	117(3)
C(13)-N(3)-C(15)	114.4(5)
C(21)-N(4)-C(23)	115.2(4)
C(28)-N(5)-C(29)	121.9(4)
C(28)-N(5)-H(2N)	117(4)
C(29)-N(5)-H(2N)	121(4)
C(33)-N(6)-C(31)	115.3(4)
N(1)-C(1)-C(6)	126.5(5)
N(1)-C(1)-Cl(1)	115.2(4)
C(6)-C(1)-Cl(1)	118.2(4)
N(1)-C(3)-C(4)	123.4(5)
N(1)-C(3)-H(3)	118.3
C(4)-C(3)-H(3)	118.3
C(3)-C(4)-C(5)	119.2(5)
C(3)-C(4)-H(4)	120.4
C(5)-C(4)-H(4)	120.4
C(4)-C(5)-C(6)	118.3(5)
C(4)-C(5)-C(7)	120.4(4)
C(6)-C(5)-C(7)	121.2(4)
C(1)-C(6)-C(5)	116.8(5)
C(1)-C(6)-H(6)	121.6
C(5)-C(6)-H(6)	121.6
C(5)-C(7)-C(8)	120.5(5)
C(5)-C(7)-C(16)	117.4(4)
C(8)-C(7)-C(16)	113.7(4)
C(5)-C(7)-C(17)	117.2(4)

C(8)-C(7)-C(17)	114.6(4)
C(16)-C(7)-C(17)	58.2(3)
O(1)-C(8)-N(2)	122.5(5)
O(1)-C(8)-C(7)	121.4(5)
N(2)-C(8)-C(7)	116.0(5)
N(2)-C(9)-C(10)	111.8(4)
N(2)-C(9)-H(9A)	109.3
C(10)-C(9)-H(9A)	109.3
N(2)-C(9)-H(9B)	109.3
C(10)-C(9)-H(9B)	109.3
H(9A)-C(9)-H(9B)	107.9
C(11)-C(10)-C(15)	117.8(5)
C(11)-C(10)-C(9)	122.0(5)
C(15)-C(10)-C(9)	120.2(5)
C(10)-C(11)-C(12)	118.9(6)
C(10)-C(11)-H(11)	120.5
C(12)-C(11)-H(11)	120.5
C(13)-C(12)-C(11)	117.9(6)
C(13)-C(12)-H(12)	121.0
C(11)-C(12)-H(12)	121.0
N(3)-C(13)-C(12)	126.1(6)
N(3)-C(13)-H(13)	117.0
C(12)-C(13)-H(13)	117.0
N(3)-C(15)-C(10)	124.9(5)
N(3)-C(15)-H(15)	117.6
C(10)-C(15)-H(15)	117.6
C(17)-C(16)-C(7)	61.0(3)
C(17)-C(16)-H(16A)	117.7
C(7)-C(16)-H(16A)	117.7
C(17)-C(16)-H(16B)	117.7
C(7)-C(16)-H(16B)	117.7
H(16A)-C(16)-H(16B)	114.8
C(16)-C(17)-C(7)	60.8(3)
C(16)-C(17)-H(17A)	117.7
C(7)-C(17)-H(17A)	117.7

C(16)-C(17)-H(17B)	117.7
C(7)-C(17)-H(17B)	117.7
H(17A)-C(17)-H(17B)	114.8
N(4)-C(21)-C(26)	126.2(5)
N(4)-C(21)-Cl(2)	115.4(4)
C(26)-C(21)-Cl(2)	118.4(4)
N(4)-C(23)-C(24)	123.6(5)
N(4)-C(23)-H(23)	118.2
C(24)-C(23)-H(23)	118.2
C(23)-C(24)-C(25)	119.4(5)
C(23)-C(24)-H(24)	120.3
C(25)-C(24)-H(24)	120.3
C(26)-C(25)-C(24)	117.4(4)
C(26)-C(25)-C(27)	120.7(5)
C(24)-C(25)-C(27)	121.8(5)
C(25)-C(26)-C(21)	117.9(5)
C(25)-C(26)-H(26)	121.0
C(21)-C(26)-H(26)	121.0
C(28)-C(27)-C(25)	120.3(4)
C(28)-C(27)-C(37)	114.4(4)
C(25)-C(27)-C(37)	117.0(5)
C(28)-C(27)-C(36)	115.0(4)
C(25)-C(27)-C(36)	116.1(4)
C(37)-C(27)-C(36)	59.1(3)
O(2)-C(28)-N(5)	121.7(5)
O(2)-C(28)-C(27)	120.8(5)
N(5)-C(28)-C(27)	117.5(4)
N(5)-C(29)-C(30)	114.6(4)
N(5)-C(29)-H(29A)	108.6
C(30)-C(29)-H(29A)	108.6
N(5)-C(29)-H(29B)	108.6
C(30)-C(29)-H(29B)	108.6
H(29A)-C(29)-H(29B)	107.6
C(31)-C(30)-C(35)	117.5(4)
C(31)-C(30)-C(29)	119.1(5)

C(35)-C(30)-C(29)	123.3(5)
N(6)-C(31)-C(30)	125.1(5)
N(6)-C(31)-H(31)	117.5
C(30)-C(31)-H(31)	117.5
N(6)-C(33)-C(34)	124.0(4)
N(6)-C(33)-H(33)	118.0
C(34)-C(33)-H(33)	118.0
C(33)-C(34)-C(35)	119.5(5)
C(33)-C(34)-H(34)	120.2
C(35)-C(34)-H(34)	120.2
C(30)-C(35)-C(34)	118.4(5)
C(30)-C(35)-H(35)	120.8
C(34)-C(35)-H(35)	120.8
C(37)-C(36)-C(27)	60.2(3)
C(37)-C(36)-H(36A)	117.7
C(27)-C(36)-H(36A)	117.7
C(37)-C(36)-H(36B)	117.7
C(27)-C(36)-H(36B)	117.7
H(36A)-C(36)-H(36B)	114.9
C(36)-C(37)-C(27)	60.6(3)
C(36)-C(37)-H(37A)	117.7
C(27)-C(37)-H(37A)	117.7
C(36)-C(37)-H(37B)	117.7
C(27)-C(37)-H(37B)	117.7
H(37A)-C(37)-H(37B)	114.8

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for p21kerr062011. The anisotropic
displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}

Cl(1)	28(1)	40(1)	49(1)	6(1)	12(1)	9(1)
Cl(2)	26(1)	43(1)	42(1)	-2(1)	11(1)	-7(1)
O(1)	16(2)	43(2)	38(2)	2(2)	1(2)	1(2)
O(2)	19(2)	43(2)	31(2)	1(2)	-1(2)	1(2)
N(1)	22(2)	27(2)	35(2)	7(2)	6(2)	-1(2)
N(2)	20(3)	35(3)	23(2)	4(2)	-1(2)	1(2)
N(3)	57(3)	86(4)	52(3)	-25(3)	8(3)	-4(3)
N(4)	22(2)	29(3)	29(2)	-3(2)	3(2)	1(2)
N(5)	17(3)	35(3)	28(2)	-4(2)	0(2)	-3(2)
N(6)	39(2)	42(3)	26(2)	-1(2)	4(2)	3(2)
C(1)	23(3)	25(3)	30(3)	8(2)	7(2)	-3(2)
C(3)	24(3)	28(3)	27(3)	4(2)	1(2)	-6(3)
C(4)	25(3)	33(3)	25(3)	7(3)	5(2)	2(3)
C(5)	23(3)	27(3)	19(2)	1(2)	3(2)	-3(2)
C(6)	23(3)	29(3)	29(3)	6(2)	1(2)	1(2)
C(7)	17(2)	26(3)	26(2)	9(2)	1(2)	3(3)
C(8)	29(3)	30(3)	21(3)	-1(2)	6(2)	3(3)
C(9)	30(3)	27(3)	28(3)	3(2)	2(2)	5(3)
C(10)	23(3)	38(3)	19(2)	4(2)	0(2)	9(3)
C(11)	27(3)	103(5)	32(3)	2(3)	0(2)	-16(3)
C(12)	26(3)	136(7)	37(3)	3(4)	9(3)	3(4)
C(13)	39(4)	131(8)	42(4)	-30(4)	3(3)	24(5)
C(15)	45(4)	66(4)	34(3)	-6(3)	6(3)	-9(3)
C(16)	27(3)	31(3)	42(3)	-3(3)	1(2)	-1(3)
C(17)	21(3)	44(4)	29(3)	6(3)	1(2)	-5(3)
C(21)	18(3)	34(3)	27(3)	-7(2)	7(2)	-5(2)
C(23)	27(3)	30(3)	26(3)	3(2)	3(2)	2(3)
C(24)	24(3)	26(3)	21(2)	1(2)	4(2)	-2(3)
C(25)	19(3)	25(3)	21(2)	-10(2)	-1(2)	2(2)
C(26)	30(3)	27(3)	18(2)	1(2)	7(2)	3(2)
C(27)	24(3)	26(3)	18(2)	0(2)	2(2)	1(3)
C(28)	23(3)	28(3)	18(2)	7(2)	0(2)	-1(3)
C(29)	28(3)	38(3)	26(3)	-7(3)	8(2)	-8(3)
C(30)	19(3)	27(3)	32(3)	0(2)	1(2)	4(2)

C(31)	27(3)	28(2)	31(3)	0(2)	0(2)	2(2)
C(33)	33(3)	54(4)	23(3)	4(3)	3(2)	7(3)
C(34)	31(3)	39(3)	34(3)	8(3)	3(2)	-1(2)
C(35)	29(3)	37(3)	28(3)	-4(2)	-2(2)	1(2)
C(36)	24(3)	36(3)	33(3)	-6(3)	7(2)	4(3)
C(37)	29(3)	24(3)	49(3)	-1(3)	2(2)	8(3)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3)
for p21kerr062011.

	x	y	z	U(eq)
H(3)	6982	2420	-159	32
H(4)	9409	2538	458	33
H(6)	8556	5322	2286	33
H(9A)	12456	1267	3611	35
H(9B)	10960	507	3458	35
H(11)	9406	802	4606	66
H(12)	9112	1687	6073	79
H(13)	10734	3154	6810	86
H(15)	12914	3014	4788	58
H(16A)	10755	6235	1715	41
H(16B)	12240	5687	2418	41
H(17A)	12715	4323	1166	38
H(17B)	11230	4871	463	38
H(23)	11984	2319	-261	34
H(24)	14394	2166	369	28
H(26)	13464	-520	2206	30
H(29A)	16119	4057	3451	36
H(29B)	17541	3191	3598	36
H(31)	16517	4618	5070	35

H(33)	15799	2108	6974	44
H(34)	15825	399	5953	42
H(35)	16102	807	4398	39
H(36A)	16120	-190	368	37
H(36B)	17634	286	1076	37
H(37A)	17090	-1088	2321	42
H(37B)	15577	-1564	1613	42
H(1N)	9940(50)	2260(50)	2640(30)	21(14)
H(2N)	14950(50)	2320(50)	2650(30)	28(15)

Table 6. Torsion angles [°] for p21kerr062011.

C(3)-N(1)-C(1)-C(6)	1.0(7)
C(3)-N(1)-C(1)-Cl(1)	179.1(3)
C(1)-N(1)-C(3)-C(4)	-1.2(7)
N(1)-C(3)-C(4)-C(5)	-0.3(7)
C(3)-C(4)-C(5)-C(6)	2.1(7)
C(3)-C(4)-C(5)-C(7)	-176.2(4)
N(1)-C(1)-C(6)-C(5)	0.7(7)
Cl(1)-C(1)-C(6)-C(5)	-177.3(3)
C(4)-C(5)-C(6)-C(1)	-2.2(7)
C(7)-C(5)-C(6)-C(1)	176.0(4)
C(4)-C(5)-C(7)-C(8)	-82.9(5)
C(6)-C(5)-C(7)-C(8)	99.0(6)
C(4)-C(5)-C(7)-C(16)	131.1(5)
C(6)-C(5)-C(7)-C(16)	-47.1(6)
C(4)-C(5)-C(7)-C(17)	64.8(7)
C(6)-C(5)-C(7)-C(17)	-113.4(5)
C(9)-N(2)-C(8)-O(1)	1.8(8)
C(9)-N(2)-C(8)-C(7)	-176.2(4)
C(5)-C(7)-C(8)-O(1)	177.9(4)
C(16)-C(7)-C(8)-O(1)	-35.0(6)
C(17)-C(7)-C(8)-O(1)	29.4(7)
C(5)-C(7)-C(8)-N(2)	-4.1(7)
C(16)-C(7)-C(8)-N(2)	143.1(5)

C(17)-C(7)-C(8)-N(2)	-152.6(4)
C(8)-N(2)-C(9)-C(10)	97.6(6)
N(2)-C(9)-C(10)-C(11)	94.8(6)
N(2)-C(9)-C(10)-C(15)	-82.0(6)
C(15)-C(10)-C(11)-C(12)	0.1(8)
C(9)-C(10)-C(11)-C(12)	-176.8(6)
C(10)-C(11)-C(12)-C(13)	-0.3(10)
C(15)-N(3)-C(13)-C(12)	-0.8(11)
C(11)-C(12)-C(13)-N(3)	0.7(12)
C(13)-N(3)-C(15)-C(10)	0.6(9)
C(11)-C(10)-C(15)-N(3)	-0.3(9)
C(9)-C(10)-C(15)-N(3)	176.7(6)
C(5)-C(7)-C(16)-C(17)	-106.5(5)
C(8)-C(7)-C(16)-C(17)	105.2(5)
C(5)-C(7)-C(17)-C(16)	106.8(5)
C(8)-C(7)-C(17)-C(16)	-103.6(5)
C(23)-N(4)-C(21)-C(26)	-2.5(7)
C(23)-N(4)-C(21)-Cl(2)	-178.7(3)
C(21)-N(4)-C(23)-C(24)	3.6(7)
N(4)-C(23)-C(24)-C(25)	-0.9(7)
C(23)-C(24)-C(25)-C(26)	-3.1(7)
C(23)-C(24)-C(25)-C(27)	174.3(4)
C(24)-C(25)-C(26)-C(21)	4.0(7)
C(27)-C(25)-C(26)-C(21)	-173.4(4)
N(4)-C(21)-C(26)-C(25)	-1.3(8)
Cl(2)-C(21)-C(26)-C(25)	174.8(3)
C(26)-C(25)-C(27)-C(28)	-98.7(6)
C(24)-C(25)-C(27)-C(28)	84.0(5)
C(26)-C(25)-C(27)-C(37)	47.9(6)
C(24)-C(25)-C(27)-C(37)	-129.4(5)
C(26)-C(25)-C(27)-C(36)	114.9(5)
C(24)-C(25)-C(27)-C(36)	-62.4(7)
C(29)-N(5)-C(28)-O(2)	-2.2(8)
C(29)-N(5)-C(28)-C(27)	176.9(4)
C(25)-C(27)-C(28)-O(2)	-170.7(4)

C(37)-C(27)-C(28)-O(2)	41.9(6)
C(36)-C(27)-C(28)-O(2)	-23.9(7)
C(25)-C(27)-C(28)-N(5)	10.3(7)
C(37)-C(27)-C(28)-N(5)	-137.2(5)
C(36)-C(27)-C(28)-N(5)	157.0(4)
C(28)-N(5)-C(29)-C(30)	-105.0(5)
N(5)-C(29)-C(30)-C(31)	-153.5(5)
N(5)-C(29)-C(30)-C(35)	29.6(7)
C(33)-N(6)-C(31)-C(30)	1.9(7)
C(35)-C(30)-C(31)-N(6)	-3.5(7)
C(29)-C(30)-C(31)-N(6)	179.4(4)
C(31)-N(6)-C(33)-C(34)	1.1(8)
N(6)-C(33)-C(34)-C(35)	-2.2(8)
C(31)-C(30)-C(35)-C(34)	2.2(7)
C(29)-C(30)-C(35)-C(34)	179.1(4)
C(33)-C(34)-C(35)-C(30)	0.4(7)
C(28)-C(27)-C(36)-C(37)	104.6(5)
C(25)-C(27)-C(36)-C(37)	-107.2(5)
C(28)-C(27)-C(37)-C(36)	-105.6(5)
C(25)-C(27)-C(37)-C(36)	105.7(5)

Symmetry transformations used to generate equivalent atoms:

Chapter 3

Towards the Total Synthesis of Agariblazeispirol C

Contents

1.	**Introduction**	217
	1.1 Agariblazeispirol C	217
	1.2 Retrosynthetic Analysis	221
	1.3 The Pauson-Khand Reaction	222
	1.4 Reaction Mechanism	223
	1.5 Intramolecular Pauson-Khand Reaction	225
	1.6 Promotion of the Pauson-Khand Reaction	226
	1.6.1 Amine *N*-oxides	226
	1.6.2 Sulfides	229
	1.7 Conjugated Alkenes	231
	1.8 Applications in Natural Product Synthesis	233
2.	**Previous and Proposed Work**	236
3.	**Results and Discussion**	238
	3.1 Preparation of Bicyclic Enone **4**	238
	3.2 Installation of the Oxygenated Sidechain – Olefination Chemistry	249
	3.2.1 Wittig Olefination	249
	3.2.2 Julia-Kocienski Olefination	256
	3.2.3 Stork-Zhao Olefination	261
	3.2.4 Ramirez Olefination	265
	3.3 Installation of the Oxygenated Sidechain – 1,2-Organometallic Addition Chemistry	268
	3.3.1 Organolithium Addition	273
	3.3.2 Organocerium Addition	276
	3.3.3 Organomagnesium Addition	278
	3.3.4 Organozinc Addition	281

3.3.5 Organolithium Addition – Barbier Conditions and Reverse Addition 283
3.4 Alkyne Introduction 288
3.5 Homologated Chain Approach 293
3.5.1 Alkyne Introduction 293
3.5.2 1,2-Organometallic Addition Chemistry 306
3.6 Stereochemical Elucidation of Diene **169** 308
3.7 Accessing the Pauson-Khand Precursor **3** 310
3.8 The Pauson-Khand Reaction 313

4. Conclusion 320

5. Future Work 322

6. Experimental 324
6.1 General 324
6.2 Synthetic Substrates and Procedures 326

7. References 418

Appendix 423

1. Introduction

1.1 Agariblazeispirol C

Traditional medicine has been employed by humanity for millennia. Even today, as much as 80% of the developing world exploit this approach as their primary source of medicinal therapy.[1] Additionally, in the developed world it is thought that between 70% and 80% of the population have used some form of alternative medicine. Of the various forms of alternative medicine, herbal treatments are the most popular, and are highly lucrative in the international marketplace. It was reported that in 2003-2004 annual revenues for herbal medicine in Western Europe reached US$ 5 billion.[1]

One of the most widely used herbal treatments is the fungus *Agaricus blazei* Murill, which is originally native to Piedade, a small village in the province of Sao Paolo, Brazil (**Figure 1**).[2] Approximately 100,000 – 300,000 Kg of the fungus is produced annually in Japan where it has been used extensively as a preventive medicine for a range of diseases.[3] Unfortunately, for commercial reasons, many suppliers have made bold, and unfounded, claims regarding the properties of the fungus. Accordingly, various clinical studies have been undertaken in recent years to verify the biological properties of the mushroom.[2]

Figure 1

One of the main attributes widely believed to be exhibited by *Agaricus blazei* Murill is its immuno-stimulating attributes. Several independent studies have verified the immuno-stimulating properties of the fungus.[4] Promisingly, it has recently been disclosed that an extract from the fungus promoted an immune response in mice harbouring leukemia. In addition, the fungus has been shown to be effective in treating hepatitis B and diabetes.[2] Interestingly, *Agaricus blazei* Murill also possesses anti-mutagenic and bactericidal properties.[5]

More specifically, it is believed that polysaccharides present in the fungus are, partly, responsible for the immuno-stimulating properties.[6] Additionally, various linoleic acid-derived species are thought to promote anti-mutagenic and bactericidal effects.[5] However, the specific compounds responsible for the full range of biological attributes are not fully understood. It stands to reason that the biological properties of the individual compounds present in *Agaricus blazei* Murill must be fully elucidated. In recent years, a range of novel compounds have been isolated from the fungus, with one of these compounds Agariblazeispirol C **1**,[7] being of particular interest to our research group (**Figure 2**). The biological activity of this compound is unknown with a full screening yet to be initiated. In addition to the potential biological effects, Agariblazeispirol C possesses an interesting structure and to date there are no reported syntheses in the chemical literature. Accordingly, the unknown biological activity of the compound, coupled with its intriguing structure, make Agariblazeispirol C a demanding yet attractive synthetic target within a total synthesis programme.

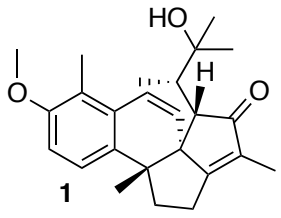
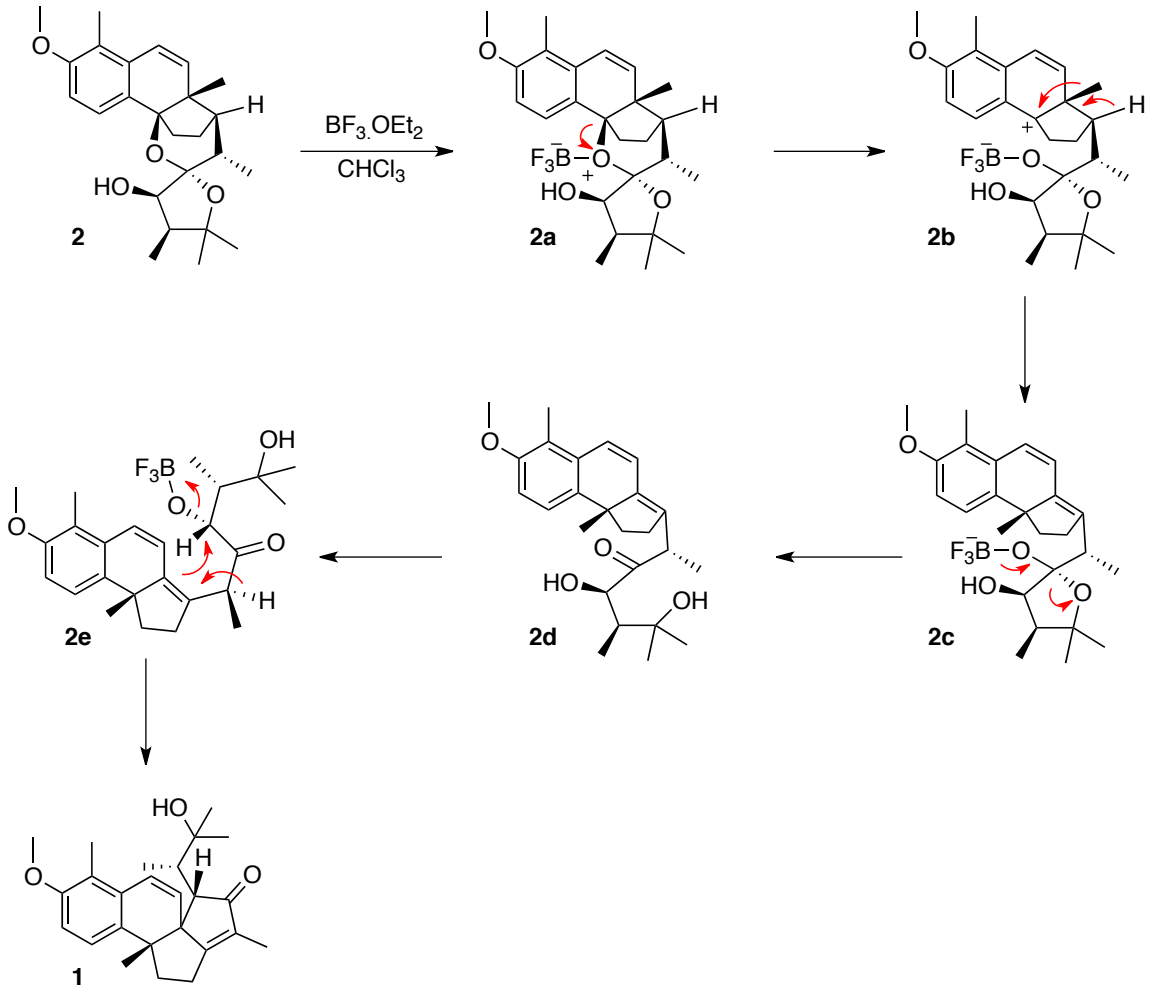


Figure 2

The salient features of Agariblazeispirol C include an unusual, and synthetically challenging, all-carbon tetracyclic core. Additionally, the presence of four contiguous stereocentres, two of which are all-carbon quaternary stereocentres at the juncture of the 5,6 ring system, further enhance the overall synthetic challenge. Furthermore, the presence of the cyclopentenone core is of particular interest to our research group. Over the last two decades work within our laboratories has encompassed the development of novel techniques to facilitate the formation of cyclopentenone units within complex molecules. This will be discussed in greater detail in a subsequent section of the introduction.

Biosynthesis

Within the original publication detailing the isolation of Agariblazeispirol C, the authors proposed that the biosynthesis of Agariblazeispirol C could proceed from the natural product Blazeispirol A, **2** (**Scheme 1**). In order to probe this hypothesis, Hirotani *et al.* attempted to replicate the natural pathway by treatment of Blazeispirol A, **2**, under Lewis acidic conditions.[7] As envisaged, this ultimately resulted in the formation of Agariblazeispirol C, **1**. It is likely that the activated oxonium ion, **2a**, formally leaves the ring system and results in a planar benzylic cationic species **2b**. Following this, the allylic methyl group of **2b** undergoes a 1,2 migration to the benzylic position. Subsequent ring opening of **2c** furnishes **2d** which undergoes a Lewis-acid-mediated rearrangement to form Agariblazeispirol C, **1**.



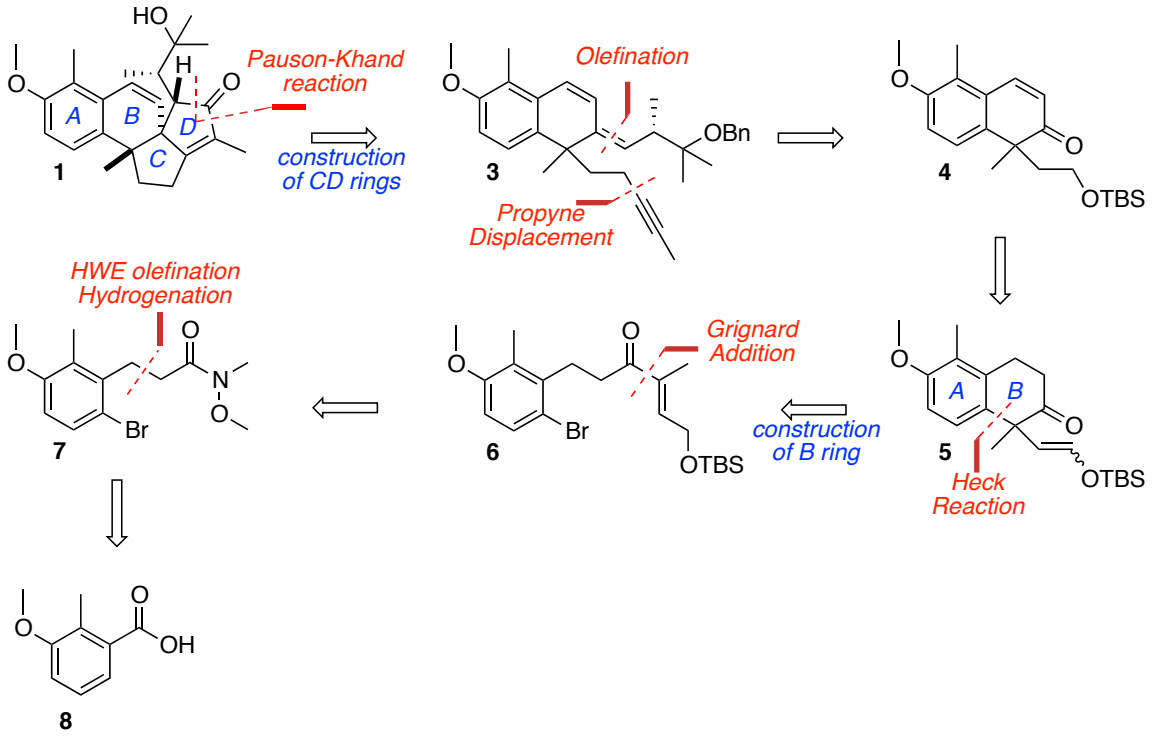
Scheme 1

In turn, the biosynthesis of blazeispirol A has been extensively investigated *via* ^{13}C-labelling studies and a relatively complete understanding of its biosynthesis is now in hand. Having stated this, further biosynthetic discussions are outwith the scope of this thesis, and, accordingly, the publications of Hirotani, and references cited therein, are excellent sources of information for interested parties.[8]

The total synthesis of Agariblazeispirol C represents an important scientific goal, as it would serve to confirm the proposed structure of the molecule and strengthen the credibility of the proposed biosynthetic pathway. Indeed, this objective is further enhanced by the potential biological activity and aforementioned synthetic challenges based on the elaborated structure of the target moleucle.

1.2 Retrosynthetic Analysis

The proposed synthetic pathway towards Agariblazeispirol C features the strategic employment of two transition metal-mediated cyclisations and an olefination reaction (**Scheme 2**). It was envisaged that a Pauson-Khand annulation would potentially grant expedient access to the tetracyclic cyclopentenone core of Agariblazeispirol C, forming the CD ring system. Additionally, the key oxygenated sidechain could be installed *via* olefination chemistry. In turn, an intramolecular Heck reaction would facilitate the formation of the bicyclic species, **5**, and install an all-carbon quaternary centre at the juncture of the BC ring system. The precursor for the Heck reaction, **6**, could be accessed *via* a Grignard addition, with the corresponding Weinreb amide, **7**, proving a suitable substrate for this reaction. Indeed, it follows that Weinreb amide **7** could be formed from the commercially available carboxylic acid **8**.



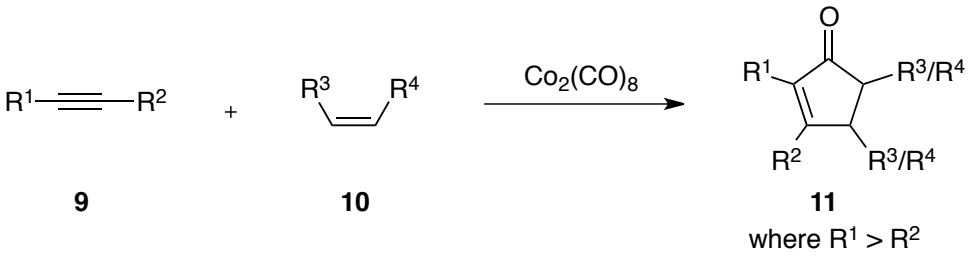
Scheme 2

As stated previously, it is envisaged that the Pauson-Khand reaction will feature as a key step and grant access to the desired natural product, **1**. Having stated this, the dienyne precursor, **3**, represents a challenging substrate for this annulation protocol due to its conjugated electronic system and densely functionalised diene unit. As such, it is important to review the relevant literature within this arena in order to enhance the likelihood of promoting the desired cyclisation. In relation to this, the following section presents an overview of the Pauson-Khand reaction and its strategic employment within other total synthesis programmes.

1.3 The Pauson-Khand Reaction

Transition-metal-mediated cyclisations have become an integral part of synthetic chemistry and represent an indispensible asset to organic chemists. In particular, the Pauson-Khand reaction has facilitated the formation of a range of densely functionalised cyclopentenone moieties. The elaborate frameworks rapidly accessed *via* this methodology beautifully illustrate the manner by which transition metal chemistry has revolutionised preparative chemistry.

The Pauson-Khand reaction (PKR) was first discovered by Khand and Pauson at the University of Strathclyde in 1971.[9] The PKR involves a formal [2+2+1] cycloaddition, featuring an alkyne, an alkene, and carbon monoxide, resulting in the formation of a cyclopentenone species in a one-pot fashion (**Scheme 3**).



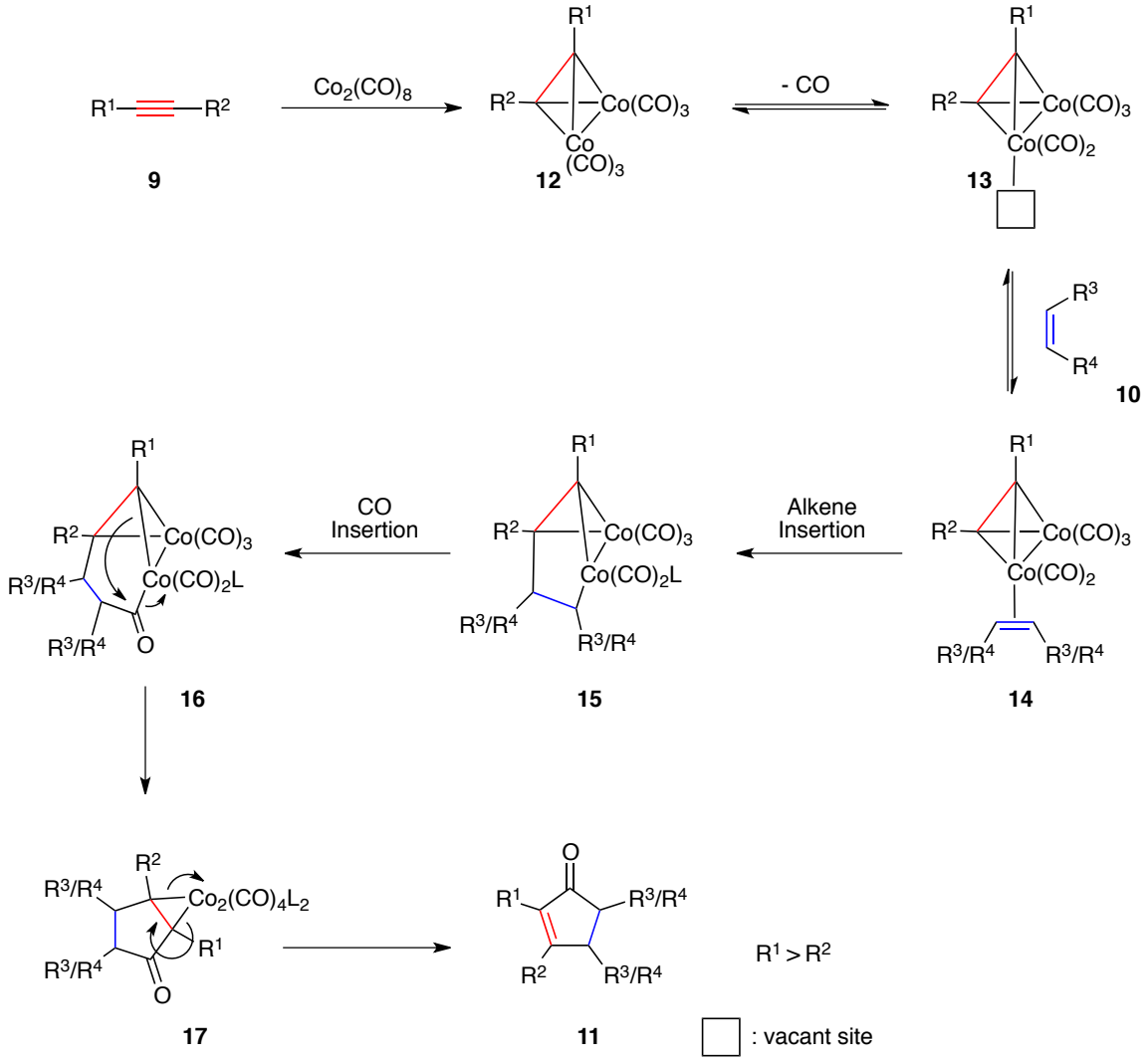
9 **10** **11**

where $R^1 > R^2$

Scheme 3

1.4 Reaction Mechanism

The mechanism through which the Pauson-Khand reaction proceeds is not fully elucidated, however the pathway proposed in 1985 by Magnus *et al*. is widely accepted as an accurate mechanistic rationale (**Scheme 4**).[10] It is believed that, following initial formation of the tetrahedral dicobalt species **12**, loss of a CO ligand from one of the cobalt centres of **12** results in the formation of the coordinatively unsaturated moiety **13**. Following this, an alkene such as **10**, can reversibly complex to the vacant coordination site to form **14**, which can then undergo an irreversible insertion process to furnish cobaltacycle **15**. This insertion occurs into the least hindered cobalt-carbon bond and, in doing so, imparts the observed regioselectivity of the final product. Migratory insertion of a carbon monoxide ligand, into the newly formed cobalt-carbon bond, grants access to intermediate **16**. Ultimately, a further two reductive elimination steps facilitate the formation of cyclopentenone **11**.

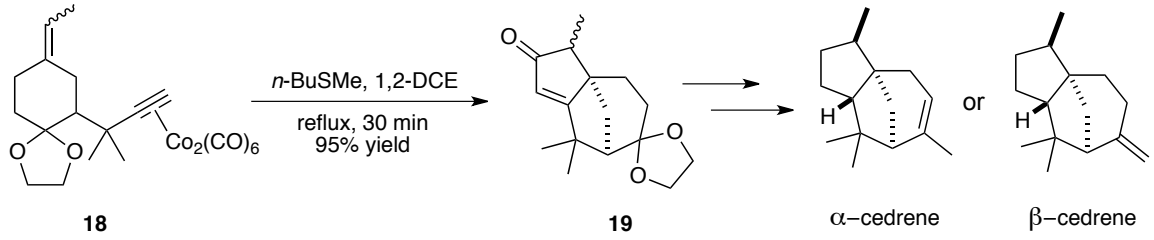


Scheme 4

There has been limited success with respect to obtaining experimental evidence for the proposed intermediates within the currently accepted mechanistic pathway. Having stated this, Gordon *et al*. successfully identified pentacarbonyl(alkyne)dicobalt species, **13**, *via* low temperature IR spectroscopy.[11] In addition, compounds analogous to species **14**, have been identified by gas phase mass spectrometry[12] and give further credence to the mechanism proposed by Magnus.

1.5 Intramolecular Pauson-Khand Reaction

The seminal disclosure of the PKR was an intermolecular process featuring an alkyne and an alkene from separate molecular entities. However, the intermolecular Pauson-Khand reaction suffers from issues regarding the regioselectivity of the annulation protocol. In contrast, the intramolecular variant circumvents the difficulties associated with the related intermolecular process. In this regard, in 1981, Schore *et al.* reported the first example of an intramolecular variant of the reaction.[13] Since this time, the intramolecular process has received considerable interest from the academic community and has facilitated the access of numerous complex molecules. Indeed, the synthetic potential of the intramolecular PKR was exploited as part of a total synthesis programme undertaken within our own laboratories. The Pauson-Khand reaction featured as the key step *en* route to both α- and β-cedrene, granting expedient access to the tricyclic core of the molecule, **19**, from the relatively simple monocyclic enyne, **18** (**Scheme 5**).[14]



18 19 α–cedrene β–cedrene

Scheme 5

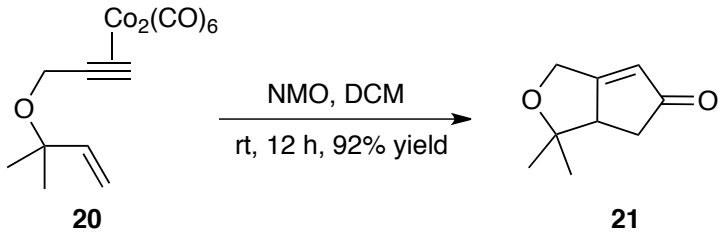
1.6 Promotion of the Pauson-Khand Reaction

The Pauson-Khand reaction exhibits excellent versatility and tolerance towards a range of functional groups. However, the annulation process has some drawbacks related to the relatively harsh reaction conditions, high temperature, and lengthy reaction times required. In an effort to address these issues, researchers have investigated means by which to circumvent these negative aspects, concomitantly facilitating the development of a milder, and more efficient, process.

1.6.1 Amine *N*-oxides

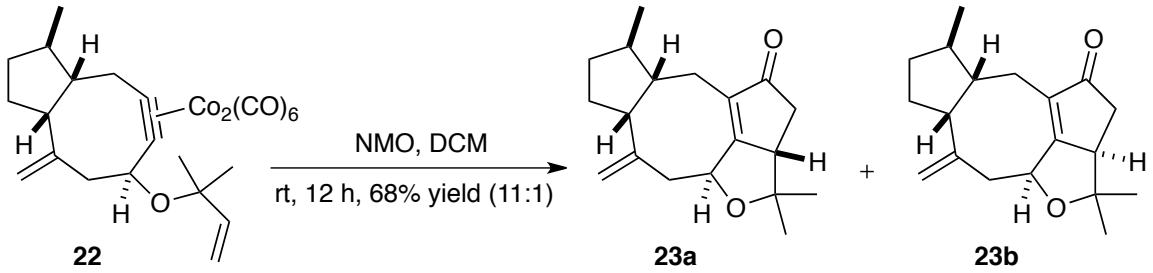
The employment of amine *N*-oxides as reaction promoters represents one of the most significant developments of the Pauson-Khand reaction. It is widely appreciated that amine *N*-oxides facilitate the irreversible dissociation of carbon monoxide ligands from transition metals.[15] Based on this, the addition of a suitable amine *N*-oxide would enhance the decarbonylation step at the outset of the PKR.

In 1990, Schreiber and coworkers first illustrated the ability of amine *N*-oxides to enhance the PKR.[16] It was shown that tertiary amine *N*-oxides, such as *N*-methylmorpholine *N*-oxide (NMO), could be employed as promoters in order to enhance the critical decarbonylative step at the outset of the reaction. Indeed, the incorporation of this additive served to promote the transformation of a range of substrates under mild reaction conditions. For example, alkyl propargyl ether **20** was converted to the desired cyclopentenone, **21**, in only 12 hours at room temperature and in excellent yield (**Scheme 6**).



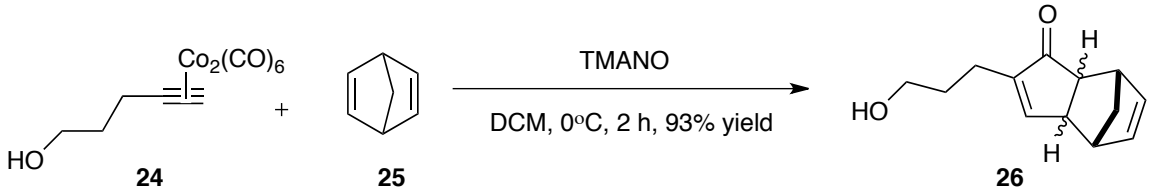
Scheme 6

Schreiber and coworkers further showcased their developed methodology in their total synthesis of (+)-epoxydictymene.[17] The desired species, **23a**, was formed with poor selectivity when employing traditional thermal PKR conditions. In contrast, the employment of an NMO-promoted PKR granted selective access to the densely functionalised cyclopentenone **23a** (**Scheme 7**).[16] The pronounced selectivity can be attributed to the milder reaction conditions employed in the NMO-promoted process.



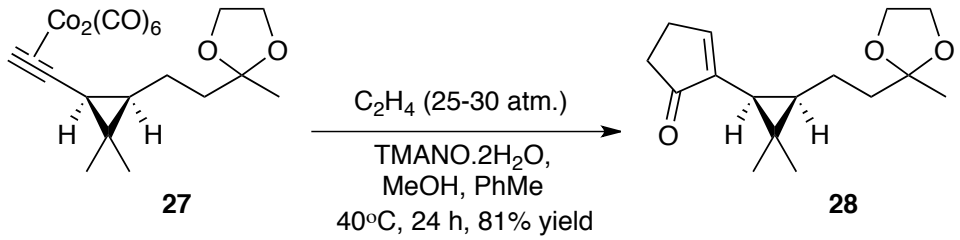
Scheme 7

Alternative amine *N*-oxides have been exploited within the Pauson-Khand reaction, for example, Jeong and Chung disclosed the employment of trimethylamine *N*-oxide (TMANO) as a promoter for the PKR **(Scheme 8)**.[18] In addition, TMANO proved efficient in promoting the annulation of alkynols, such as **24**, in the PKR. These substrates had previously reacted in poor yield when exposed to more traditional Pauson-Khand reaction conditions.



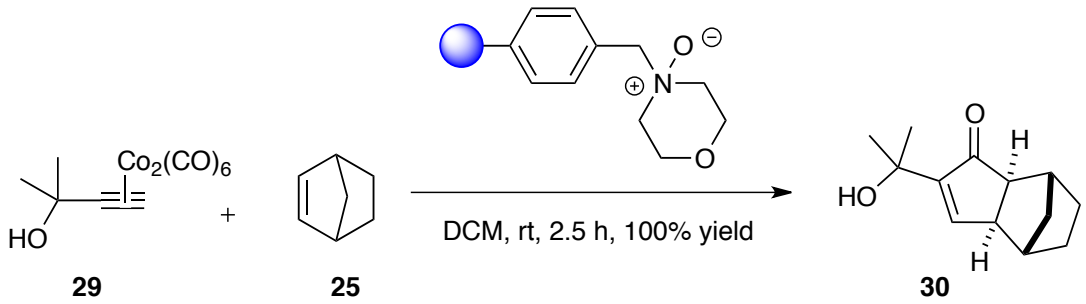
Scheme 8

Indeed, work within our own lab expanded the scope of amine *N*-oxide promoted reactions to encompass those involving a gaseous alkene component. In this vein, Kerr and coworkers employed this newly developed methodology *en* route to the total synthesis of (+)-taylorione, **28** (**Scheme 9**).[19]



Scheme 9

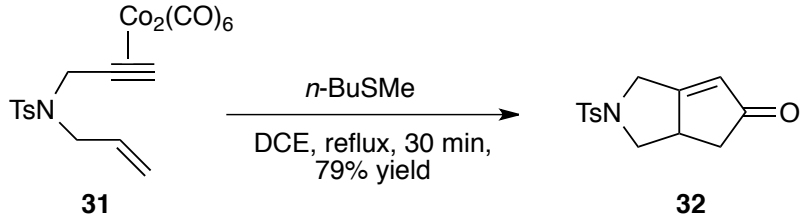
In addition, further developments by Kerr *et al*. have illustrated the potential for employment of a polymer-supported NMO additive (**Scheme 10**).[20] The benefits of this enhanced methodology are two-fold: minimal purification techniques are required upon completion of the reaction, and in addition the amine species can be efficiently recycled. It should be noted that the reactions conducted under this promotion method proceed extremely efficiently and in up to quantitative yield, as shown in **Scheme 10**.



Scheme 10

1.6.2 Sulfides

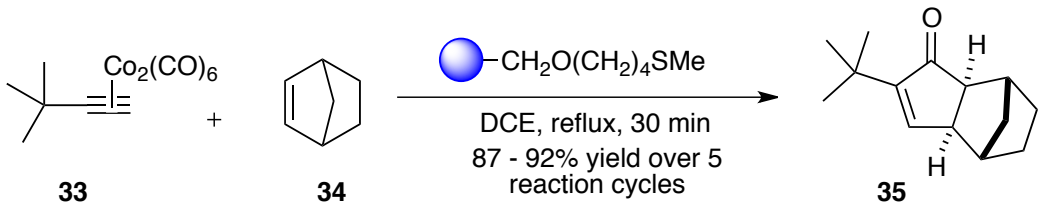
Sulfide additives have been shown to greatly enhance the efficacy of the Pauson-Khand reaction. In this regard, Sugihara and Yamaguchi carried out an extensive screening study and identified alkyl methyl sulfides as the most efficient sulfide promoters.[21] It was suggested that *n*-butyl methyl sulfide was the most robust enhancer and facilitated the rapid formation of a variety of cyclopentenones in impressive yields. In the example illustrated below, the use of NMO and thermal promotion were less successful (**Scheme 11**). In contrast, the sulfide-promoted reaction granted access to the desired cyclopentenone, **32**, in good yield.



Scheme 11

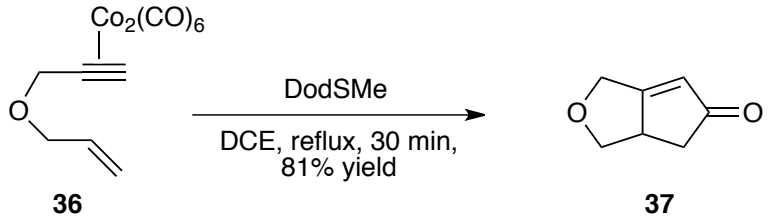
The sulfide-promoted methodology offers access to a range of products that are generally afforded in poor yields *via* alternative promotion techniques. Having stated this, there are drawbacks associated with this approach. In addition to the high reaction temperatures

routinely required, the volatile *n*-butyl methyl sulfide (*n*-BuSMe) possesses an offensive odour and lachrymatory properties. Further still, the reagent is relatively expensive and cannot be recycled from the existing reaction protocol. In an effort to address these shortcomings, Kerr and coworkers developed an odourless, reusable polymer-supported sulfide analogue, **34**, which exhibits the same promoting ability as the more problematic *n*-BuSMe **(Scheme 12)**.[22] Furthermore, the supported sulfide can be used over numerous reaction cycles and is readily removed from the reaction mixture, simplifying the purification sequence to filtration and minimal chromatography.



Scheme 12

In a further development to the sulfide promoted Pauson-Khand reaction, Kerr and coworkers offered a subtle alternative to *n*-BuSMe.[23] It was shown that *n*-dodecyl methyl sulfide (*n*-DodSME), an inexpensive and commercially available sulfide, efficiently promoted the PKR and circumvented the issues associated with the volatile *n*-BuSMe (**Scheme 13**). The alternative protocol granted access to a range of products in good to excellent yields.

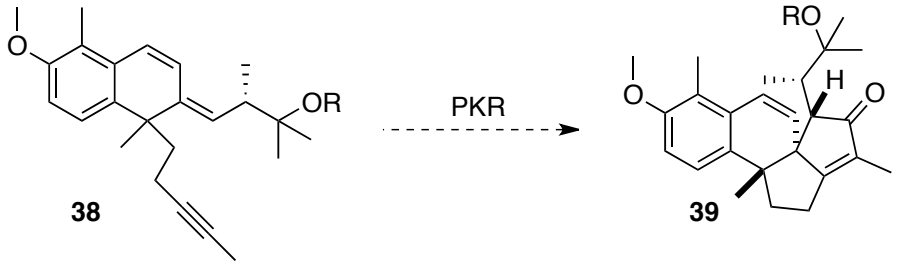


Scheme 13

Through sustained research efforts the Pauson-Khand reaction has become an extremely efficient manner by which to synthesise cyclopentenones. In particular, the development of the amine *N*-oxide promoted reaction, and sulfide promoted protocol, has granted access to a range of cyclopentenones in an expedient fashion. In addition, there has been considerable research into the asymmetric variant of the reaction and also the development of the catalytic Pauson-Khand reaction.[24] Indeed, any review on this area would be vast and is outside the scope of this text. Having stated this, with respect to the research programme detailed herein, it is pertinent to address the issues arising within PKR chemistry relating to the employment of conjugated alkenes.

1.7 Conjugated Alkenes

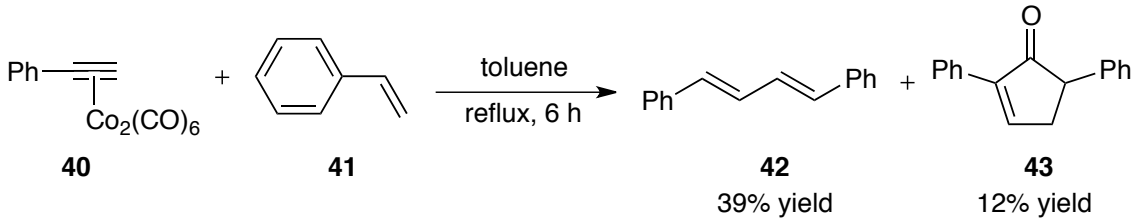
The Pauson-Khand annulation substrate, within the proposed synthetic pathway to Agariblazeispirol C, features a conjugated diene system (**Scheme 14**). It is widely understood that conjugated alkenes represent challenging coupling partners within the cyclisation protocol.[25] This is attributable to the ability of such substrates to undergo undesired side reactions when subjected to Pauson-Khand reaction conditions.



Scheme 14

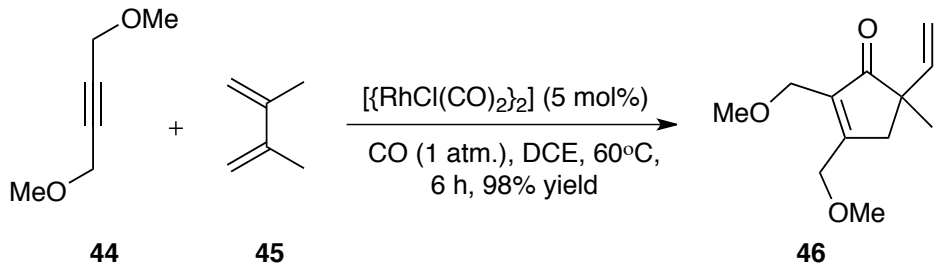
The most commonly encountered issue associated with these substrate types is the competing hydrogen migration pathway, which results in the formation of the conjugated

diene product without the incorporation of carbon monoxide. This undesired pathway is illustrated by the reaction of styrene, **41**, with phenylacetylene cobalt complex **40**, which predominantly results in the formation of the linear conjugated alkene product **42** (**Scheme 14**).[26] It should be noted that this issue is common to both diene systems and styrene derivatives.



Scheme 15

Based on their unpredictable nature, and capacity for side reactions, conjugated alkenes have not readily been employed in the Pauson-Khand reaction. Having stated this, Wender and coworkers developed a reaction protocol that led to the enhanced formation of the desired cyclopentenone product *via* a rhodium-promoted PKR (**Scheme 15**).[27] The use of a rhodium catalyst granted access to a range of cyclopentenone products that were inaccessible *via* the analogous cobalt-mediated process. Indeed, this represents an auspicious result with respect to promoting the Pauson-Khand reaction of the dienyne Agariblazeispirol C precursor, **3**.

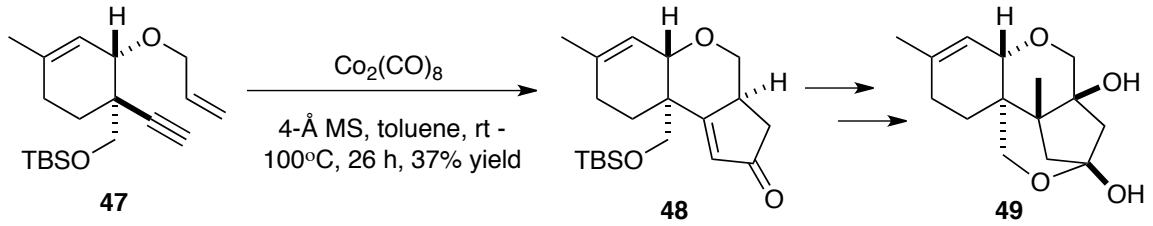


Scheme 16

1.8 Applications in Natural Product Synthesis

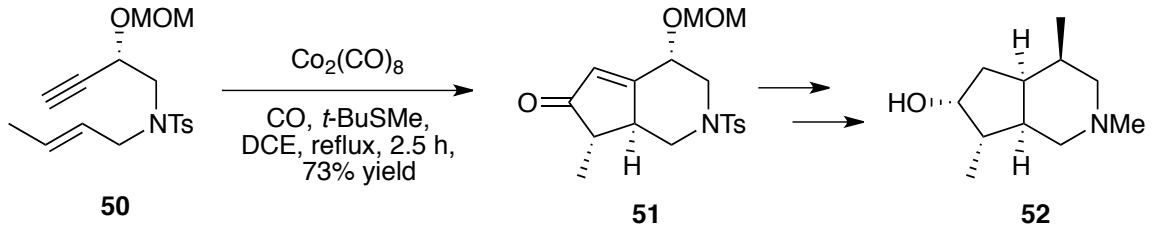
The Pauson-Khand annulation has been utilised in the synthesis of a range of natural products. The cyclopentenone core is common to many natural products and the PKR represents a powerful method of accessing such carbocycles in an expedient fashion. In relation to this, there are numerous examples of the PKR underpinning the synthetic strategy towards a range of natural products.

In 2007, Danishefsky and Min reported the synthesis of Paecilomycine A, **49**, a potential drug target for neurodegenerative disorders.[28] The 6,5 ring system at the core of the molecule was assembled through the strategic employment of the Pauson-Khand reaction (**Scheme 17**). The intramolecular PKR granted access to the advanced intermediate **48**, as a single stereoisomer, in a moderate 37% yield. The authors note that, although the yield was disappointing, the reaction was scalable and the product readily purified.



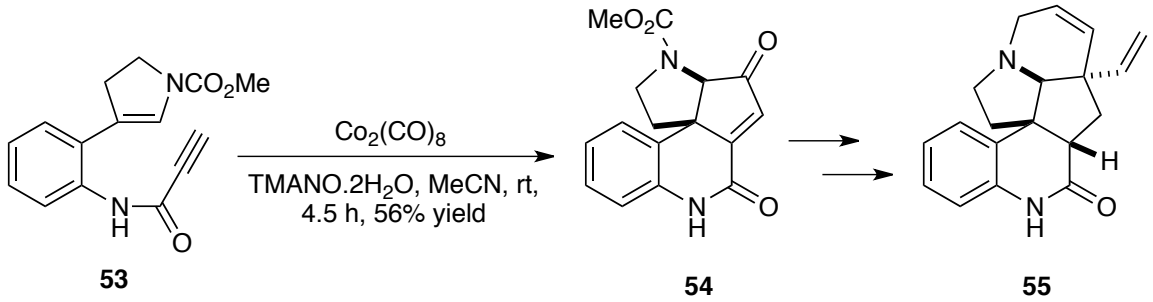
Scheme 17

Another interesting application of the Pauson-Khand reaction comes from Honda and Kaneda where the PKR features as the key step in the formal synthesis of (-)-Incarvilline **52**.[29] The authors reported the employment of an efficient sulfide-promoted annulation protocol, to gain access to the advanced intermediate **51** (**Scheme 18**).



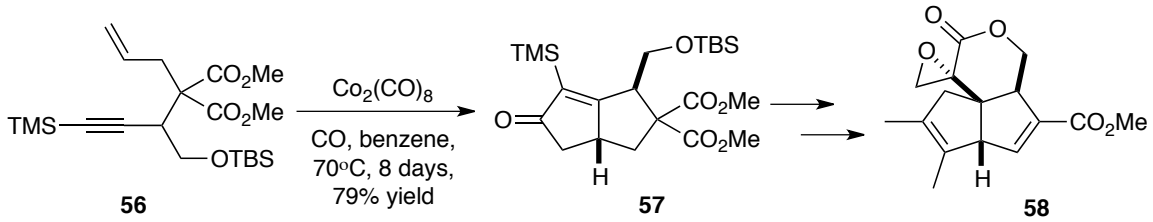
Scheme 18

Mukai and coworkers implemented the Pauson-Khand reaction as a key step in the synthesis of (±)-Meloscine, **55**.[30] After significant study, it was discovered that a TMANO-promoted annulation protocol granted access to the tetracyclic system, **54**, in one synthetic step (**Scheme 19**).



Scheme 19

Another impressive and relatively recent example of the Pauson-Khand cyclisation was disclosed by Yang and coworkers, in the recent synthesis of (±)-Pentalenolactone A methyl ester, **58**, a potential candidate for the development of new antibiotic agents.[31] The PKR was employed in the establishment of the core 5,5-fused bicycle. Notably, the annulation substrate is relatively bulky and as such a lengthy reaction time of eight days was necessary (**Scheme 20**). Having stated this, the synthetic utility is evident as the annulation formed two five-membered rings, embedded two stereocentres, and installed key functional groups.

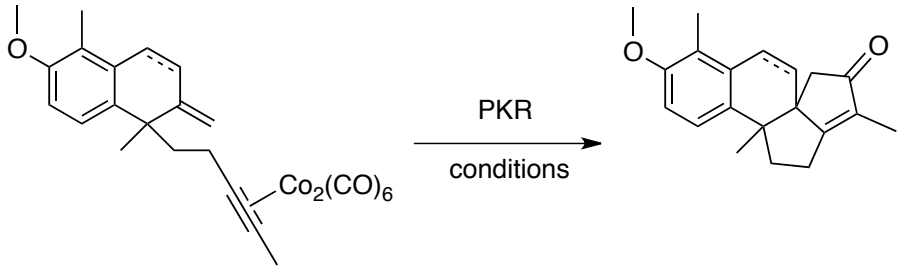


Scheme 20

In summary, it has been shown that the Pauson-Khand reaction is of significant synthetic value to preparative chemists. The annulation protocol has facilitated the direct, and expedient, access of a range of functionalised cyclopentenone moieties. More specifically, the intramolecular Pauson-Khand reaction has shown enormous synthetic employability and has featured as a key step in the synthesis of a wide variety of natural products. In turn, the development of reaction promoters has expanded upon the substrate scope and significantly enhanced the synthetic appeal of the cyclisation process. Based on this, the Pauson-Khand reaction represents one of the most efficient annulation processes employed by chemists and is likely to be regularly employed for years to come.

2 Previous and Proposed Work

Whilst studies towards the total synthesis of Agariblazeispirol C had already been initiated within our lab, the target molecule has yet to be accessed. Previous research has focused on the development of the Pauson Khand reaction protocol in order to facilitate access to the tetracyclic core of the molecule. In this regard, the annulation of alkene **I** had been performed in an impressive 86% yield to furnish the tetracyclic skeleton of the natural product (**Scheme 21**).[32] Further still, diene **II** was shown to undergo the PKR to facilitate access to the tetracyclic species in a 61% yield. In this case the product possessed an internal point of unsaturation, which is present in the natural product. Despite these promising results and significant synthetic efforts, the key oxygenated sidechain had yet to be successfully introduced to any precursor units. [33,34]

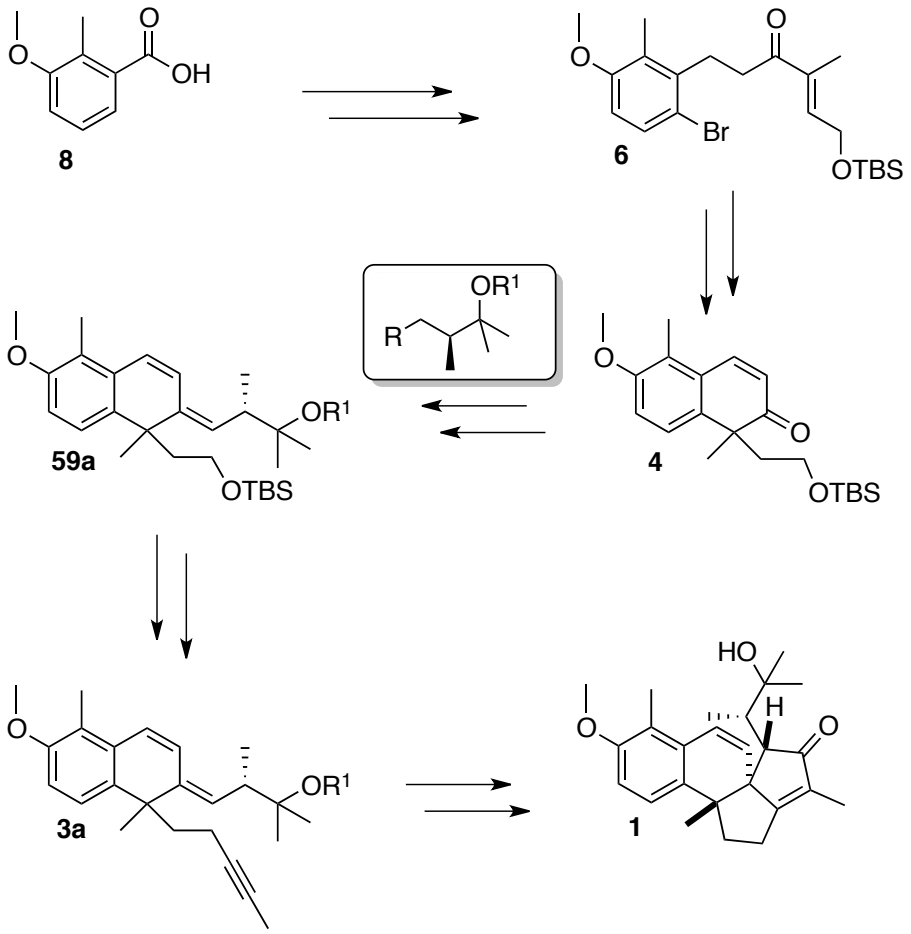


I alkene: 5 h, 86% yield
II diene: 5 days, 61% yield

Scheme 21

In relation to the above, it was rationalised that an improved synthetic approach, would be key to gaining access to the desired natural product, Agariblazeispirol C **1**. As such, it was reasoned that the installation of the sidechain moiety should precede the Pauson-Khand annulation. Based on this, the PKR would now function as either the final, or penultimate, step in the overall preparative approach. Having stated this, the oxygenated sidechain had never been successfully introduced at any part of the synthesis towards the natural product. As such, the installation of this moiety represents a significant synthetic challenge. In this regard, a synthetic strategy, incorporating the above rationale, was

developed (**Scheme 22**). It was rationalised that the commercially available carboxylic acid could be transformed to enone **6**, before ultimately furnishing the bicyclic species **4**. At this juncture, the sidechain unit could potentially be introduced *via* olefination chemistry to form species **59a**. Following this, the requisite alkyne functionality could be introduced to grant access to the key Pauson-Khand precursor **3a**. It is envisaged that a Pauson-Khand annulation, followed by alcohol deprotection would result in the formation of the desired natural product, **1**.



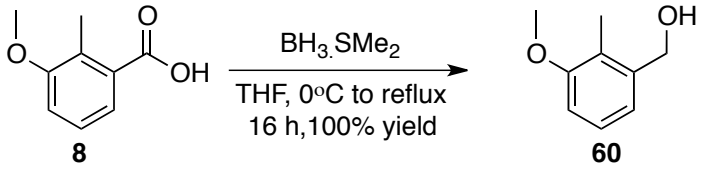
Scheme 22

It should be reiterated that, at present, there isno reported total synthesis of the target molecule in the chemical literature. Based on all of the above and with a promising synthetic approach planned, attention turned towards the total synthesis of the Agariblazeispirol C.

3 Results & Discussion

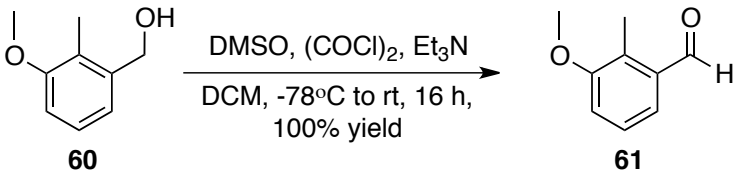
3.1 Preparation of Bicyclic Enone, 4

At the outset of the research programme, initial work focused on the synthesis of bicyclic enone **4** in multi-gramme quantitities. The synthetic sequence began with the reduction of commercially available benzoic acid **8**, to yield benzyl alcohol **60**. Borane reduction of acid **8** provided alcohol **60** in quantitative yield (**Scheme 23**).



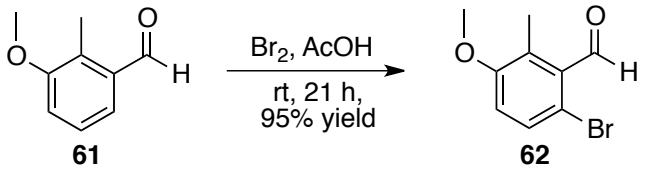
Scheme 23

Following this, benzyl alcohol **60** was oxidised to the corresponding benzaldehyde derivative **61** *via* standard Swern oxidation conditions.[35] Gratifyingly, the desired aldehyde, **61**, was obtained in quantitative yield (**Scheme 24**).



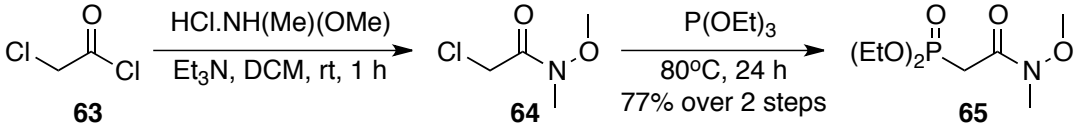
Scheme 24

Owing to the unstable nature of aldehyde **61**, the resulting regioselective bromination was performed under relatively mild conditions, previously disclosed by Kende.[36] Pleasingly, the bromination proceeded in a completely regioselective manner with only the desired regioisomer detected by ^{1}H NMR analysis. Further still, bromoaldehyde **62** was isolated in an excellent 95% yield (**Scheme 25**).



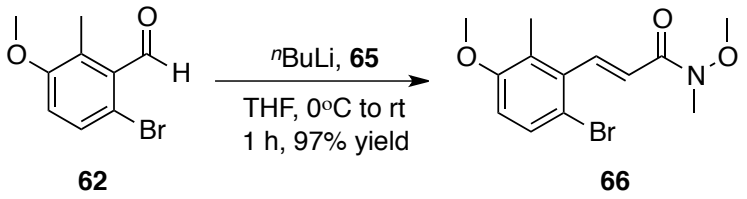
Scheme 25

Following the successful isolation of bromoaldehyde **62**, attention turned to the aldehyde moiety, which would serve as a functional handle in order to introduce the extended carbon chain. This was to be achieved through employment of a Horner-Wadsworth-Emmons (HWE) olefination, which required the synthesis of functionalised phosphonate ester **65**. The desired intermediate, **65**, was accessed *via* a literature protocol,[37] whereby chloroacetyl chloride **63** was reacted with *N*,*O*-dimethylhydroxylamine to form **64**, which in turn was reacted with triethylphosphite. The resulting phosphonate ester **65** was isolated *via* Kugelrohr distillation in an excellent 77% yield over 2 steps (**Scheme 26**).



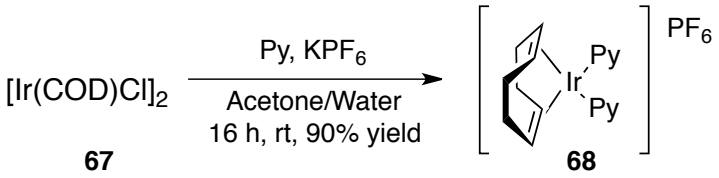
Scheme 26

With both coupling partners in hand, the olefination was conducted under standard HWE conditions.[38] Accordingly, phosphonate ester **65** was treated with *n*-BuLi before the addition of bromoaldehyde **62**. The reaction occurred in an excellent 97% yield furnishing *E*-α,β-unsaturated amide **66** selectively (**Scheme 27**).



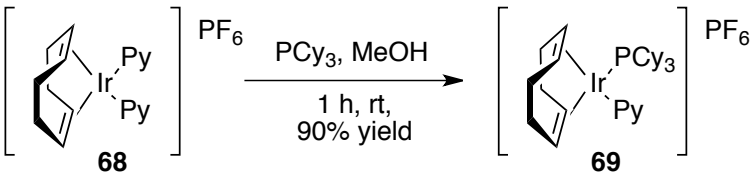
Scheme 27

Following the successful isolation of enamide **66**, attention turned to removing the newly installed unsaturated component of the molecule. This required careful consideration of catalyst systems as many traditional hydrogenation conditions result in proto-dehalogenation of the sensitive aryl bromide functionality.[33] Accordingly, the mild homogenous hydrogenation conditions of Crabtree's catalyst **69** would serve to selectively reduce the olefin moiety. Crabtree's catalyst was accessed *via* an efficient and robust literature protocol.[39] Intermediate **68** was accessed from commercially available iridium dimer **67**, which was reacted with potassium hexafluorophosphate and an excess of pyridine, delivering bispyridine complex **68** in a pleasing 90% yield (**Scheme 28**).



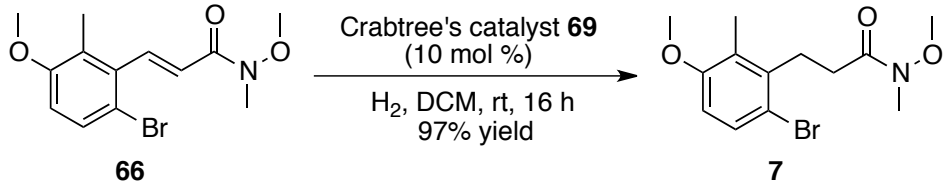
Scheme 28

Intermediate **68** was then reacted with tricyclohexylphosphine to furnish Crabtree's catalyst, **69**, in an excellent 90% yield (**Scheme 29**).



Scheme 29

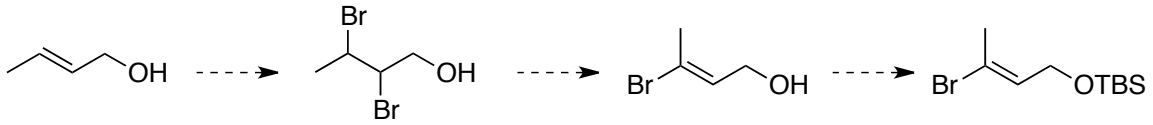
With Crabtree's catalyst **69** in hand, attention turned to the hydrogenation of unsaturated Weinreb amide **66**. Under an atmosphere of hydrogen, catalyst **69** facilitated the complete and selective removal of the undesired olefin component to furnish the saturated Weinreb amide **7** in a 97% yield (**Scheme 30**).



66 **7**

Scheme 30

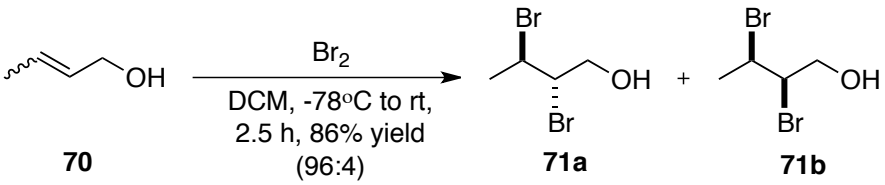
Following the isolation of multi-gramme quantities of Weinreb amide **7**, the formation of the key Heck precursor **6** was the next priority. This was to be achieved by reacting Weinreb amide **7** with a suitable coupling partner in order to introduce the necessary olefin moiety, which is integral to the proposed intramolecular Heck reaction. Accordingly, the synthetic approach required accessing appreciable quantities of vinyl bromide **73**. The strategy implemented towards **73**, which had previously been reported by Schlosser and Hammer, is illustrated below (**Scheme 31**).[40]



70 **71** **72** **73**

Scheme 31

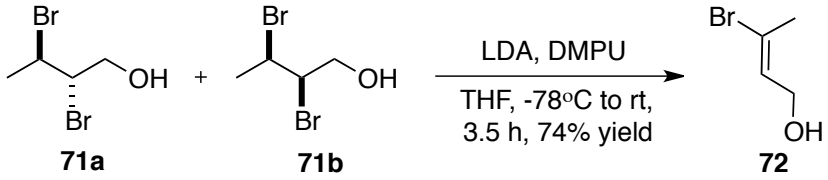
The synthesis began with the bromination of commercially available crotyl alcohol, present as a mixture of *trans*- and *cis*-isomers (96:4), resulting in the formation of compounds **71a** and **71b** in the corresponding ratio (**Scheme 32**).



70 **71a** **71b**

Scheme 32

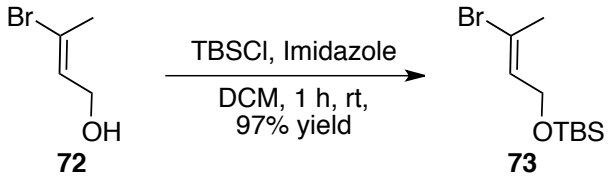
The resulting diastereomers **71a** and **71b** were then treated with LDA and the desired *E*-vinyl bromide **72** was isolated, by fractional distillation, in a good yield (**Scheme 33**).



71a **71b** **72**

Scheme 33

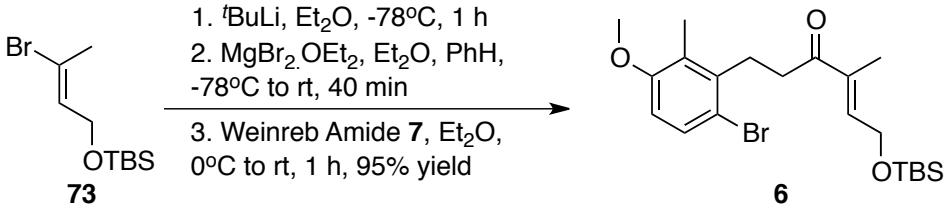
The final step towards the requisite vinyl bromide was protection of the alcohol functionality with a suitable silyl protecting group. In this regard, a *tert*-butyldimethylsilyl (TBS) group was employed to mask the hydroxyl functionality. Pleasingly, this transformation delivered the desired vinyl bromide **73** in an excellent 97% yield (**Scheme 34**).



72 **73**

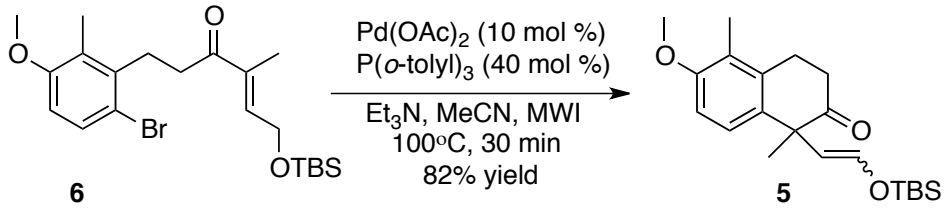
Scheme 34

With efficient and high yielding routes towards both Weinreb amide **7** and vinyl bromide **73**, attention turned to accessing the key Heck precursor **6**. This was achieved by employing a Grignard reaction, which involved initial lithiation of vinyl bromide **73**. The lithiated species was treated with freshly prepared $MgBr_2.OEt_2$, resulting in transmetallation to yield the analogous Grignard reagent. It is important to highlight that preliminary investigations employing the vinyl lithiated nucleophile directly resulted in transmetallation and subsequent undesired reaction on introduction of the aryl bromide functionality.[33] Treatment of Weinreb amide **7** with the analogous Grignard reagent of **73** resulted in the isolation of Heck precursor **6** in an excellent 95% yield (**Scheme 35**).



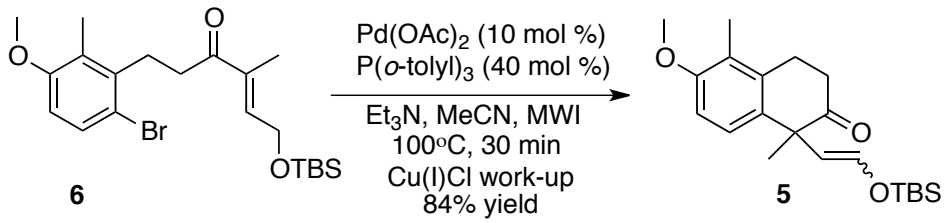
Scheme 35

Accessing the bicyclic core *via* an intramolecular Heck reaction is one of the key steps within this total synthesis programme. Indeed, this approach represents an efficient manner by which to install the integral quaternary centre in a single preparative step. The microwave-promoted Heck reaction facilitated the formation of **5** in excellent yield (**Scheme 36**). Having stated this, the purification process was complicated, and rendered rather labourious, by the presence of the phosphine additive.



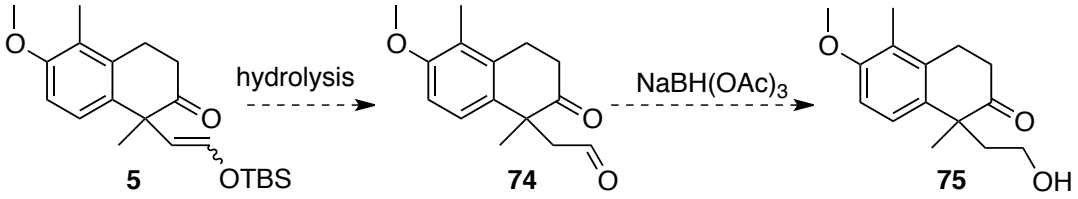
Scheme 36

In an effort to circumvent the issues relating to the efficient isolation of **5**, alternative purification techniques were investigated. The most problematic impurity present in the reaction mixture is the Lewis basic tri(*o*-tolyl)phosphine species, which effectively poisons organometallic complexes employed in subsequent reaction. As a result, it was necessary to perform repeat flash column chromatography (FCC) in an effort to completely remove the phosphine impurity. In addition, it is important to highlight that the silyl enol ether, **5**, is readily cleaved under flash column conditions and, as such, repeat FCC results in poor recovery of **5**. With this in mind a literature search of potential phosphine scavengers highlighted an interesting approach from Lipshutz and coworkers, whereby copper chloride acts to sequester unwanted phosphine impurities.[41] Accordingly, this was trialled in the Heck reaction work-up and, pleasingly, resulted in removing the phosphine impurity, which in turn simplified the requisite chromatography allowing the reaction to be performed on a larger scale. Based on this, the amended purification protocol granted expedient access to silyl enol ether **5** in an 84% yield (**Scheme 37**).



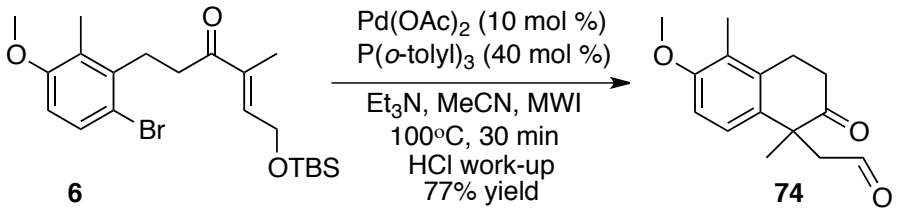
Scheme 37

At this stage, it was envisaged that the facile hydrolysis of silyl enol ether, **5**, could potentially be exploited to grant access to aldehyde **74**, which, in turn, could undergo a selective reduction to furnish alcohol **75** (**Scheme 38**).



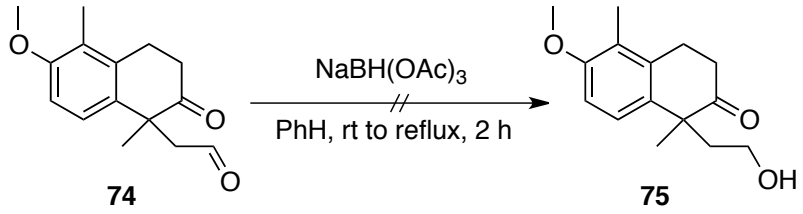
Scheme 38

Based on the above synthetic strategy, the desired aldehyde **74** was accessed by subtly modifying the existing Heck reaction protocol, whereby an aqueous acidic wash led to the hydrolysis of silyl enol ether present in **5** (**Scheme 39**).



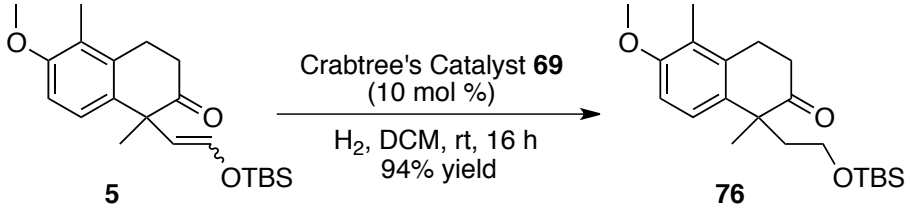
Scheme 39

With aldehyde **74** in hand, attention turned to its selective reduction. After consulting the literature, it was uncovered that sodium triacetoxyborohydride has been shown to selectively reduce aldehydes, in the presence of ketones, in a refluxing solution of benzene.[42] As such, it was decided to implement this strategy in an effort to access alcohol **75**. Based on this, the freshly generated aldehyde, **74**, was treated with sodium triacetoxyborohydride and the resulting solution stirred at room temperature for 1 hour, before stirring at reflux for 1 hour. Unfortunately, a complex mixture of products was observed after this time, and it was reasoned that the capricious aldehyde, **74**, was potentially undergoing degradation pathways. In addition, alcohol **75** may have proved unstable under the relatively harsh reaction conditions.



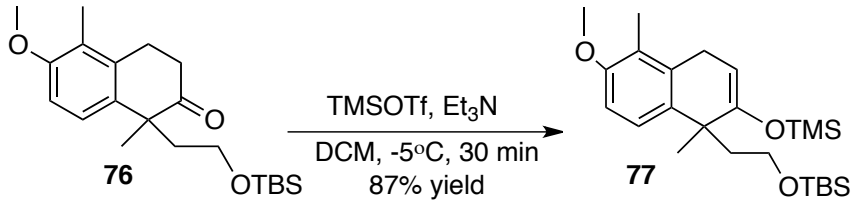
Scheme 40

Based on the disappointing result obtained with the selective reduction protocol, a more robust, and traditional, reduction strategy was employed. Owing to the excellent activity observed previously, Crabtree's catalyst was employed in the hydrogenation of silyl enol ether **5**. The catalyst proved extremely effective and reduced the hindered olefin moiety in an excellent yield (**Scheme 41**).



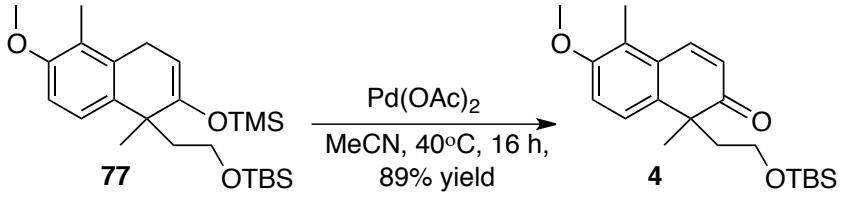
Scheme 41

At this juncture, obtaining the desired enone, **4**, in appreciable quantities remained the immediate priority. Accordingly, with bicyclic ketone **76** in hand, attention turned to the installation of the enone functionality. This transformation was to be achieved *via* a Saegusa-Ito oxidation.[43] The first step of this preparative approach required the formation of enol ether **77**, which proceeded in an 87% yield (**Scheme 42**).



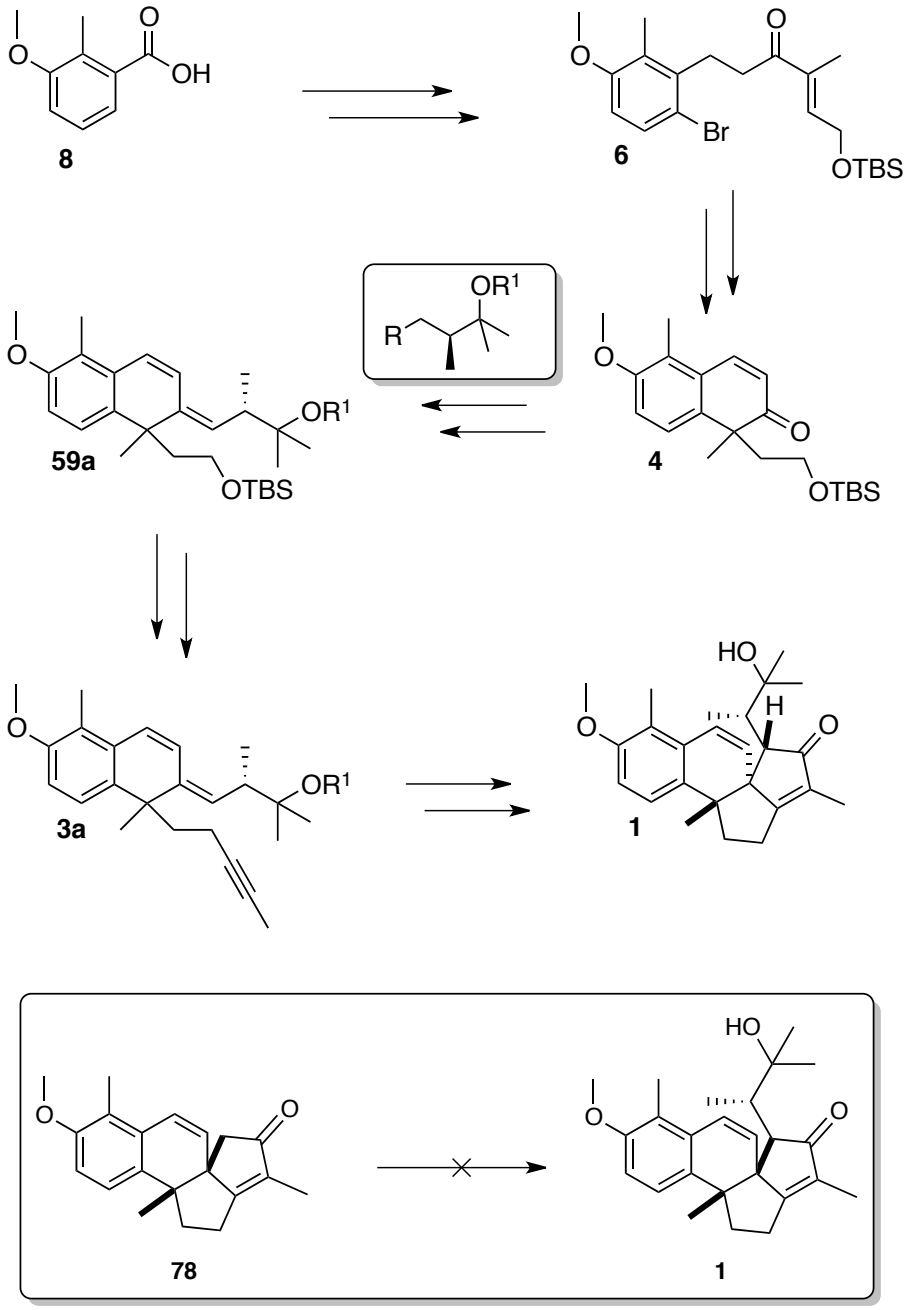
Scheme 42

The freshly prepared enol ether **77** was then subjected to palladium-mediated Saegusa-Ito oxidation conditions to generate the requisite enone **4** in a pleasing 89% yield (**Scheme 43**).



Scheme 43

With appreciable quantities of enone **4** in hand, the overall synthetic strategy could be evaluated (**Scheme 43**). The next step in the synthetic sequence was the installation of the oxygenated sidechain, which would furnish intermediate **59a**. As stated previously, it was hypothesised that the Pauson-Khand precursor, **3a**, could be rapidly accessed from this species. Following this, the annulation protocol could proceed on the elaborated bicyclic framework, which would hopefully furnish the tetracyclic species possessing the requisite sidechain functionality, **1**. It should be noted that despite previous efforts, the direct introduction of the sidechain species to tetracycle **78** had been met with no success.[32,33,34] Based on this, the successful introduction of the sidechain moiety, before the key PKR, would represent an auspicious step towards the synthesis of Agariblazeispirol C.



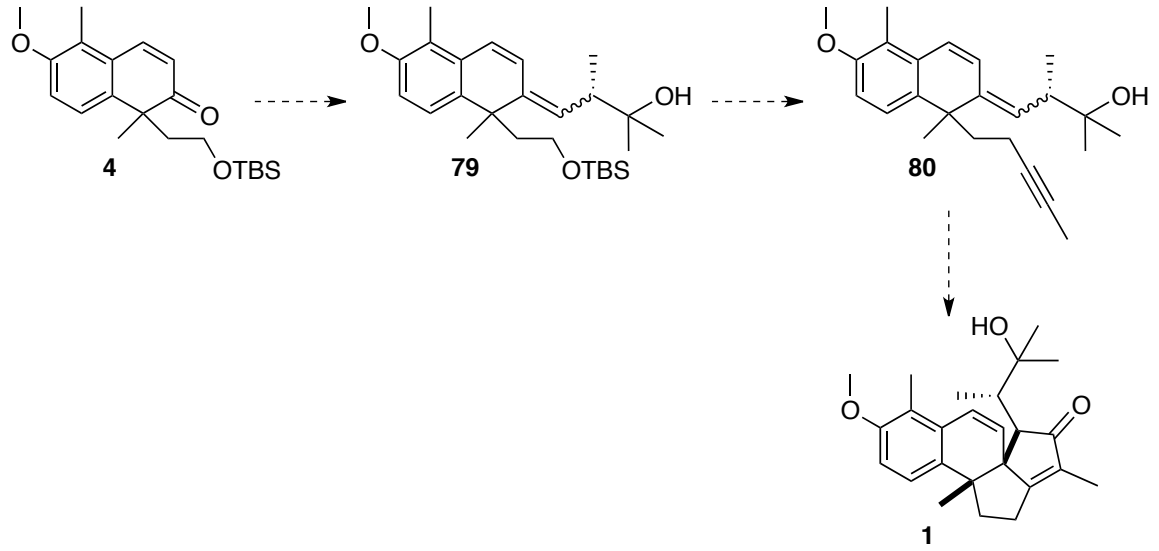
Scheme 44

3.2 Installation of the Oxygenated Sidechain – Olefination Chemistry

3.2.1 Wittig Olefination

As stated previously, the installation of the oxygenated sidechain had previously eluded researchers working towards the total synthesis of Agariblazispirol C.[32,33,34] As a result of the difficulties encountered in introducing the sidechain, it was decided to re-evaluate the approach in relation to the installment of the key moiety.

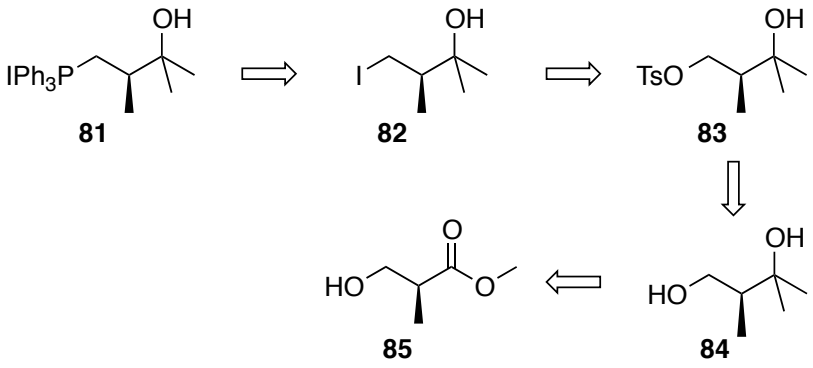
It was envisaged that the functionality of the bicyclic enone **4** could be exploited in order to establish the oxygenated sidechain. There are a variety of olefination techniques that may facilitate the procurement of the salient diene unit **79**. Compound **79** could conceivably undergo further transformations in order to access alkyne **80** prior to, ultimately, cyclising under Pauson-Khand annulation conditions to furnish Agariblazispirol C (**Scheme 45**).



Scheme 45

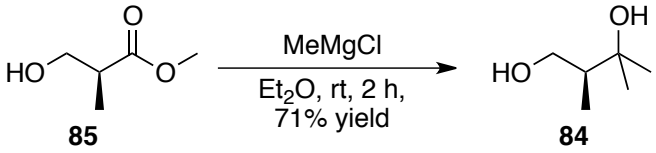
It was hypothesised that a Wittig olefination of enone **4** could potentially introduce the oxygenated sidechain. The conjugated electronic nature of enone **4** coupled with the appreciable α,α-disubstituted steric environment would, indeed, render this transformation extremely challenging. However, introducing the sidechain at this stage in the synthetic sequence was of paramount importance and, accordingly, it was reasoned that a resilient and exhaustive approach would eventually yield the desired diene **79**.

The requisite chiral phosphonium salt had to first be synthesised before embarking upon investigations into the Wittig olefination. Hanekamp and coworkers had previously disclosed a synthetic approach towards phosphonium salt **81** in the chemical literature.[44] Pleasingly, the synthesis of this species commenced from the commercially available chiral Roche ester **85** (**Scheme 46**).



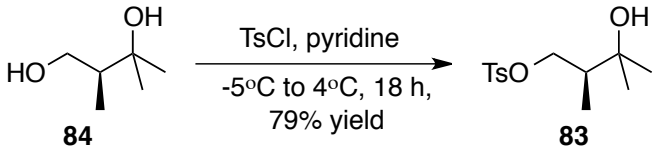
Scheme 46

Following the literature procedure, enantiomerically pure Roche ester was treated with excess methyl magnesium chloride in order to access diol **84** (**Scheme 47**). There were two main issues relating to this deceivingly simple transformation: the reaction temperature must remain below 25°C in order to prevent undesired polymerization; and, additionally, reaction work-up proved complicated by the water-soluble nature of diol **84**. The temperature could easily be controlled by the aid of an ice-bath, however, even after numerous diethyl ether extractions of the aqueous phase only a modest 71% yield of **84** was obtained, despite full conversion of **85** being observed.



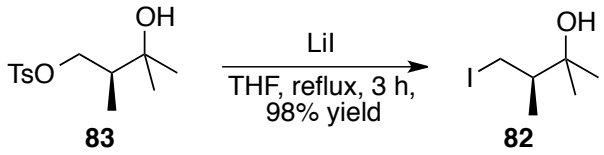
Scheme 47

With diol **84** in hand, attention turned to activating the primary alcohol as a tosyl group. The tosylation reaction proceeded in a pleasing 79% yield, and importantly the tertiary alcohol unit remained untouched (**Scheme 48**).



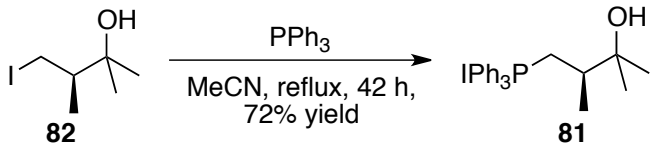
Scheme 48

The iodination of tosylate **83** proceeded without incident to generate iodide **82** in an excellent 98% yield (**Scheme 49**).



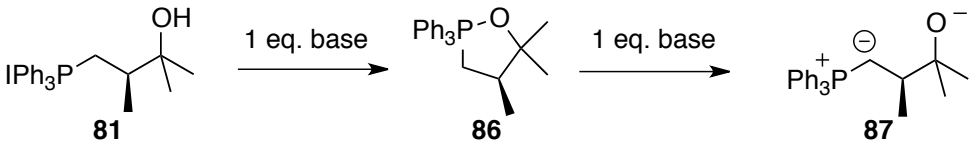
Scheme 49

Towards the formation of **81**, the optimised conditions disclosed by the authors in the literature proved effective, with eight equivalents of triphenylphosphine in refluxing acetonitrile facilitating the formation of phosphonium salt **81** in a 72% yield (**Scheme 50**). As an array of preparative conditions had been utilised in the preparation of **81**, an optical rotation experiment was performed, which pleasingly showed that the chiral nature of the substrate remained wholly intact, based on comparison with literature data.



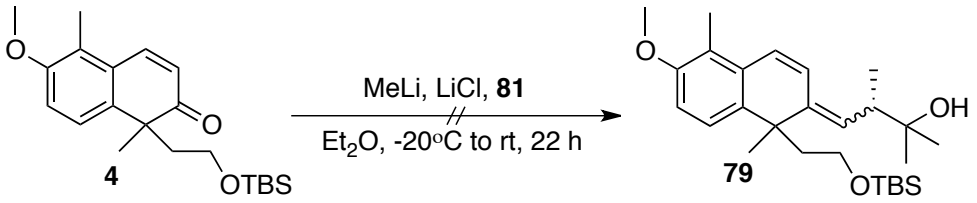
Scheme 50

Phosphonium salt **81**, exhibits an interesting reaction profile within Wittig olefination chemistry. The species is initially treated with one equivalent of base, resulting in deprotonation of the alcohol unit, which facilitates cyclisation to form oxaphospholane **86**.[44] A second equivalent of base will deprotonate the methylene carbon adjacent to the phosphorus to yield the highly reactive anion **87** (**Scheme 51**). Hanekamp and coworkers conducted an exhaustive optimisation study in order to deduce the most efficient base to facilitate rapid ylide formation.[44] After extensive study, it was discovered that methyl lithium (MeLi), treated with lithium chloride (LiCl), was the optimum base; the small size of the base is key to facilitating deprotonation of the sterically hindered methylene unit of **86**.



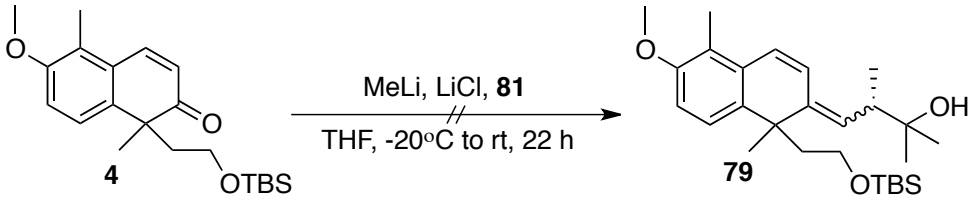
Scheme 51

Inspired by the reports of Hanekamp *et al*.[44] the freshly generated phosphonium salt, **81**, was treated with a solution of MeLi and LiCl (**Scheme 52**). Pleasingly, a red solution was formed, a colour change indicative of the formation of the desired ylide. Accordingly, enone **4** was added as a solution in diethyl ether and the resulting mixture was allowed to stir for a sustained period of time. Unfortunately, upon quenching the reaction, ^{1}H NMR analysis indicated that the desired product had failed to form.



Scheme 52

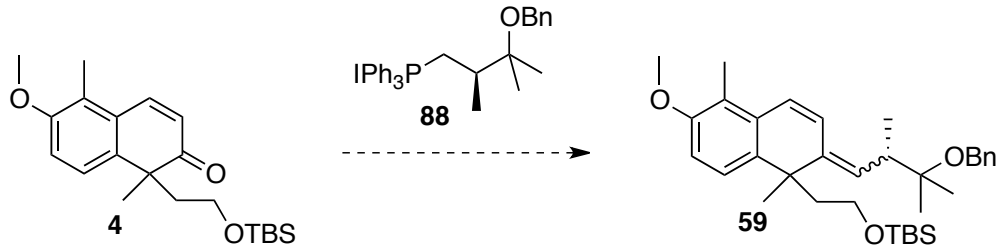
It was reasoned that the sterically hindered nature of the carbonyl unit, was potentially too cumbersome for the ylide to attack. Having stated this, Hanekamp and coworkers employed diethyl ether and THF interchangeably as the reaction solvent. It was envisaged that employing THF may offer a subtle enhancement to the reaction protocol. As such, ylide **87** was formed in a solution of THF, before the addition of the enone electrophile **4** (**Scheme 53**). Disappointingly, this protocol failed to deliver the desired species.



Scheme 53

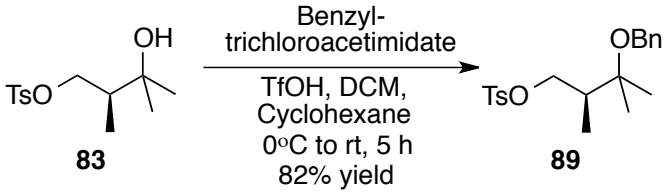
The frustrating outcome of these initial Wittig reactions led to the reevaluation of the ylide species. As proposed earlier, it was envisaged that the enhanced reactivity of the ylide species could potentially overcome the steric issues relating to the reaction. However, a less reactive and more robust ylide may offer a greater chance of success. It was reasoned that the lifetime of the enhanced ylide, **87**, may be limited. Based on this, it is possible that species **87** undergoes a degradation pathway before gaining the opportunity to react with enone **4**. As such, it was envisaged that a more traditional phosphonium ylide may offer the greatest chance of success. It was reasoned that protecting the alcohol functionality of phosphonium salt **81** as a benzylic ether would

grant access to a more robust nucleophile, **88**, that may facilitate the formation of the desired diene **59** (**Scheme 54**).



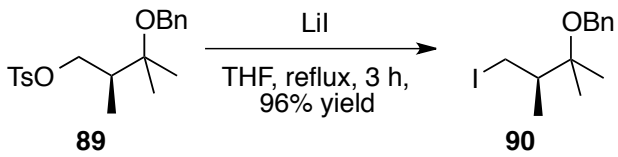
Scheme 54

With this revised plan in hand, attention turned to accessing the desired phosphonium salt, **88**. With this in mind, the previously prepared tosylate **83** was utilised in order to access the benzyl protected analog **89**. The tertiary alcohol of tosylate **83** was reacted with benzyltrichloroacetimidate under acidic conditions to furnish intermediate **89** in an 82% yield (**Scheme 55**).



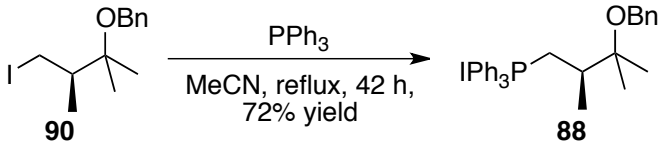
Scheme 55

Pleasingly, tosylate **89** was converted to the corresponding iodide **90** in near quantitative yield (**Scheme 56**).



Scheme 56

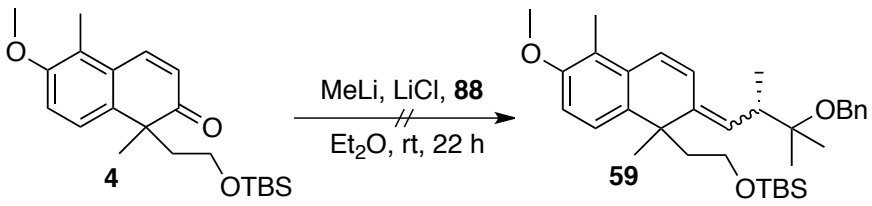
The requisite phosphonium salt **88** was accessed *via* the same preparative approach as applied previously, delivering **88** in a 72% yield (**Scheme 57**).



Scheme 57

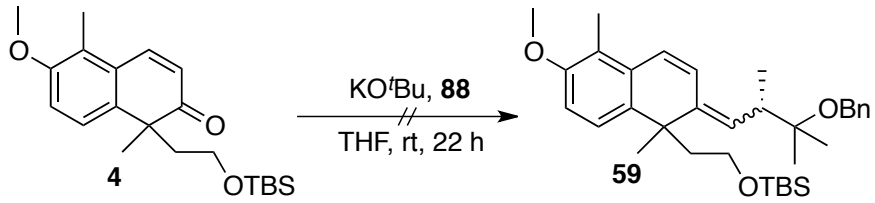
It should be noted that although the phosphonium ylide resulting from salt **88** is likely to be less reactive than that afforded from salt **81**, the ylide derived from **88** should prove much more robust. The deprotonation of oxaphospholane **86** is complicated by the steric bulk surrounding the methylene carbon, and as a result, many bases traditionally employed in the Wittig reaction proved unsuitable in terms of inducing the necessary anion formation. As such, the amended phosphonium salt, **88**, afforded the opportunity to evaluate alternative bases that could expedite the formation of a comparatively more stable phosphonium ylide species.

Before investigating an alternative base, it was decided to simply transpose the conditions utilised in the previous Wittig attempt. Accordingly, phosphonium salt **88**, was treated with a solution of methyllithium and lithium chloride (**Scheme 58**). Pleasingly, upon addition of the base, a distinct colour change was observed; the white suspension became a clear yellow solution. Following this, enone **4** was added as a solution in diethyl ether. Unfortunately, after a prolonged reaction time the desired diene, **59**, failed to form.



Scheme 58

Based on the above result, it was decided that employing an alternative base system under room temperature reaction conditions may offer access to conjugated alkene **59**. As such, phosphonium salt, **88**, was treated with potassium *tert*-butoxide at room temperature before the addition of enone **4** (**Scheme 59**). It was rationalized that this method of forming the ylide at a higher temperature with a different counter-ion may have resulted in accessing the desired diene, **59**. However, in a similar outcome to the previous attempts, diene **59** failed to form and a complex mixture of products was observed.

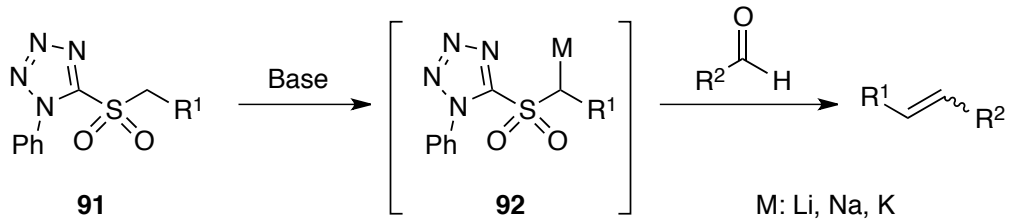


Scheme 59

Based on the outcome of the Wittig olefination study, it was decided to investigate alternative olefination techniques.

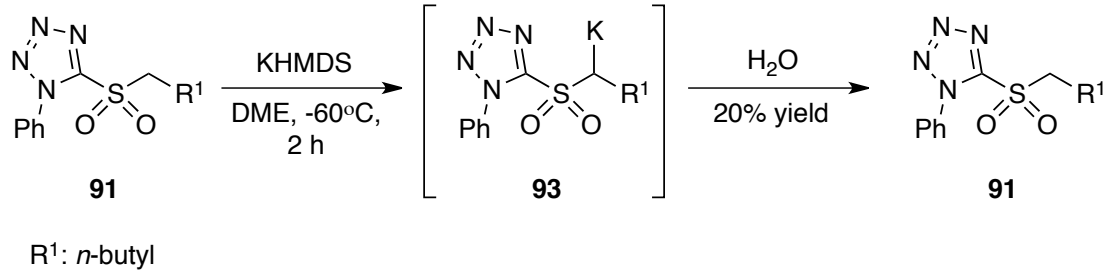
3.2.2 Julia-Kocienski Olefination

The Julia-Kocienski olefination has proven to be a widely efficient method of carbon-carbon bond formation.[45] Traditionally, the reaction employs a functionalised sulfone unit, such as **91**, and an aldehyde, or ketone, coupling partner (**Scheme 60**). The Julia-Kocienski reaction proceeds *via* a carbanion, of type **92**, formed by the deprotonation of the sulfone moiety, which attacks the aldehyde, or ketone, present to ultimately afford an olefin product.



Scheme 60

Based on the results obtained with the highly reactive phosphonium ylide species, **87**, it was evident that the highly reactive oxaphospholane species, was potentially degrading before reacting with the carbonyl unit. As such, forming a stable carbanion was at the forefront of the amended synthetic strategy. Kocienski has shown that a potassium metallate can attain impressive yields within olefination processes, however the anionic species degrades rapidly. This hypothesis was verified by the formation of a potassium metallate, **93**, which was subsequently quenched with water. If the metallate was stable it stands to reason that a quantitative amount of the starting material would be recovered. However, the starting material was recovered in a poor 20% yield suggesting that alternative pathways were involved (**Scheme 61**).

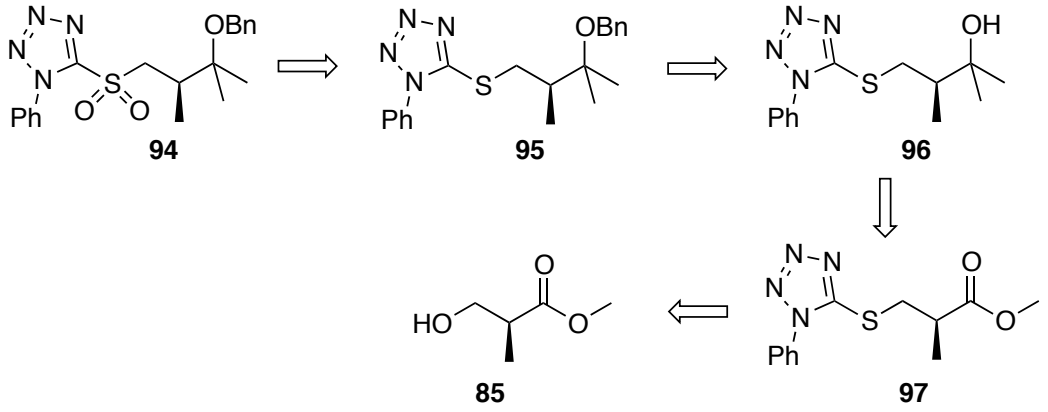


Scheme 61

In relation to this, maintaining a reactive anionic species in the reaction mixture for a sustained period of time was reasoned to offer the greatest chance of success. The sterically encumbered nature of enone **4** would undoubtedly hinder the reaction, potentially leading to an extended reaction time. As such, it was reasoned that judicious

choice of base would be instrumental in successfully promoting the formation of diene **59**. In addition, the employment of enones and ketones, as opposed to aldehydes, in the Julia-Kocienski reaction is not readily encountered in the chemical literature. Having stated this, there is precedent for such a reaction: Markó and Craig reported a modified Julia-Lythgoe olefination that granted access to a range of trisubstituted alkenes.[46] Based on this, it was reasoned that the Julia-Kocienski reaction could offer access to the desired diene **59**.

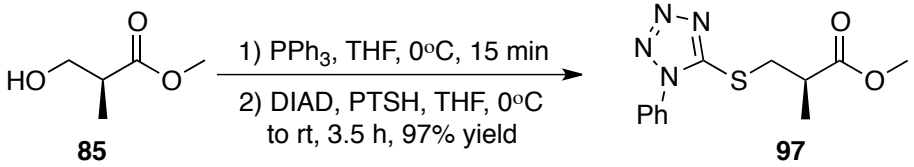
At this juncture, the immediate priority was accessing the suitably functionalised sulfone unit **94**. Accordingly, an expedient synthetic strategy, starting from the previously utilised chiral Roche ester, was devised (**Scheme 62**). It was rationalised that sulfone **94**, could be accessed from the analogous thioether, **95**, which in turn could be accessed from alcohol **96**. The alcohol could conceivably be accessed *via* a Grignard reaction with the corresponding ester **97**. In turn, this intermediate could potentially be accessed from the previously utilised chiral Roche ester, **85**.



Scheme 62

On consulting the literature, thioether **97** was readily accessible, albeit in the form of the opposite enantiomer.[47] Accordingly, the synthetic protocol employed by Kirschning and coworkers was replicated and a Mitsunobu reaction, utilising diisopropyl azodicarboxylate (DIAD) and phenyltetrazole thiol (PTSH), was carried out on the chiral

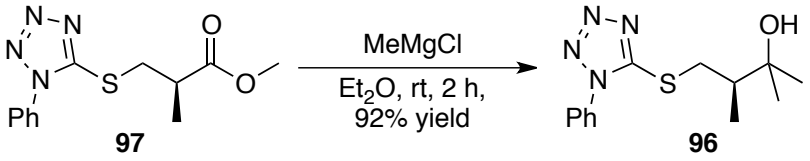
Roche ester **85**. Pleasingly an excellent 97% yield of enantiomerically-enriched thioether **97** was obtained (**Scheme 63**).



85 **97**

Scheme 63

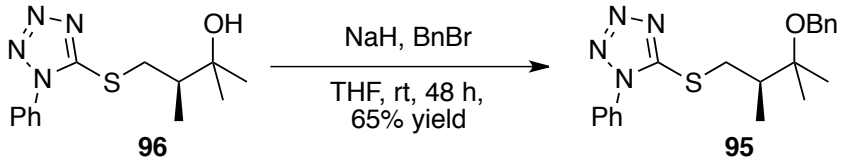
In an analogous approach to that employed with substrate **85**, thioether **97** was treated with an excess of methylmagnesium chloride to deliver the corresponding alcohol in a gratifying 92% yield (**Scheme 64**). The improved yield of **96**, in comparison to diol **84**, is attributed to the comparatively greater hydrophobic character of thioether **96**.



97 **96**

Scheme 64

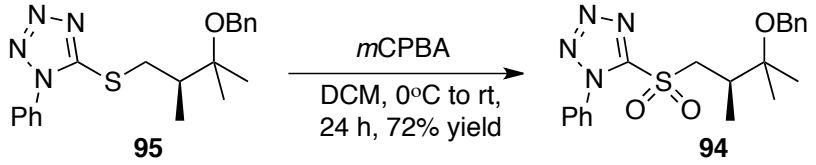
It was deemed necessary to protect the newly formed tertiary alcohol. Accordingly the alcohol was transformed to its benzylic ether, which was reasoned to afford adequate protection of the hydroxyl unit. In this regard, a traditional Williamson ether synthetic approach was employed to afford the desired protected thioether **95** in a moderate 65% yield.



96 **95**

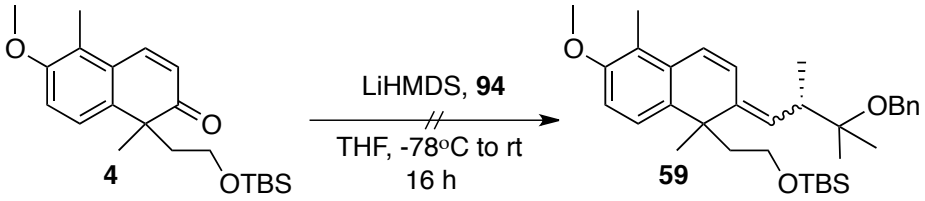
Scheme 65

Following this, *meta*-chloroperoxybenzoic acid was employed to oxidise thioether **95** to the desired sulfone **94**. The reaction proceeded smoothly to deliver **94** in a pleasing 72% yield.



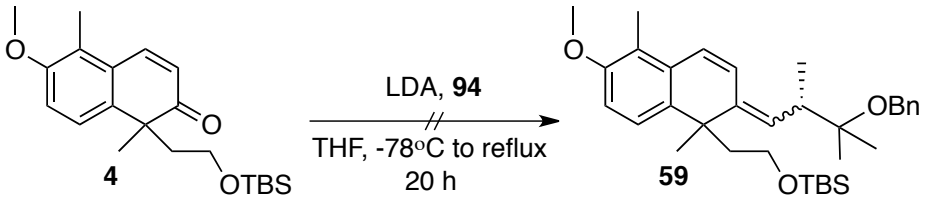
Scheme 66

With both coupling partners prepared, attention turned to the Julia-Kocienski olefination. It was decided that a lithiated sulfone would potentially grant the greatest chance of successful olefination, owing to the comparably more robust nature of lithium metallates over their potassium analogues (*vide supra*). Based on this, lithium bis(trimethylsilyl) amide (LiHMDS) was employed under traditional Julia-Kocienski olefination conditions (**Scheme 67**). Disappointingly, the desired transformation failed to occur and a complex range of products was observed.



Scheme 67

In order to probe the reactivity of an alternative base, lithium diisopropylamide (LDA) was employed in the Julia-Kocienski reaction (**Scheme 68**). Disappointingly, a similar result was obtained whereby a complex range of products formed under the reaction conditions.



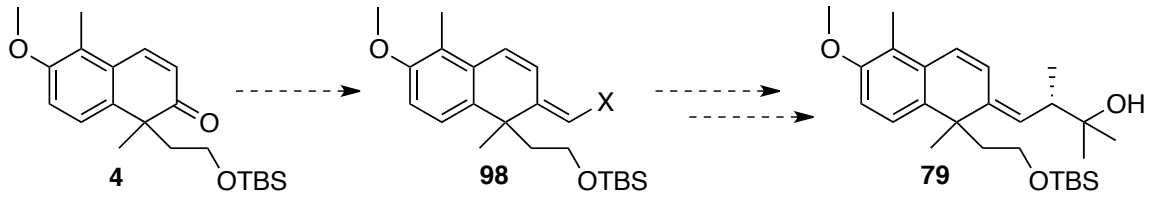
Scheme 68

At this juncture, the synthetic approach was given serious consideration. There remained the potential for exhaustive, and potentially time-consuming, investigative studies relating to the promotion of the Julia-Kocienski and/or Wittig reaction. As highlighted previously, Marko and Craig had reported the synthesis of tri-substituted olefins *via* a modified Julia-Lythgoe reaction.[46] However, as discussed, accessing diene **59** in an expedient fashion was of paramount importance and the installation of the oxygenated sidechain underpinned the entire synthetic strategy. Based on this, a difficult decision required addressing: would a sustained investigation of the aforementioned olefination techniques offer access to the diene or would an amended strategy prove more successful? The choices made at this stage would almost certainly resonate throughout the remainder of the research programme.

3.2.3 Stork-Zhao Olefination

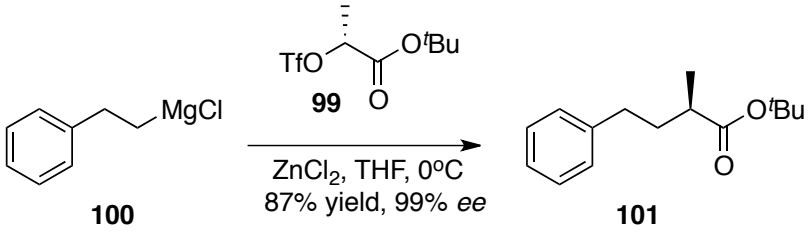
After careful consideration it was reasoned that the functionalised sidechain units required for the Wittig and Julia-Kocienski reactions, respectively, where potentially too sterically encumbered to interact with the ensconced carbonyl unit of enone **4**. It was obvious that a less sterically hindered nucleophile would be key in the amended protocol. Based on this, it was decided to investigate a simplified olefination that would allow access to diene **79** *via* subsequent synthetic manipulations. Accordingly, a hypothetical synthetic pathway was formulated (**Scheme 69**). In an ideal situation, a simple carbon homologation of enone **4** would deliver functionalised diene **98**, with X being a

functional handle that could be exploited in order to install the desired oxygenated sidechain.



Scheme 69

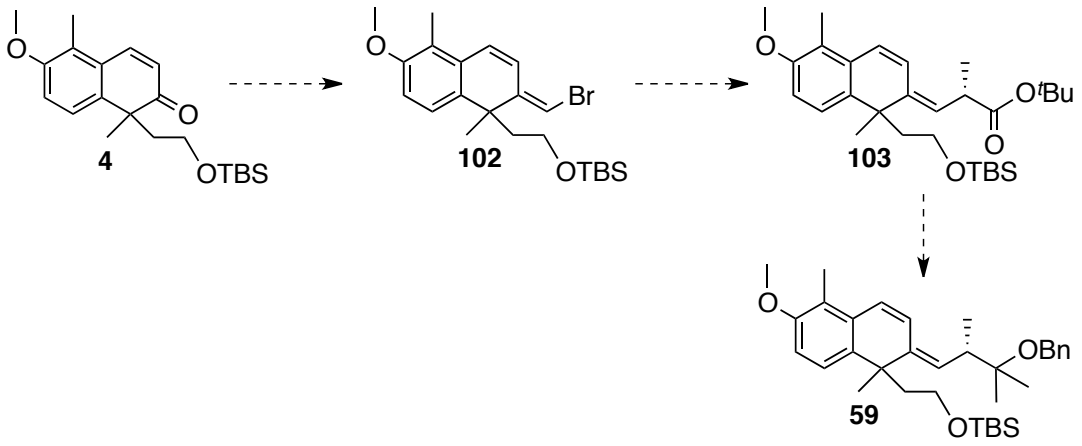
After an extensive literature search a suitable synthetic approach was devised. It is widely appreciated that organometallic derivatives of vinyl bromides reproducibly undergo nucleophilic addition reactions. Accordingly, identifying a suitable electrophilic coupling partner was imperative. Pleasingly, upon consulting the literature it was discovered that triflate **99** had previously been employed in stereospecific organometal-mediated displacement reactions, with excellent results obtained with respect to chemical yields and, importantly, optical purity (**Scheme 70**).[48] As such, this represented a promising a synthetic strategy towards diene **79**.



Scheme 70

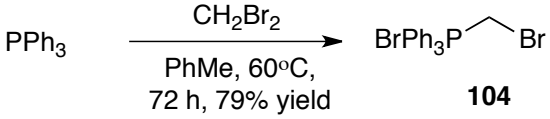
With the above information in hand, attention turned to devising a specific synthetic approach. It was envisaged that a Stork-Zhao olefination of enone **4** would deliver bromo-olefin **102**,[49] which could undergo an organometal-mediated displacement to

introduce the optically pure sidechain unit in **103**. Further synthetic manipulations would facilitate access to diene **59**.



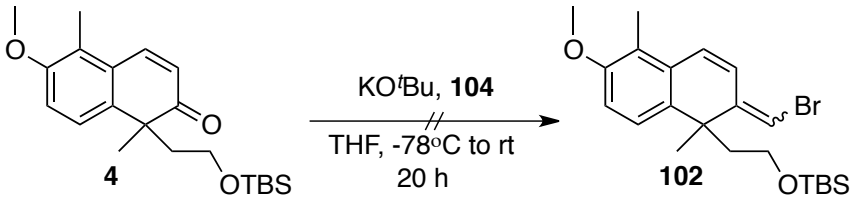
Scheme 71

Following this, attention turned towards accessing the vinyl bromide coupling partner **102**. Before this could be attempted, the requisite bromomethyl phosphonium salt **104** had to first be prepared. In this vein, salt **104** was accessed in a 79% yield *via* a scalable approach disclosed in the literature (**Scheme 72**).[50]



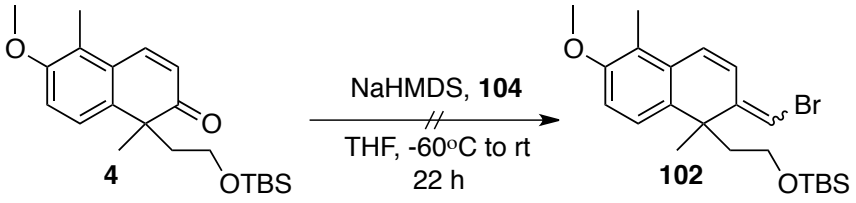
Scheme 72

With both components for the required Stork-Zhao olefination prepared, initial attempts at this reaction commenced. Unfortunately, employing potassium *tert*-butoxide under literature disclosed Stork-Zhao reaction conditions failed to promote the desired reaction and several unwanted by-products were formed (**Scheme 73**).[51]



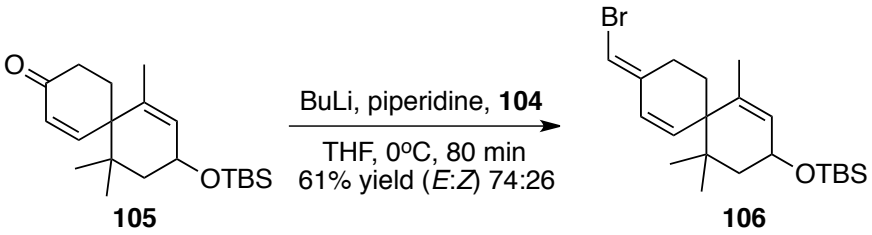
Scheme 73

Undeterred, an alternative base, sodium bis(trimethylsilyl) amide (NaHMDS), was employed in a subsequent Stork-Zhao reaction (**Scheme 74**). Using a literature protocol, a staggered temperature approach was employed whereby the reaction mixture was stirred for 3 hours at -60°C, 2 h at -40°C, and 12 hours at -5°C before warming to room temperature.[52] The reaction was carefully monitored during this time but unfortunately this protocol failed to promote the formation of the desired product and a complex mixture of products was observed.



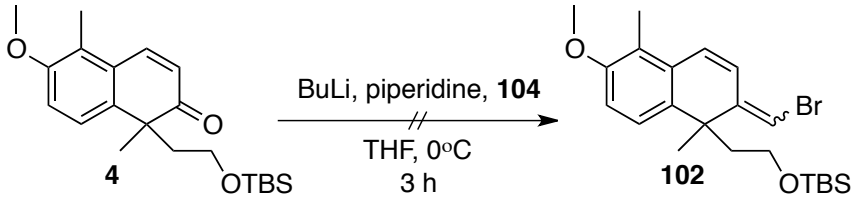
Scheme 74

In an effort to address the issues encountered, an extensive literature search was carried out in order to identify an enone moiety that readily underwent a Stork-Zhao olefination. After a comprehensive search such an example was found (**Scheme 75**).[53] Zhu *et al*. employed a Stork-Zhao olefination, with a lithium piperidide base, in the formation of key vinyl bromide, **106**, as a part of a total synthesis programme. As such, it was reasoned that employing the exact conditions employed by Zhu may offer access to the desired vinyl bromide **102**.



Scheme 75

Based on the reports of Zhu, lithium piperidide was utilised in the attempted formation of vinyl bromide, **102** (**Scheme 76**). Disappointingly, this reaction protocol failed to deliver the desired olefinic species and ^{1}H NMR analysis revealed the absence of **102**, and an extensive mixture of products. Based on the results obtained throughout the olefination study, it was decided that more forcing conditions might offer access to the desired species, albeit *via* an extended synthetic pathway.

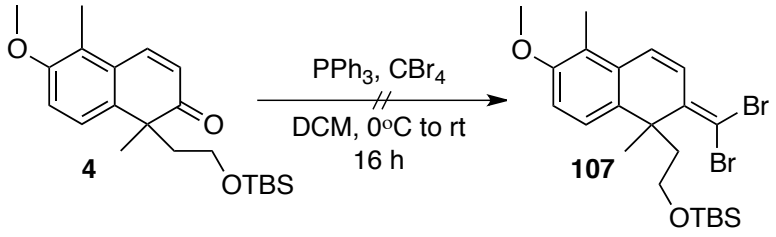


Scheme 76

3.2.4 Ramirez Olefination

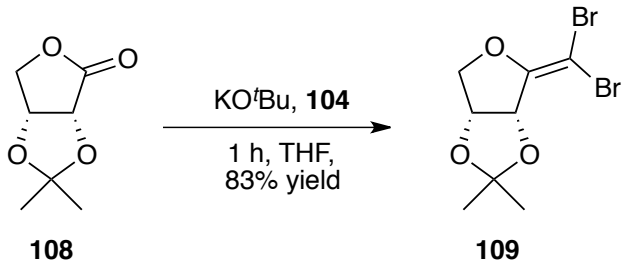
Due to the difficulties encountered in accessing vinyl bromide **102**, it was decided to investigate an alternative approach employing a more robust and widely encountered nucleophile. Based on this, it was reasoned that a Ramirez olefination would satisfy these requirements and could offer access to the dibromo olefin **107**.[54] With **107** in hand it may be possible to selectively reduce the dibromoolefin moiety **107** to the desired vinyl

bromide **102**. Accordingly, enone **4** was subjected to traditional Ramirez reaction conditions (**Scheme 77**). Disappointingly, the desired product, **107**, failed to form.



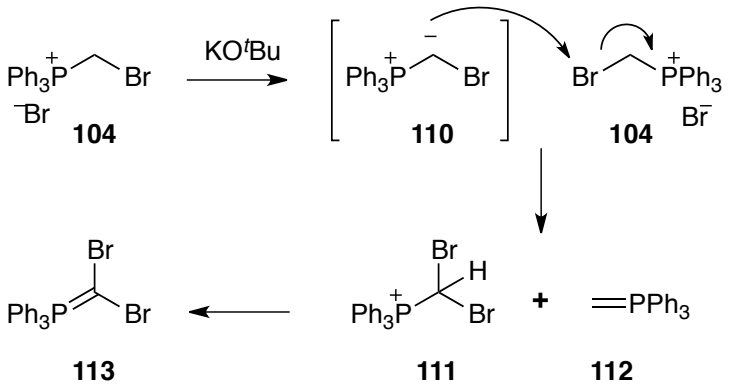
Scheme 77

Despite the above, it has been demonstrated that compounds traditionally considered poor substrates within the Ramirez reaction are able to undergo reaction when explicit forcing conditions are employed. Chapleur *et al.* facilitated the dibromo olefination of lactone substrates utilising phosphonium salt **104** and potassium *tert*-butoxide at high temperatures.[55]



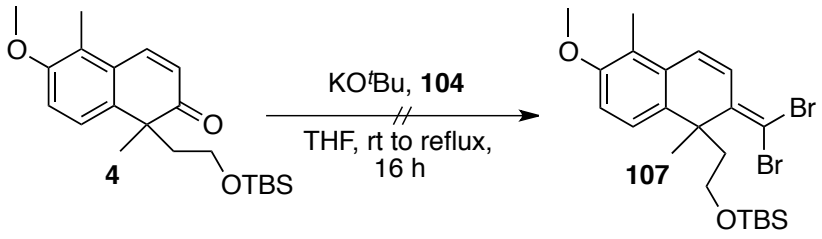
Scheme 78

Chapleur proposed a mechanism to account for this transformation as described in **Scheme 79**. At increased temperatures the ylide, **110**, quenches itself to result in **113**. Species **110** can abstract the bromine functionality from the phosphonium salt **104** to form **111** and **112**, the newly formed methylene ylide **112** can then deprotonate **111** to form the dibromo unit **113**. The resulting ylide is then capable of undergoing a traditional Ramirez reaction to deliver the desired dibromo olefin.



Scheme 79

Inspired by this, it was anticipated that Chapleur's conditions could be transposed to enone **4** (**Scheme 80**). However, even these extremely forcing conditions failed to deliver the desired diene **107**.

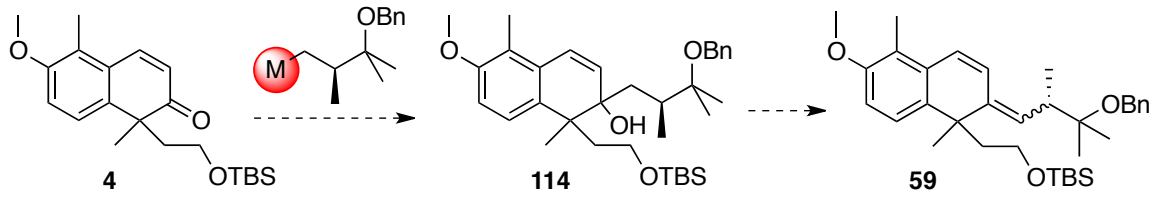


Scheme 80

Based on the aforementioned poor reactivity of enone **4** within the realm of olefination chemistry, an impasse had been reached. It was considered unlikely that an olefination reaction would serve to readily introduce the desired oxygenated sidechain. With this in mind, the synthetic strategy towards diene **79** was, again, re-evaluated. It was envisaged that a 1,2-organometallic addition protocol, followed by elimination, would offer a greater chance of success.

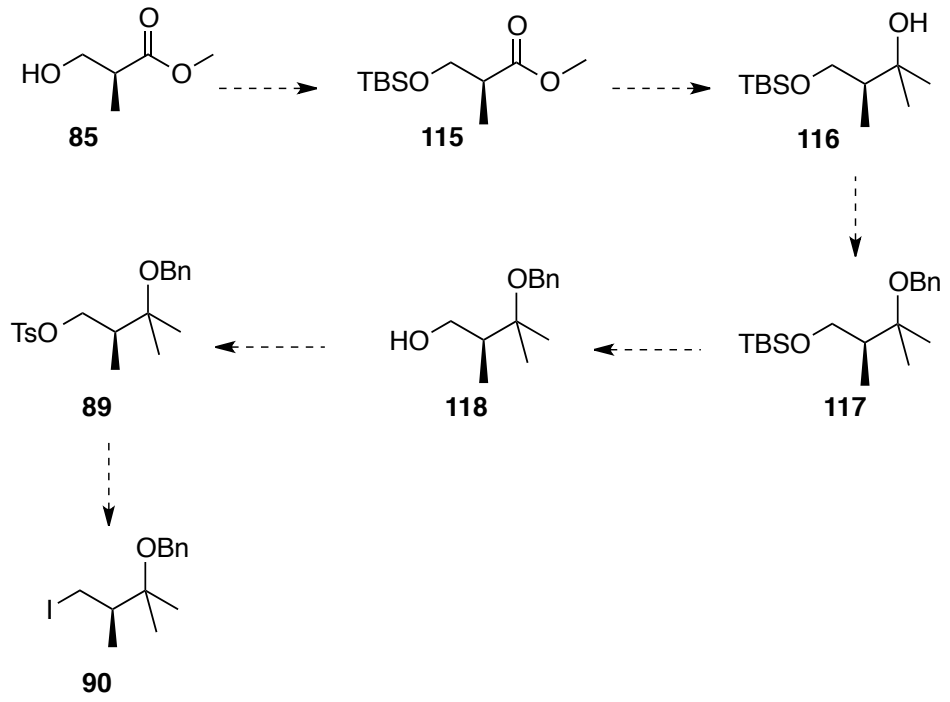
3.3 Installation of the Oxygenated Sidechain – 1,2-Organometallic Addition Chemistry

It was envisaged that a suitably functionalised organometallic species would grant access to diene **59**, either directly or *via* subsequent synthetic manipulations (**Scheme 81**). Having said this, this synthetic approach is complicated by two major factors; formation of a primary sp^3 organometallic species is a non-trivial task and, in addition, selective 1,2-addition is complicated by the steric bulk of the moiety, with a competing 1,4-addition pathway also being possible. If these issues can be successfully overcome then this approach would offer access to the integral diene species **59**.



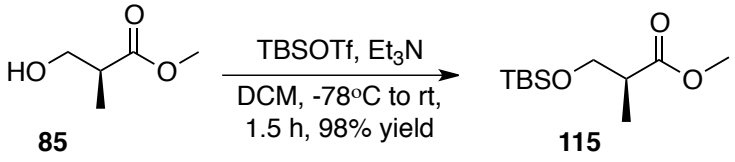
Scheme 81

It was decided that the previously formed alkyl iodide, **90**, would grant access to a range of analogous organometallic species. Having stated this, it was desirable to improve upon the existing synthetic strategy to alkyl iodide **90**. Previously, the isolation of the key diol intermediate, at the outset of the synthesis, had proven inefficient with a moderate yield obtained (**Scheme 47**). In contrast, the corresponding reaction performed *en* route to the Julia-Kocienski coupling partner proceeded in a much improved yield (**Scheme 64**). Inspired by this, it was deemed advantageous to protect the alcohol unit of the Roche ester, **85**, before attempting the Grignard reaction, as this would render the isolation of the tertiary alcohol, **116**, much more facile (**Scheme 82**). Although this adds a protection, and deprotection, step it would hopefully facilitate the formation of an improved quantity of alkyl iodide **90**.



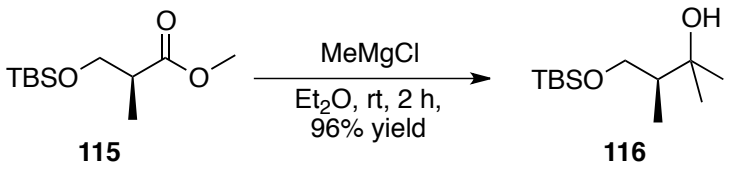
Scheme 82

The amended strategy commenced with protection of the free alcohol unit of the Roche ester starting material (**Scheme 83**). Accordingly, a silyl protecting group was selected as it would afford adequate protection of the alcohol unit, and would offer orthogonal deprotection conditions relative to the benzyl protected tertiary alcohol present in subsequent intermediate **117**. Pleasingly, the protection proceeded in a near quantitative yield of 98% after only 1.5 h reaction time.



Scheme 83

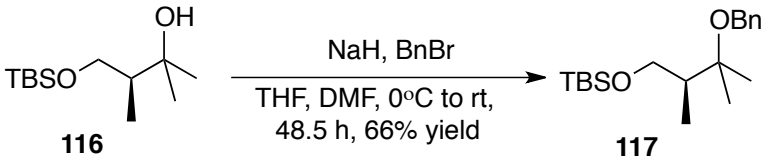
With the protected material in hand, attention turned to the formation of the tertiary alcohol unit of alkyl iodide **90**. As stated previously, during the initial synthetic sequence the formation of a diol species led to incomplete recovery of the product as the water soluble diol species proved difficult to extract. It was envisaged that the protected species, **115**, would circumvent this issue as the resulting alcohol would be less water-soluble relative to the aforementioned diol **84**. Pleasingly, this proved to be the case and following addition of methylmagnesium chloride, alcohol **116** was isolated in an excellent 96% yield (**Scheme 84**).



115 **116**

Scheme 84

It was decided that a Williamson ether synthesis would grant access to the benzyl ether species **117**. Accordingly, alcohol **116** was treated with sodium hydride and reacted with benzyl bromide. Disappointingly, after a prolonged reaction time a moderate 66% yield was obtained (**Scheme 85**). This poor result was attributed to the steric bulk around the anionic oxygen restricting access of the electrophile.

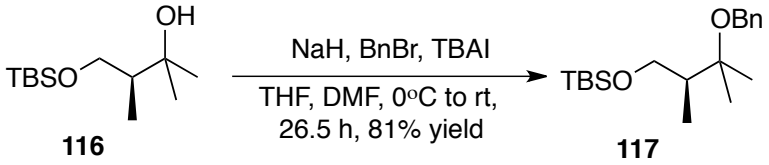


116 **117**

Scheme 85

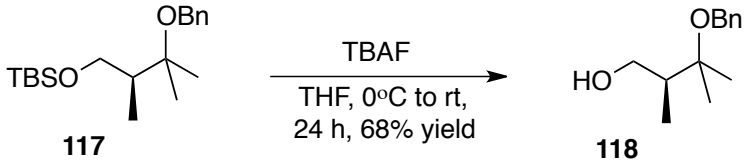
Owing to the poor reactivity observed above, it was envisaged that a more reactive electrophile may offer access to intermediate **117** in an improved yield. Based on this, *tetra*butylammonium iodide (TBAI) was added to the reaction mixture in an effort to

promote an *in-situ* Finkelstein reaction to form benzyl iodide. Pleasingly, this led to a significantly enhanced 81% yield (**Scheme 86**).



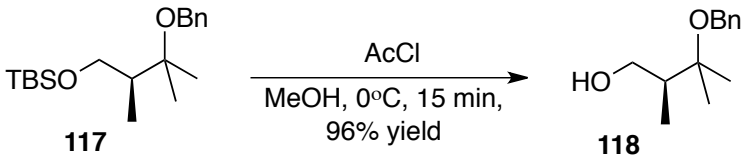
Scheme 86

Following this, the removal of the silyl protecting group was to be carried out. This was facilitated by treatment with TBAF over the course of 24 hours to afford alcohol **118** in a 68% yield (**Scheme 87**). The liberation of the primary alcohol proved to be a rather lengthy process and employed several equivalents of TBAF. In an effort to address the inefficiencies of this transformation an alternative deprotection strategy was envisaged.



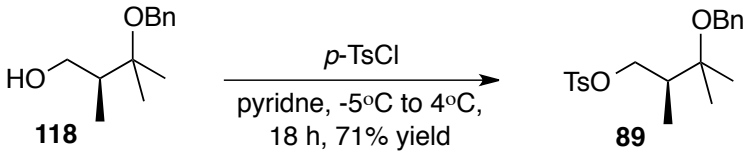
Scheme 87

On consulting the chemical literature it was discovered that acetyl chloride efficiently removed silyl protecting groups over the course of a few minutes. The deprotection is attributable to small quantities of hydrochloric acid present in acetyl chloride. Pleasingly, this approach granted access to alcohol **118** in a 96% yield with the reaction progressing to completion over the course of 15 minutes (**Scheme 88**).



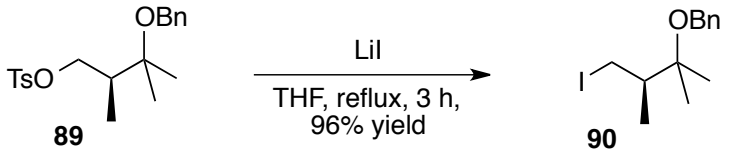
Scheme 88

With alcohol **118** in hand, attention turned to activating the alcohol as a tosylate intermediate **89**. In this regard, alcohol **118** was treated with tosyl chloride and pyridine to deliver the tosylate species **89** in a 71% yield (**Scheme 89**).



Scheme 89

Finally, tosylate **89** was transformed to the key alkyl iodide species **90** upon treatment with lithium iodide. This delivered the key species **90** in a 96% yield (**Scheme 90**).

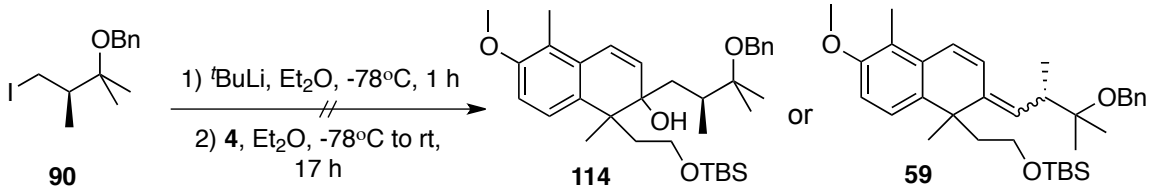


Scheme 90

With a robust and high yielding strategy towards alkyl iodide **90** in hand, focus turned to introducing the requisite oxygenated sidechain to the bicyclic core of the molecule *via* the use of a 1,2-organometallic addition process.

3.3.1 Organolithium Addition

It was reasoned that a suitably functionalised organolithium species represents a promising nucleophile with respect to promoting the desired transformation.[56] Based on this, alkyl iodide **90** was to be employed in the organometallic addition reaction. The capricious nature of primary sp^3 organolithium species was given careful consideration in the design of the preliminary reaction. It was likely that maintaining a low temperature environment throughout the course of the reaction would likely lead to an enhanced lifetime of the organolithium agent. As such, a stirred solution of alkyl iodide, **90**, was treated with a solution of *tert*-butyllithium (^{t}BuLi) at -78°C for 1 hour (**Scheme 91**). After this time, the lithiated material was transferred *via* cannula, to a solution of enone **4**. Upon complete addition, the reaction mixture was stirred for 3 hours at -78°C, before warming to room temperature and stirred for a further 14 hours. Unfortunately, this approach proved unsuccessful and an appreciable quantity of alkyl iodide, **90**, was obtained from the reaction mixture. As such, it can be deduced that the initial lithiation conditions failed to deliver appreciable quantities of the desired organolithium species.

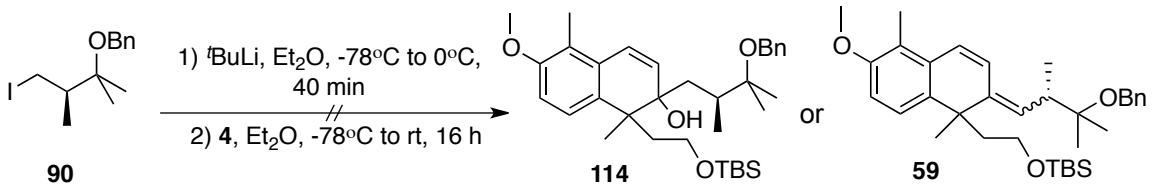


90 **114** **59**

Scheme 91

Based on the failure to form the desired organolithium species, a modified protocol was employed. It was thought that, comparably, more forcing conditions may grant access to the requisite organolithium species and hence facilitate access to alcohol **114** or diene **59**. With this in mind, alkyl iodide **90** was treated with a solution of ^{t}BuLi at -78°C. This time, upon complete addition, the mixture was warmed to 0°C over the course of 30 minutes (**Scheme 92**). Upon reaching 0°C, the reaction mixture was stirred for 10

minutes before re-cooling to -78°C. The material was transferred to a solution of enone **4** *via* cannula, as before, and left to react overnight. In contrast to the previous attempt, complete conversion of the alkyl iodide, **90**, was observed, however, the desired allylic alcohol, **114**, and/or diene, **59**, were not present in the reaction mixture. Based on this, it was surmised that the alkyl iodide, **90**, had underwent degradation upon exposure to the harsh lithiation conditions.

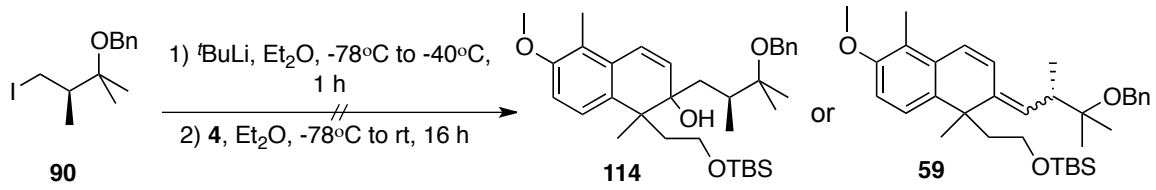


90 **114** **59**

Scheme 92

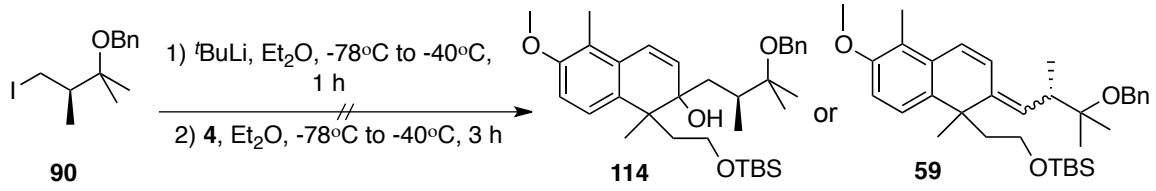
Taking an overview of the previous attempts it was decided that careful control of the initial lithation conditions would offer the greatest chance of success. Inspired by the preliminary investigations, alkyl iodide was treated with a solution of ^{t}BuLi at -78°C, followed by warming to -40°C (**Scheme 93**). The mixture was stirred at this temperature for 1 hour before re-cooling to -78°C. In order to monitor the lithiation process, a small aliquot of the reaction mixture was removed and quenched with acetone. The resulting solution was examined by thin-layer chromatography (TLC) and analysis of this indicated complete consumption of the alkyl iodide, **90**, and the presence of several new spots of differing intensities. It was naïve to expect a clean reaction profile for such a capricious substrate, therefore, based on the complete consumption of **90** it was decided that this lithiation protocol potentially offered the greatest chance of success. The lithiated material was transferred *via* cannula to a stirred solution of enone **4**, stirred for 2 hours at -78°C, before warming to room temperature and stirred overnight. Dishearteningly, the desired allylic alcohol, **114**, and/or diene **59** failed to form over the course of the reaction and instead a complex range of products was observed. It was reasoned that the lithiation was proceeding as hoped, however, it was unlikely to occur in an efficient manner. Having stated this, this lithiation protocol represented the most

efficient to date and, as such, it was decided to emulate the lithiation conditions in subsequent attempts, whilst simultaneously modifying the enone addition protocol.



Scheme 93

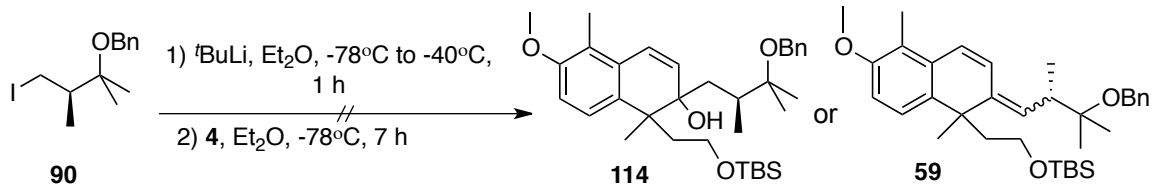
It was reasoned that allowing the organolithium and enone mixture to warm to room temperature may have been proving detrimental to the reaction. It is likely that at these temperatures, the organolithium species is able to undergo numerous side reactions. As such it was decided to maintain a low temperature environment for the duration of the reaction (**Scheme 94**). Upon addition of the organolithium agent to the enone, the resulting mixture was allowed to warm to -40°C over the course of 3 hours, before the reaction was quenched. Unfortunately, this modified protocol failed to offer access to the desired compound(s), **114**/**59**. In a similar fashion to that above, a range of products was observed. Based on this, it was proposed that maintaining the reaction temperature at -78°C for the duration of the reaction may offer the greatest chance of success.



Scheme 94

The reaction was repeated as before, but upon addition of the lithiated material to enone **4** the reaction temperature was maintained at -78°C for 7 hours before being quenched

(**Scheme 95**). Frustratingly, this approach failed to grant access to **114** and/or **59**, and instead led to the formation of a range of compounds.



Scheme 95

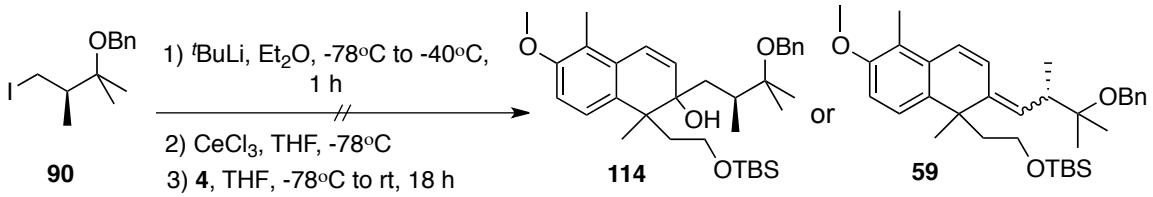
Upon reflection, it was reasoned that the organolithium species represents an especially capricious substrate and may be unsuitable for the desired transformation. The sterically hindered carbonyl unit serves to further complicate matters and as such the synthetic strategy was re-considered. As stated previously, the two major barriers to overcome in the promotion of the desired reaction are the formation of a suitable, and stable, organometallic agent and circumventing the steric issues relating to attack at the carbonyl unit of **4**. Indeed, alkyl iodide, **90**, was undergoing complete conversion, which was relatively satisfying, however it may be likely that the species was unable to access the encumbered carbonyl unit. As such, enhancing the nucleophilicity of the organometallic species may prove efficient with respect to inducing the desired 1,2-addition reaction pathway.

3.3.2 Organocerium Addition

Organocerium compounds are generally considered to be amongst the most nucleophilic organometallic species known. In addition, they are especially oxophilic and, as such, offer pronounced 1,2-addition selectivity in α,β-unsaturated ketone systems.[57] Based on this, it was decided to employ an organocerium reagent in an effort to access alcohol **114** and/or diene **59**. One of the most widely employed methods of generating an

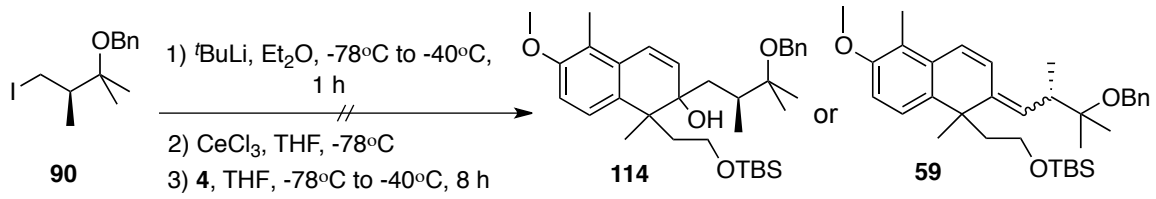
organocerium species is *via* transmetallation from the analogous organolithium complex.[58] As such, it was decided to employ this protocol in the attempted synthesis of diene **59**.

The initial lithiation was carried out as before and the lithiated material transferred, *via* cannula, into a stirred solution of cerium trichloride ($CeCl_3$). Following this, a solution of enone **4** was added and the resulting mixture stirred for 4 hours at -78°C before being stirred overnight at room temperature (**Scheme 96**). After this time, a complex mixture of products was observed, disappointingly, allylic alcohol **114** and/or diene **59** had failed to form. Upon reviewing the literature, it was reported that organocerium complexes are not robust at elevated temperatures. Accordingly, it was decided to employ comparably lower temperatures in the subsequent organocerium addition attempt.



Scheme 96

In a similar manner to that employed previously, alkyl iodide, **90**, was treated with ^{t}BuLi before transferring to a stirred solution of $CeCl_3$ (**Scheme 97**). Following this, enone **4** was added and the temperature held at -78°C for 1 hour. After this time, the mixture was warmed to -40°C and stirred for 7 hours at this temperature. Disappointingly, this failed to facilitate the formation of the desired compound(s), **114**/**59**, and again, a complex range of products was observed.



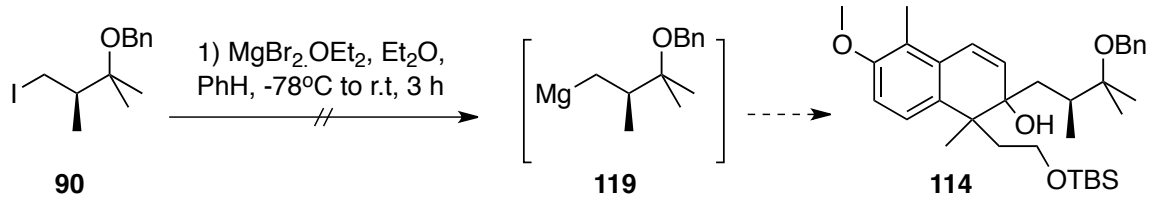
Scheme 97

In summary, the organocerium approach had proven unsuccessful and as such, consideration was given to the likely cause of this failure. Although, the ^{t}BuLi lithiation sequence was offering complete conversion of the alkyl iodide species, **90**, it was evident that this was not an efficient method of cleanly generating an appropriate organometallic moiety. Based on this, it was decided that an alternative organometallic species would offer an improved chance of success.

3.3.3 Organomagnesium Addition

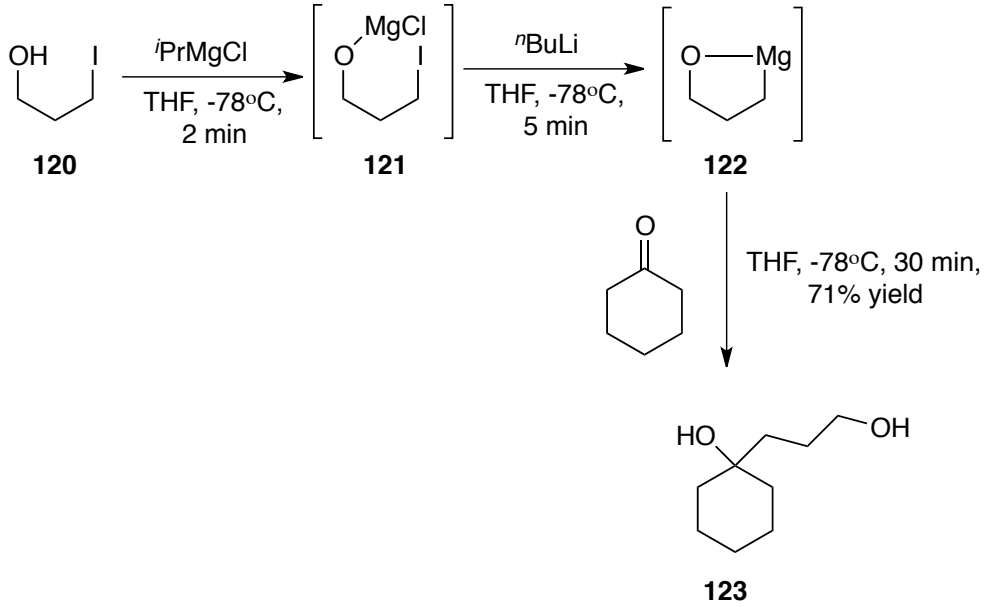
As stated previously, it was likely that the highly reactive organolithium was proving too capricious to utilise in a successful synthetic manipulation. As such, it was reasoned that employing an organometallic species that features a tempered reactivity profile may prove advantageous with respect to facilitating the formation of the desired diene **59**. Based on this, it was predicted that a suitably functionalised organomagnesium species would prove an efficient nucleophile in the organometallic addition sequence.[59] Having stated this, there remains the possibility for a 1,4-addition protocol over the desired 1,2-addition pathway.

The initial organomagnesium addition attempt employed $MgBr_2.OEt_2$ as the reagent to promote Grignard formation, however, the requisite organometallic species failed to form (**Scheme 98**). Based on this, it was decided that a review of the chemical literature would identify a suitable reaction protocol to facilitate the formation of the Grignard species.



Scheme 98

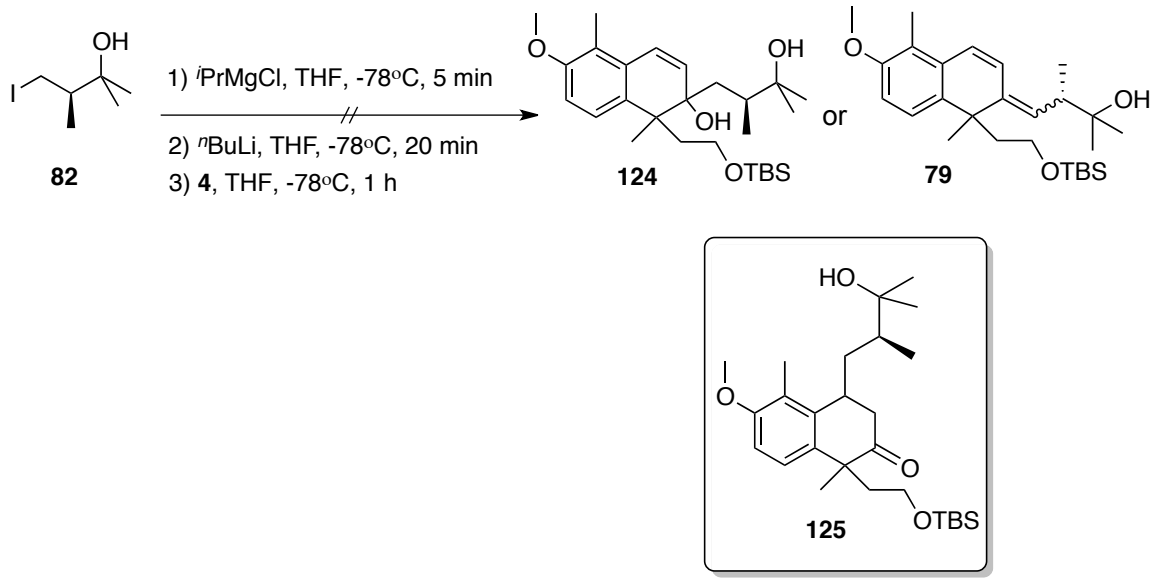
An extensive literature search uncovered an attractive method developed by Knochel and coworkers.[60] It was disclosed that sequential addition of isopropylmagnesium chloride (^{i}PrMgCl) and *n*-butyllithium (^{n}BuLi) to sp^3 hybridised iodoalcohols facilitated a facile iodine-metal exchange (**Scheme 99**).



Scheme 99

Encouragingly, 3-carbon δ-iodoalcohols, bearing alkyl substituents, represented the optimum substrates for this reaction protocol. Based on this, the previously accessed iodoalcohol **82** was subjected to the organomagnesium formation process. Alcohol, **82**, was treated with ^{i}PrMgCl and ^{n}BuLi in order to access to the requisite Grignard species.

Following this, the organometallic species was treated with enone **4**, and the resulting mixture stirred for a period of time (**Scheme 100**). The result of this reaction was initially rather pleasing, although this was to prove short-lived. It was apparent that a coupling reaction had taken place and the preliminary mass spectrometry trace contained a promising mass ion, however, the ^{1}H NMR spectrum was not representative of the 1,2-addition product. Subsequent IR analysis indicated the presence of a carbonyl unit, which suggested the formation of the 1,4-addition product, **125**, not the desired 1,2-addition product **124**.

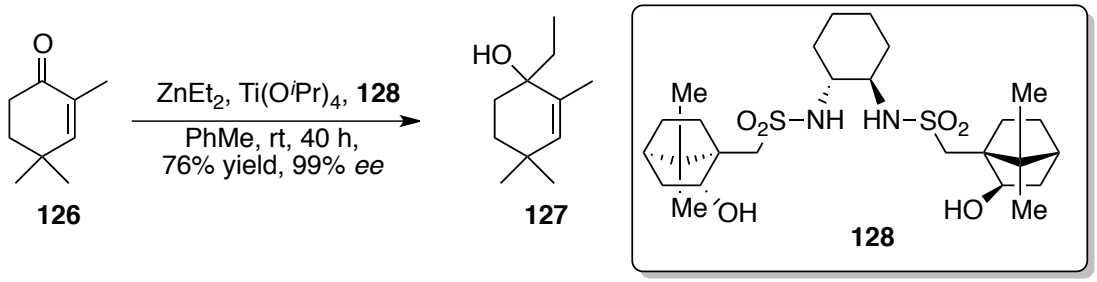


Scheme 100

Although the reaction had failed to deliver the desired product, there were a few positive aspects uncovered during the process. Chiefly among them was the formation of a suitably functionalised organomagnesium species. Based on this, it can be concluded that stable organometallic compounds of this ilk can be accessed, and reacted accordingly. As such, tempering the reactivity of the organometallic species may offer access to the desired 1,2-addition product.

3.3.4 Organozinc Addition

A review of the chemical literature highlighted the employment of alkylzinc reagents in the formation of tertiary alcohols.[61] Organozinc compounds are often employed in organometallic addition protocols, however, the reduced polarity of the zinc-carbon bond, in comparison to their organolithium counterparts, renders them soft nucleophiles. Based on this, it would seem likely that an addition protocol employing an organozinc species would offer access to the 1,4-addition product. Having stated this, Walsh and coworkers reported an organozinc, and sulfonamide-assisted, addition protocol that led to the formation of a range of tertiary alcohols when employing numerous α,β-unsaturated ketone substrates (**Scheme 101**).[62]

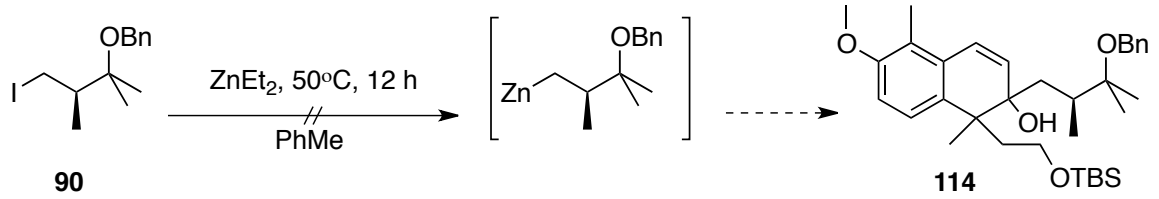


Scheme 101

Based on this disclosure it was decided to attempt the selective 1,2-addition of a suitably functionalised organozinc compound into enone **4**. The formation of organozinc compounds is a non-trivial process and requires manipulation of pyrophoric reagents under reduced pressure. Based on this, many examples of organozinc addition chemistry employ simple straight chain alkyl nucleophiles. However, it was desirable to attempt this transformation, as accessing diene **59** was integral to the synthetic programme.

In an effort to access a suitably functionalised organozinc species, alkyl iodide, **90**, was employed in a method disclosed by Knochel and co-workers.[63] Using this approach, alkyl

iodide, **90**, was treated with several equivalents of diethyl zinc before heating to 50°C for 12 hours (**Scheme 102**). After this time, the pyrophoric, and volatile, materials were removed under reduced pressure, theoretically resulting in the isolation of the desired organozinc species. The residue was immediately solubilised in toluene to provide an approximately 1 M solution. The organozinc species was subsequently hydrolysed and analysed by TLC and ^{1}H NMR. Disappointingly, upon analysing the reaction mixture it was noted that the key organozinc species had failed to form. Based on this, it was decided that due to the difficulties associated with forming the organozinc moiety, and the requirement to employ 3 equivalents of the precious chiral sidechain relative to the enone, an alternative approach would be investigated.



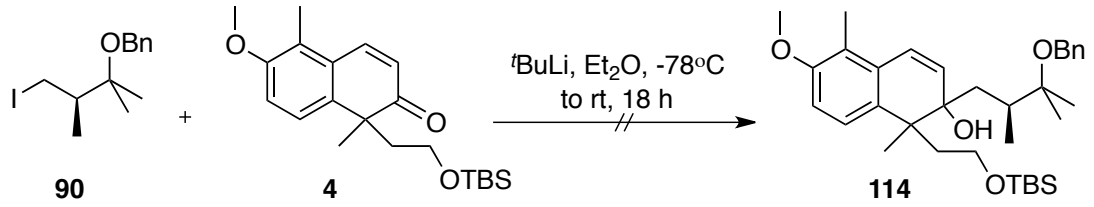
90 **114**

Scheme 102

To this point, four different organometallic agents had be employed in the attempted synthesis of allylic alcohols **114** & **124**, and dienes **59** & **79**. The organomagnesium approach had granted access to undesired product of 1,4-addition and the organozinc method proved too inefficient to merit sustained research. Based on this, organolithium and organocerium compounds represented the optimum reagents for an intensive study. Organocerium compounds are not easily accessed and are generally formed *via* the transmetallation of an existing organometallic species. This process of elimination suggested that the organolithium chemistry warranted further research.

3.3.5 Organolithium Addition – Barbier Conditions and Reverse Addition

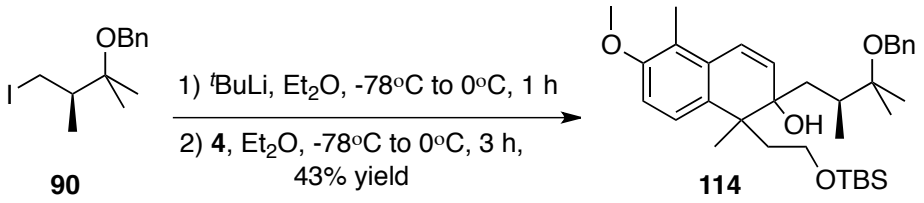
Previously, the generation of the requisite organolithium species had employed traditional lithiation conditions whereby ^{t}BuLi was added to a stirred solution of alkyl iodide **90**. However, this approach had proven unsuccessful and alternative organometallic species were investigated. However, due to the lack of success with other organometallic reagents it was decided that amending the lithiation protocol may offer access to allylic alcohol **114**. Based on this, Barbier conditions were employed in an attempt to access the desired compound (**Scheme 103**). As such, ^{t}BuLi was added to a stirred solution of enone **4** and, alkyl iodide, **90**, in contrast to the previously employed traditional lithiation protocol. This approach proved unsuccessful and a complex range of products was observed. In an effort to further expand the lithiation process an alternative approach was devised.



Scheme 103

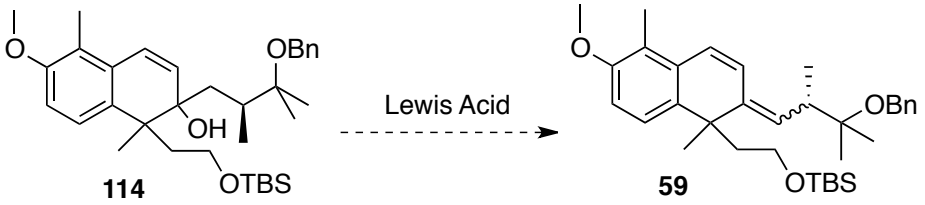
It was reasoned that the ^{t}BuLi was potentially reacting directly with the enone, **4**, under Barbier conditions. In a bid to address this unwanted reaction pathway, it was decided that a reverse addition protocol might prove successful. Accordingly, a solution of alkyl iodide **90**, was added to a stirred solution of ^{t}BuLi, and the resulting mixture was stirred at -78°C for 30 min, followed by stirring at 0°C for 30 min (**Scheme 104**). As before, a small aliquot of the reaction mixture was quenched with acetone and analysed by TLC. Incredibly, a single spot was evident on the TLC plate, which implied that a clean lithiation was occurring. This was particularly pleasing and represented an auspicious step. Following this, a solution of enone **4** was added to the reaction mixture and the

resulting solution was stirred for 3 hours before being quenched. Gratifyingly, allylic alcohol **114** was obtained in a 43% yield following column chromatography.



Scheme 104

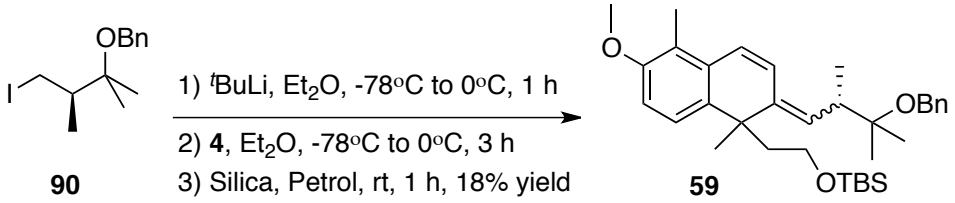
After a comprehensive and sustained investigation it was especially pleasing to access allylic alcohol **114**. However, allylic alcohol proved extremely unstable and rapidly underwent degradation pathways. It was hoped that **114** may be undergoing a spontaneous elimination reaction to furnish diene **59**. Accordingly, additional purification of the mixture indicated trace quanitities diene **59**. Although diene **59**, was not obtained in a significant yield, the strategy employed could be optimised to grant access to appreciable quantities of diene **59**. It was reasoned that the Lewis acidic silica employed in the purification of allylic alcohol **114** was serving to promote the desired elimination pathway (**Scheme 105**).



Scheme 105

Based on the above rationale, it was decided to employ the same conditions as before but upon quenching the reaction mixture, the crude material would be treated with a suspension of silica. It was envisaged that this two-step approach would offer access to

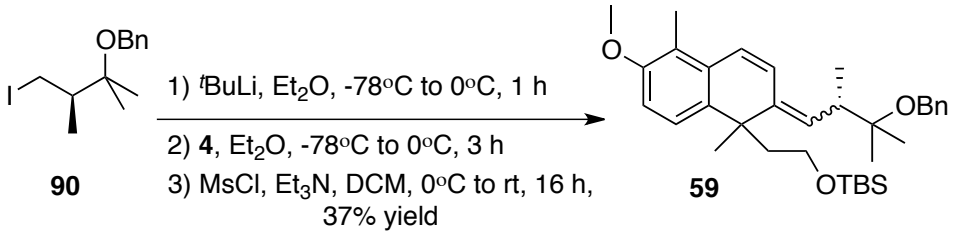
diene **59** (**Scheme 106**). As such, the reaction was conducted as described above and the key diene species obtained in an 18% yield. It seemed likely that the Lewis acid elimination protocol was promoting additional side reactions alongside the desired elimination. As such, it was reasoned that a more traditional elimination strategy may grant access to requisite diene in synthetically useful quantities.



90 **59**

Scheme 106

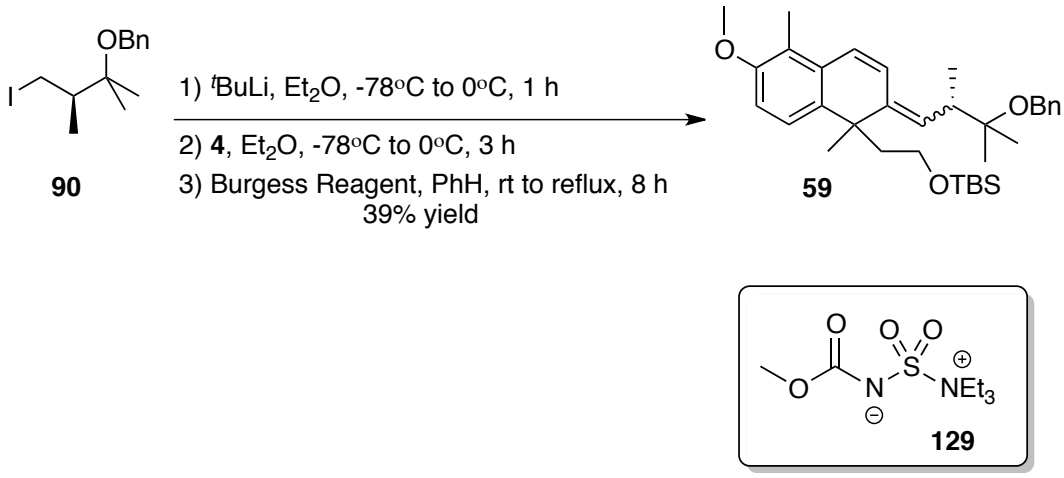
As part of an amended synthetic strategy, the initial lithiation, and subsequent addition reaction, was performed as before (**Scheme 107**). However, in contrast to the previous reaction, after quenching the mixture, and performing a suitable work-up, the crude material was treated with triethylamine and mesyl chloride (MsCl). Pleasingly, this promoted the desired elimination pathway and diene **59** was obtained in a 37% yield, based over two steps. This represented a significant breakthrough in the research programme as the introduction of the integral unsaturated sidechain unit was achieved in a synthetically useful quantity. It should be noted that the stereochemistry of the diene product will be discussed in a subsequent section.



90 **59**

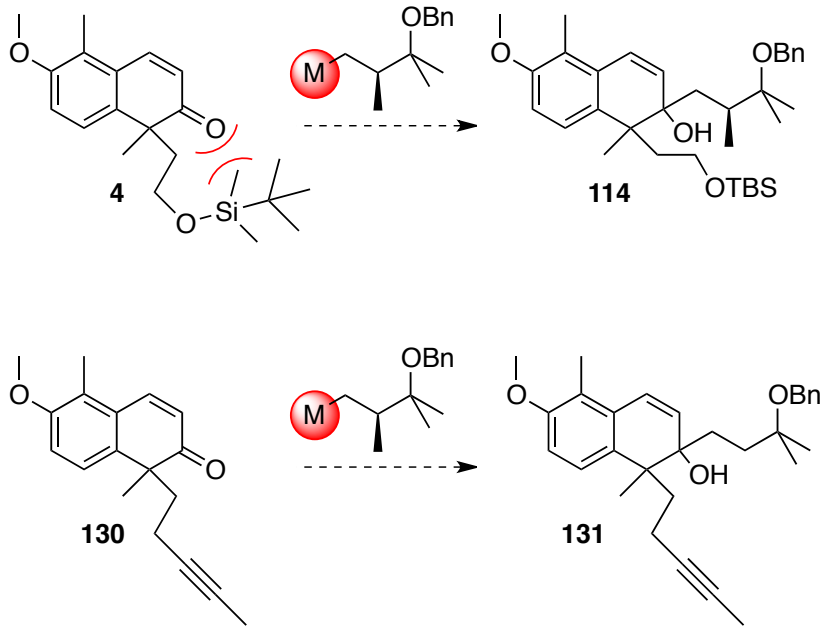
Scheme 107

It was decided to investigate an alternative elimination method in the hope of further enhancing the yield of diene **59**. As such, the addition protocol was conducted as before and the resulting crude reaction mixture treated with Burgess's reagent **129** (**Scheme 108**).[64] The desired diene was formed in a 39% yield, which is comparable to that obtained with the MsCl elimination procedure.



Scheme 108

In summary, after a sustained and exhaustive investigation, a robust protocol that facilitates the formation of diene **59** was identified. This was extremely gratifying and represented an auspicious step towards synthesising the target molecule. With diene **59** in hand, attention turned to the alkyne appendage present in the Pauson-Khand substrate, **3**. It was envisaged that the alkyne unit could be installed in a facile manner, however the steric nature of the alkyne portion raised an interesting point. If the alkyne unit was to be introduced before the sidechain addition, then the steric bulk around the carbonyl unit should be considerably decreased (**Scheme 109**). As such, this may offer the organolithium nucleophile easier access to the carbonyl unit, which could enhance the efficiency of the addition protocol.

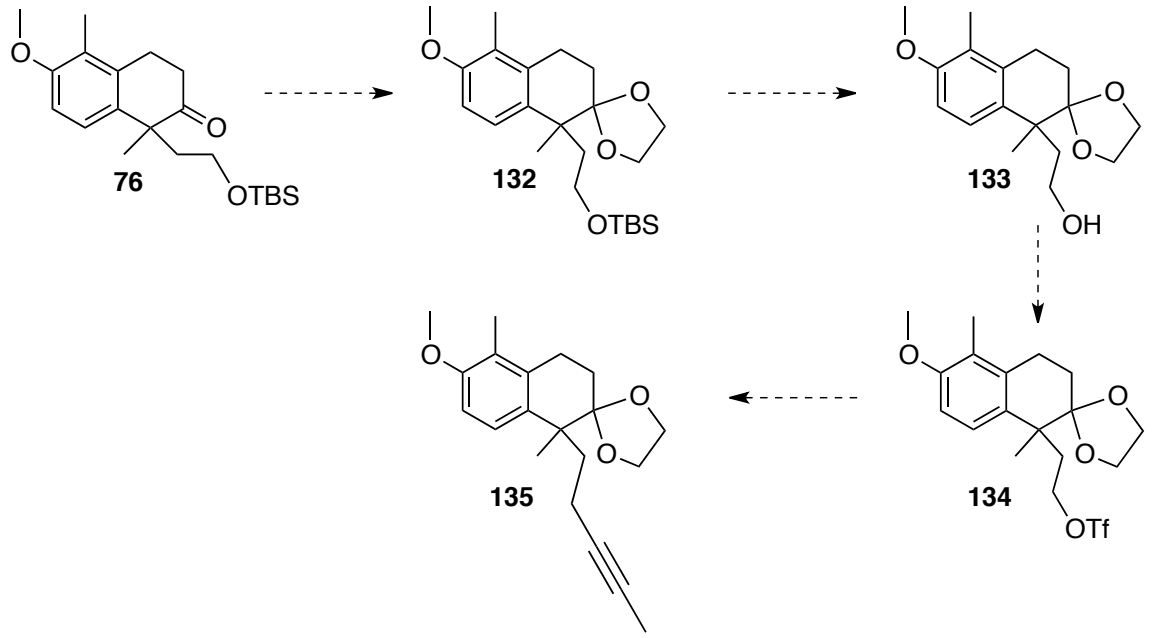


Scheme 109

Based on this it was decided to investigate means by which to introduce the alkyne component before addition of the sidechain moiety.

3.4 Alkyne Introduction

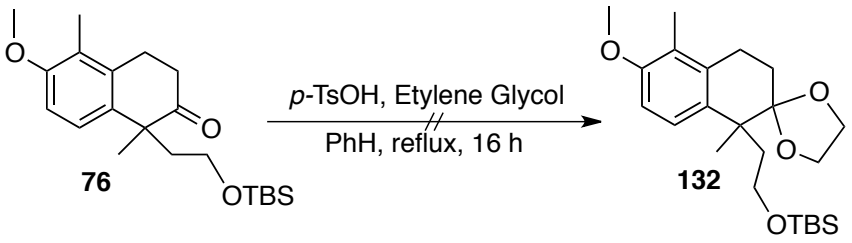
It was envisaged that installing the alkyne moiety before attempting the 1,2-organometallic addition would serve to reduce the steric encumbrance around the carbonyl electrophile. Accordingly, a synthetic strategy to install the desired alkyne unit was devised (**Scheme 110**). Ketone **76** could be protected as the ketal species **132**, and subsequently, the silyl protecting group could be removed to form alcohol **133**. The resulting alcohol could be transformed to the analogous triflate species **134** before installation of the alkyne moiety *via* a propyne displacement reaction to access alkyne **135**.



Scheme 110

With the above synthetic strategy in mind, attention turned to the protection of the carbonyl unit as the corresponding ketal species, **132**. It was decided to employ traditional acid promoted ketal formation conditions wherby ketone **76** was treated with

ethylene glycol and tosic acid (**Scheme 111**).[65] Disappointingly, the desired ketal species, **132**, did not form.



Scheme 111

The major product isolated from the reaction mixture appeared to be lactol species **136**, which could conceivably be formed under the reaction conditions (**Figure 3**). Based on this, it is likely that the *tert*-butyldimethylsilyl protecting group is cleaved under the acidic reaction conditions, before cyclising to form lactol **136**.

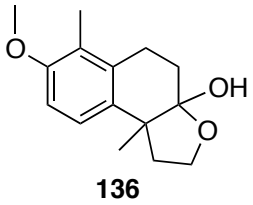
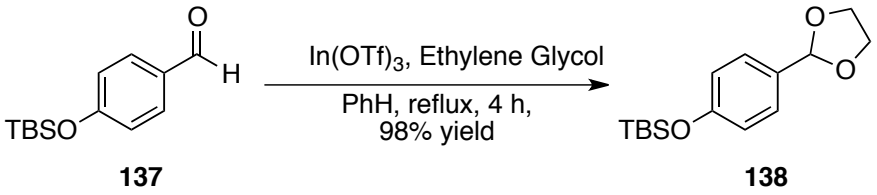


Figure 3

Due to the undesired outcome of the acid-promoted reaction an alternative ketal formation strategy was devised. On consulting the chemical literature, a potential solution was identified. Gregg and coworkers reported employing indium triflate as a mild Lewis acid in the formation of a range of acetals and ketals.[66] Importantly, the substrate scope reported by Gregg included a sensitive TBS protected phenol unit (**Scheme 112**). It follows that ketone **76** may be transformed to the analogous ketal species by employing the reported indium triflate conditions.



137 **138**

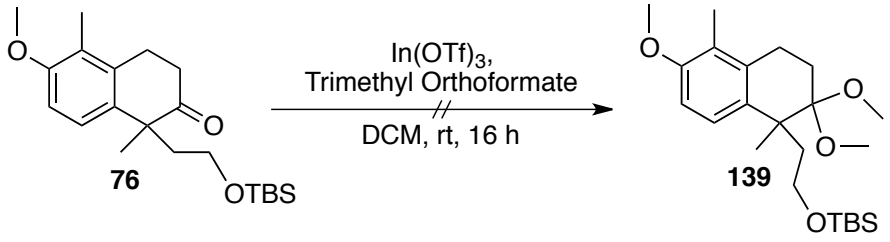
Scheme 112

With a refined synthetic approach in mind, attention turned to the employment of $In(OTf)_3$ and ethylene glycol in refluxing benzene to afford compound **132** (**Scheme 113**). Unfortunately, as before, lactol **136** was obtained as the major product with none of the desired species being observed.

76 **132**

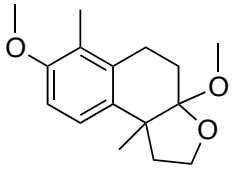
Scheme 113

It was reasoned that employing less forcing conditions could potentially circumvent the issue of protecting group cleavage and, as such, promote the desired transformation. Accordingly, conditions reported by Graham and Smith were implemented, whereby ketone **76** was treated with $In(OTf)_3$ and trimethyl orthoformate at room temperature (**Scheme 114**).[67] Unfortunately, once again, ketal formation failed to occurunder these reaction conditions.



Scheme 114

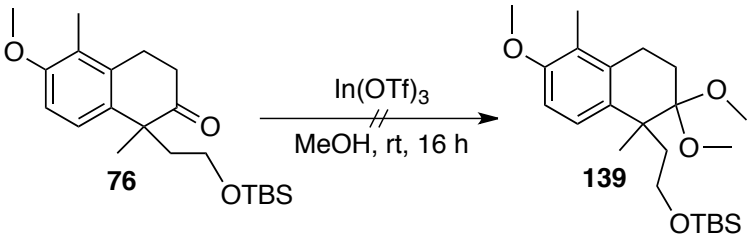
Further analysis of the crude ^{1}H NMR suggested the formation of lactol **140** (**Figure 4**). Based on this, it was decided to investigate the employment of a modified reaction protocol.



140

Figure 4

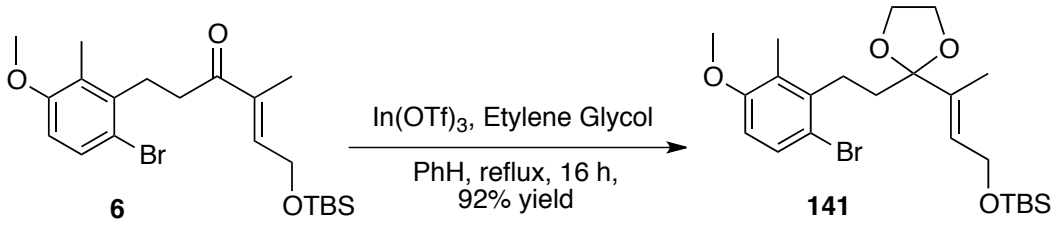
In a final effort to access a protected analogue of ketone **76**, it was reasoned that simply employing an excess of methanol, alongside $In(OTf)_3$ could potentially grant access to the desired compound, **139** (**Scheme 115**). Frustratingly, this failed to deliver the desired species, **139**, and lactol **140** was formed as the major product.



Scheme 115

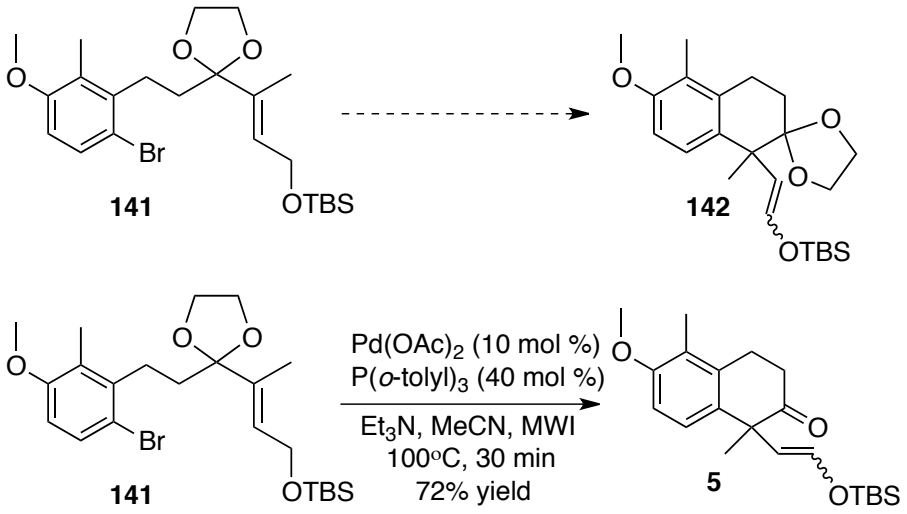
In summary, the above attempts to directly access the protected variant of ketone **76** had proven unsuccessful. It was reasoned that the Lewis acidic conditions promoted the pendent protected-alcohol to undergo cyclisation, accompanied by concomitant loss of the silyl group, to form lactols **136** and **140**. In an effort to avoid this outcome it was decided that installing the ketal moiety at an earlier stage in the synthesis would potentially offer access to a suitably protected bicyclic ketone species.

Undeterred by the above results, it was reasoned that the previously accessed Heck precursor, **6**, could be protected as the analogous ketal species, **141**, *via* the employment of ethylene glycol and $In(OTf)_3$ (**Scheme 116**). Gratifyingly, the desired transformation furnished ketal **141** in a 92% yield.



Scheme 116

With the ketal-protected Heck precursor, **141**, in hand, attention turned to the Heck reaction. The conditions employed previously in the Heck reaction were transposed in an effort to directly access species **142**. As envisaged, the cyclisation occurred as before, however, the integral ketal functionality was lost during the transformation and the bicyclic ketone, **5**, was formed in a 72% yield (**Scheme 117**).



Scheme 117

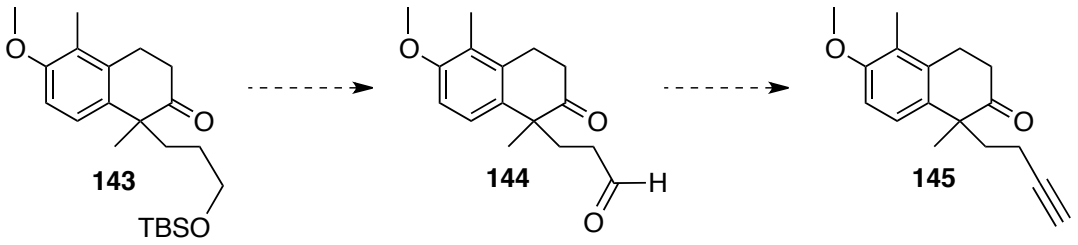
At this juncture, careful consideration was given to the current synthetic strategy. As before, the goal of introducing the alkyne functionality before installation of the sidechain remained at the forefront of the synthetic plan. As stated previously, it was envisaged that the alkyne unit could be installed *via* a lithiated propyne unit. With this in mind, minimising the presence of additional electrophilic reaction sites on the requisite enone, **4**, was of paramount importance. However, alternative methods of installing alkyne functionality would circumvent the need to protect the reactive electrophilic sites. More specifically, it was envisaged that employing an enone species featuring a homologated carbon chain would allow the employment of either the Ramirez-Corey-Fuchs protocol or the Ohira-Bestmann method, and, as such, facilitate access to the desired alkyne species.

3.5 Homologated Chain Approach

3.5.1 Alkyne Introduction

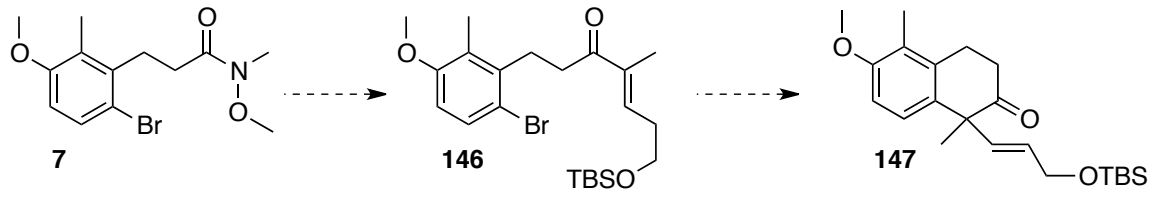
It was reasoned that employing the homologated species, **143**, could potentially facilitate the installation of the alkyne unit in a facile manner. More specifically, aldehyde **144** could be readily accessed *via* a deprotection-oxidation sequence. Following this,

aldehyde **144** could be transformed to the desired alkyne species, **145**, by exploiting the inherent reactivity of the aldehyde functionality (**Scheme 118**).



Scheme 118

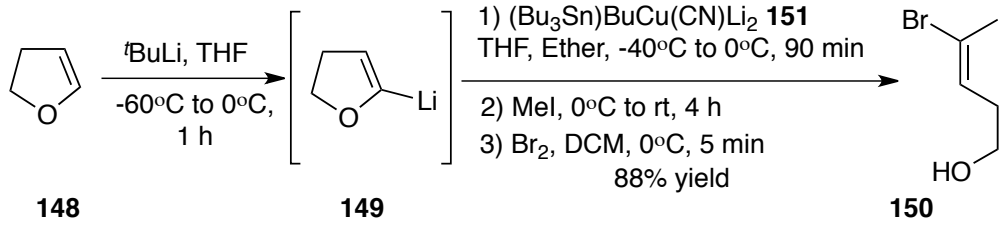
With the above points in mind, the synthetic route detailed below would grant expedient access to ketone **147** (**Scheme 119**). As part of preliminary studies towards Agariblazeispirol C, bicyclic ketone **147** had been accessed *via* a similar intramolecular Heck reaction as to that reported previously (*vide supra*).[34] The Heck precursor can be accessed, as before, from the previously prepared Weinreb amide, **7**, and the homologated vinyl bromide **150**.



Scheme 119

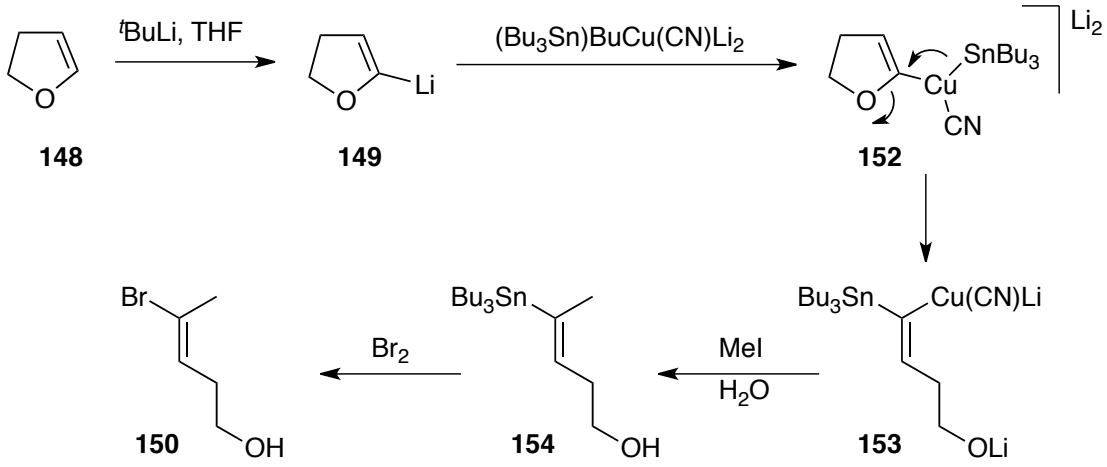
With the above synthetic strategy in mind, attention turned to the synthesis of the homologated vinyl bromide **150**. Encouragingly, an expedient synthesis towards **150** was disclosed by Sulikowski.[68] Based on this report, the synthesis began with the lithiation of the commercially available 2,3-dihydrofuran **148**, which was subsequently treated with the cuprous stannane species **151**. Following this, methyl iodide was introduced before

the addition of bromine (**Scheme 120**). Gratifying, the reaction proceeded in an 88% yield to deliver the desired alcohol, **150**.



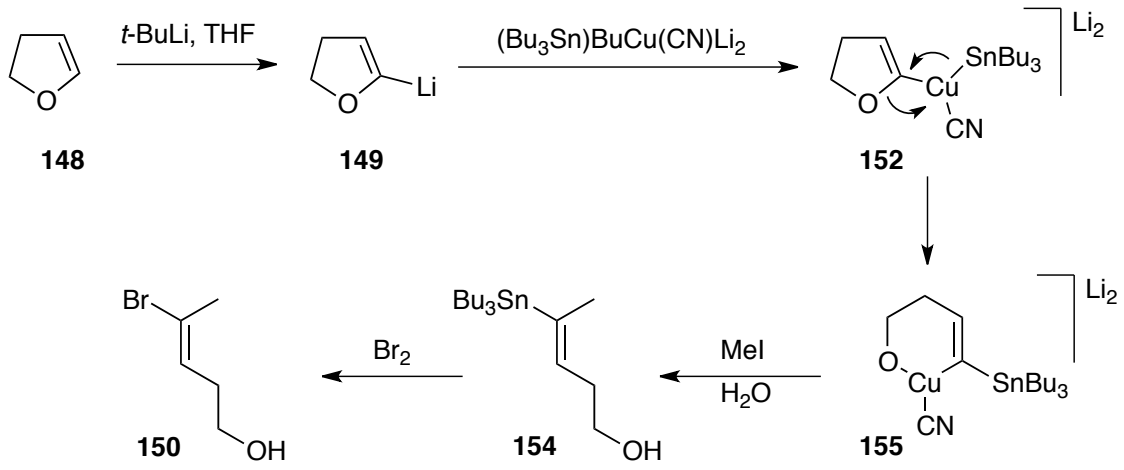
Scheme 120

The exact mechanistic pathway of the reaction is not understood, however two potential mechanisms have been proposed.[69] Initially, and common to both theorized pathways, formation of the higher-order cuprate **152** from the lithiated 2,3-dihydrofuran **149** occurs. In one of the proposed reaction sequences, species **152** undergoes a 1,2 migration to yield vinyl cuprate **153**, which is quenched with methyl iodide to deliver vinyl stannane **154**. Bromine addition serves to facilitate the formation of **150** (**Scheme 121**).



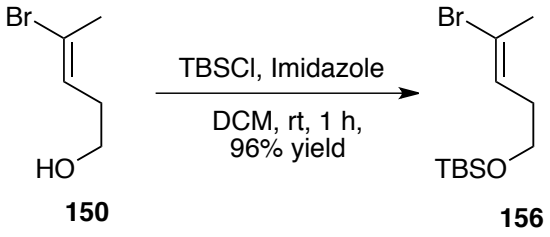
Scheme 121

The alternative mechanistic pathway proceeds *via* the same higher-order cuprate species **152**, which undergoes a dyotropic rearrangement to form metallocycle **155** (**Scheme 122**). Intermediate **155** is quenched with methyl iodide to deliver **154** and proceeds by the same pathway to that described above to provide alcohol **150** (*vide supra*).



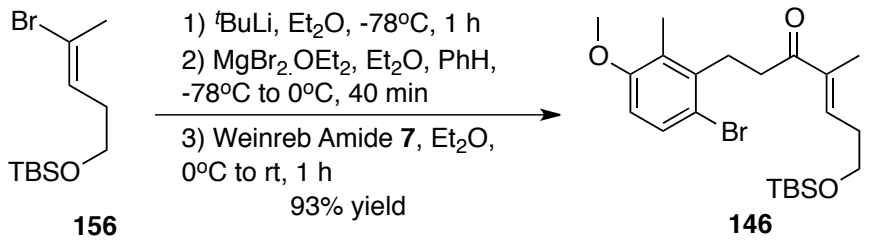
Scheme 122

With alcohol **150** in hand, attention turned to introducing the silyl protecting group, this was achieved in a near quantitative 96% yield (**Scheme 123**).



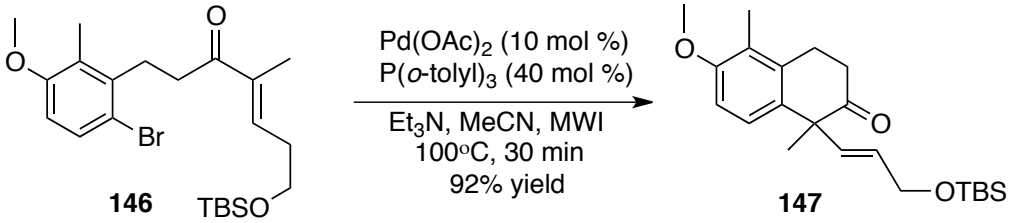
Scheme 123

In line with the previously employed approach, lithiation of vinyl bromide **156** was followed by transmetalation with magnesium to form the analogous Grignard species. The organomagnesium intermediate was delivered into Weinreb amide **7** to deliver the desired enone **146** in a pleasing 93% yield (**Scheme 124**).



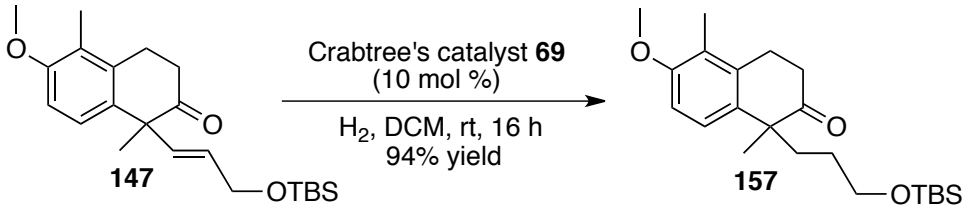
Scheme 124

Following this, the immediate priority was installing the first all-carbon quaternary centre. This was to be achieved by employing a similar intramolecular Heck reaction to that utilised previously (*vide supra*). Pleasingly, this approach facilitated the formation of bicyclic ketone **147** in a 92% yield (**Scheme 125**). Interestingly, in contrast to the previous Heck reaction, the newly formed olefin possessed exclusive *E*-geometry.



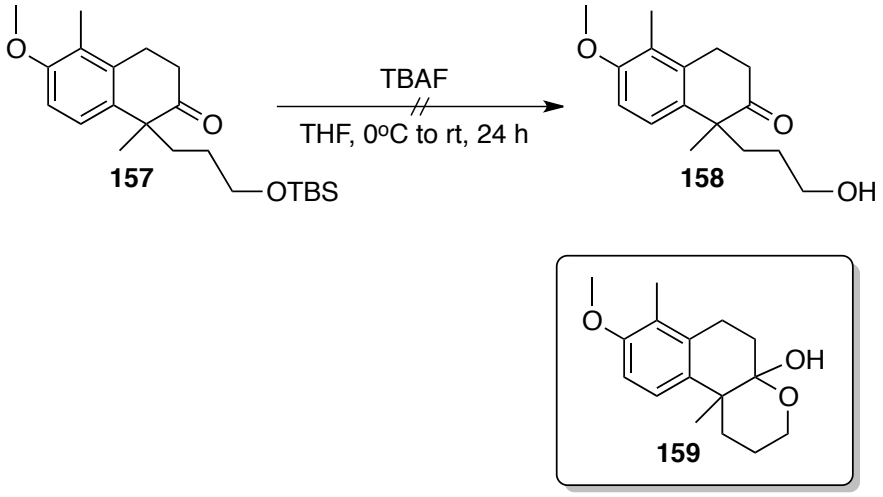
Scheme 125

The newly formed olefin unit was subsequently reduced by Crabtree's catalyst under a hydrogen atmosphere. The reaction proceeded in near quantitative conversion to furnish compound **157** in a 94% yield (**Scheme 126**).



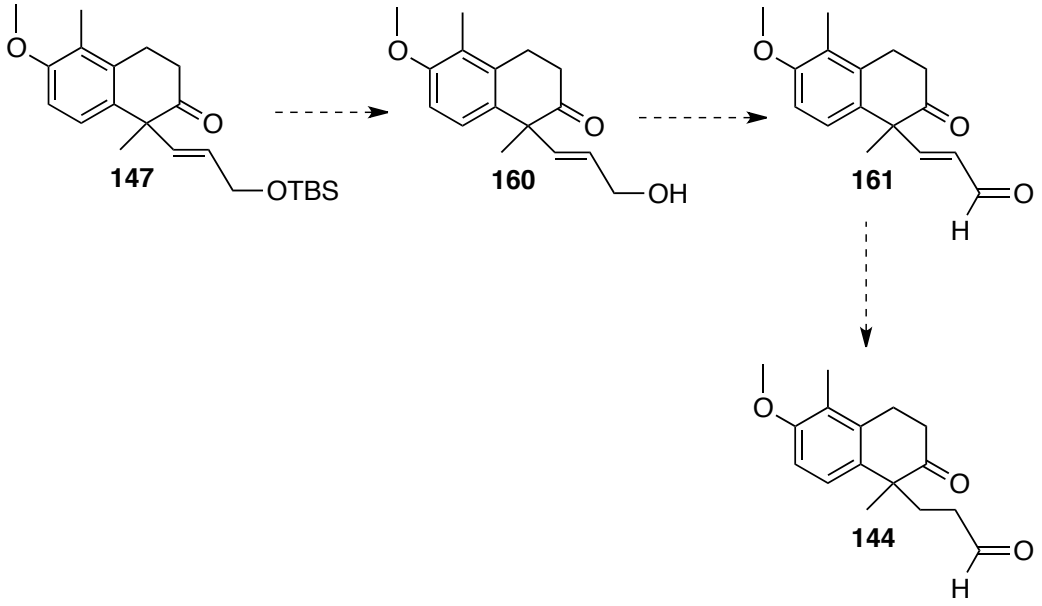
Scheme 126

As discussed previously, it was envisaged that the alkyne component could be installed before attempting the sidechain addition protocol. In an effort to achieve this goal, bicyclic ketone **157** was treated with TBAF in order to remove the silyl-protecting group (**Scheme 127**). Unfortunately, isolation of the desired primary alcohol, **158**, was not achieved, and instead the analogous lactol species **159** was formed as the major product. Although not completely unsurprising, this outcome was disappointing as the aforementioned synthetic strategy required access to the corresponding aldehyde unit **144**, in order to facilitate installment of the requisite alkyne moiety for the downstream Pauson-Khand annulation.



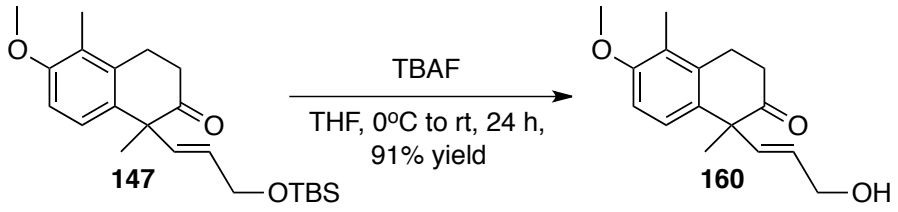
Scheme 127

In a bid to access the desired aldehyde **144**, a modified synthetic strategy was devised (**Scheme 128**). It was envisaged that retaining the *E*-olefin functionality post Heck reaction would circumvent lactol formation. Instead, allylic alcohol **160** could undergo oxidation to enal **161**, and, in turn, hydrogenation of this compound would yield the desired aldehyde **144**.



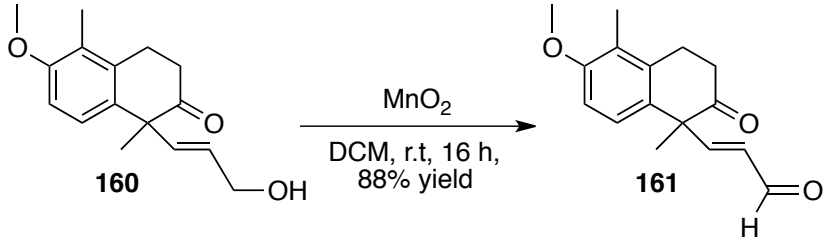
Scheme 128

Gratifyingly, this approach successfully avoided the intramolecular cyclisation. The Heck product was treated with TBAF and, pleasingly, resulted in the formation of allylic alcohol **160** in an excellent 91% yield (**Scheme 129**).



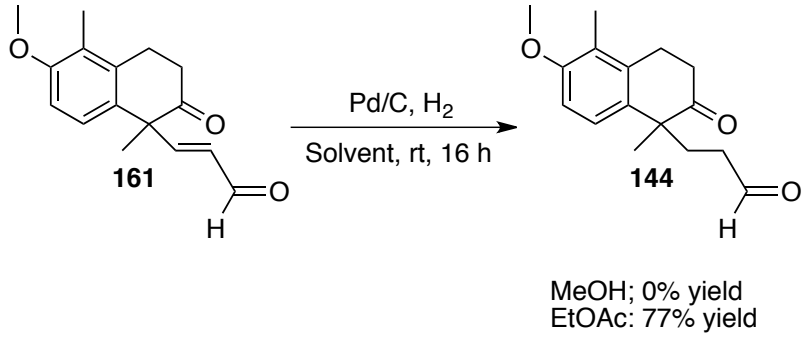
Scheme 129

Upon reviewing the experimental procedures in the literature it was decided that enal **161** should be readily accessed *via* a manganese dioxide-mediated oxidation.[70] Accordingly, alcohol **160** was treated with an excess of manganese dioxide to result in an excellent 91% yield of enal **161** (**Scheme 130**).



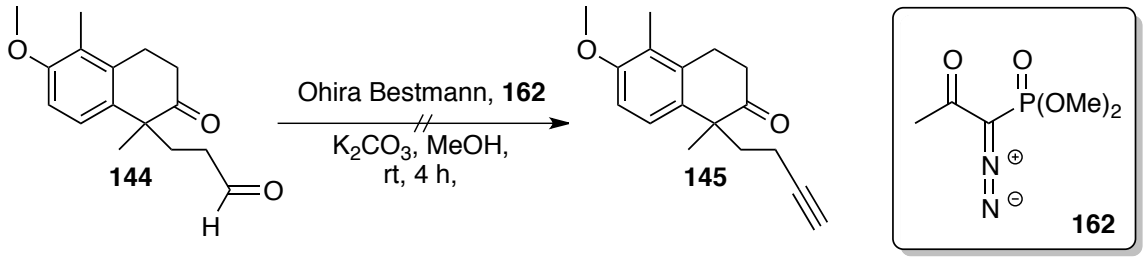
Scheme 130

With enal **161** in hand, attention turned to potential hydrogenation conditions. Owing to their ubiquitous use in enal reductions, palladium-mediated conditions were investigated. Initially, palladium on charcoal was employed under an atmosphere of hydrogen in methanol (**Scheme 131**). Frustratingly, this led to complete degradation of enal **161**. On reviewing the literature, it was noticed that ethyl acetate is regularly employed as the solvent in such palladium-mediated reductions.[71] Accordingly, enal **161** was solubilised in ethyl acetate, before the introduction of palladium on charcoal. The resulting suspension was subjected to a hydrogen atmosphere. Gratifyingly, this subtle modification furnished the previously inaccessible aldehyde **144** in a 77% yield.



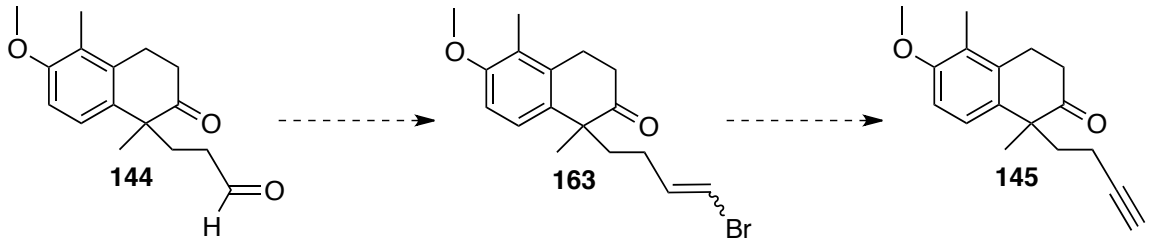
Scheme 131

With aldehyde **144** in hand, attention could now focus on introducing the alkyne unit to furnish compound **145**. With this synthetic goal in mind, an Ohira Bestmann reaction was employed in an effort to gain access to alkyne **145**.[72] Unfortunately, the desired product failed to form, and a complex mixture was obtained (**Scheme 132**).



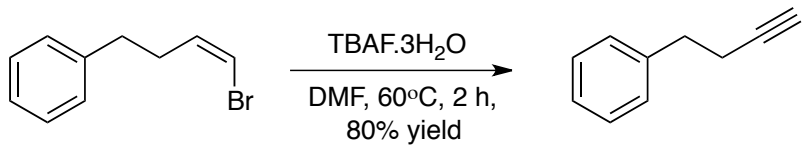
Scheme 132

The sensitive nature of the ketone moiety present in compound **144** was given careful consideration with respect to devising an appropriate synthetic strategy to access alkyne **145**. It was decided that a Stork-Zhao olefination could allow access to vinyl bromide **163** (**Scheme 133**). Owing to the steric encumbrance of the ketone unit, and the lack of reactivity of the analogous enone **4**, it seemed likely that the ketone moiety would remain unreacted under these reaction conditions. Following this, a suitable elimination reaction could grant access to alkyne **145**.



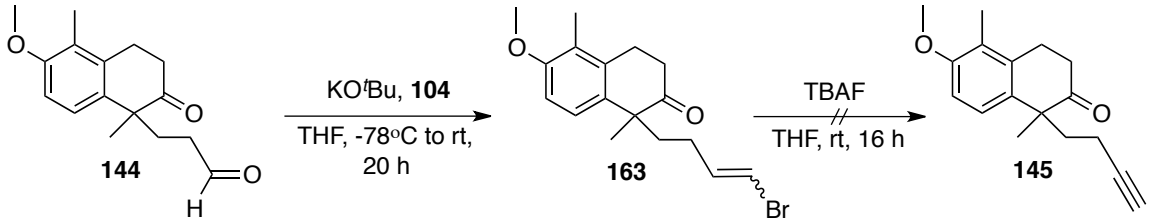
Scheme 133

On consulting the literature a TBAF-mediated elimination reaction, disclosed by Mori and Okutani, granted access to a range of alkynes in appreciable yield (**Scheme 134**).[73] The mild nature of this transformation would be advantageous with respect to the base sensitive ketone moiety present in vinyl bromide **163**. It should be noted that a 1 M TBAF solution in THF was equally effective but required longer reaction times.



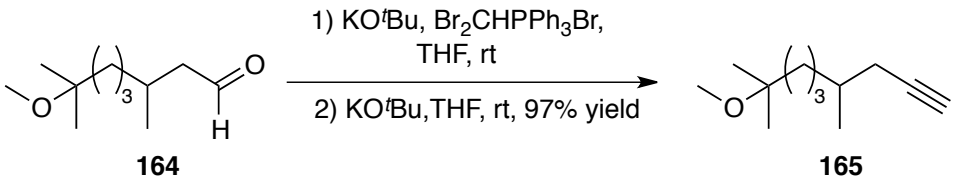
Scheme 134

With the above information at hand, a two-step process was employed whereby aldehyde **144** was converted to vinyl bromide **163** before attempting a TBAF-mediated elimination (**Scheme 135**). Pleasingly, the vinyl bromide was accessed in a rapid fashion however the resulting elimination reaction failed to occur and a complex mixture of products was observed.



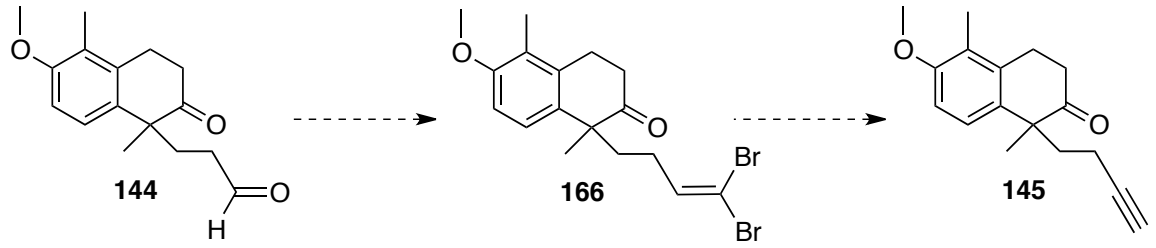
Scheme 135

Due to the disappointing results obtained from the above elimination attempt, the proposed elimination sequence was reevaluated. On consulting the literature, an interesting approach employed by Michel *et al.* was considered (**Scheme 136**).[74] It was disclosed that potassium *tert*-butoxide is capable of promoting the elimination of a range of dibromo olefins to the analogous bromoalkyne, and terminal alkyne, species.



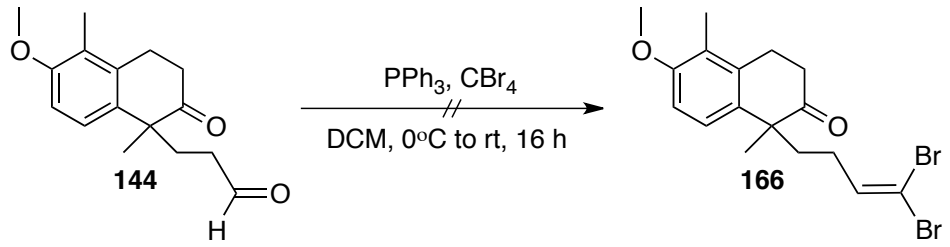
Scheme 136

Inspired by this approach, it was envisaged that aldehyde **144** could conceivably be transformed to dibromo olefin **166** which could potentially undergo an elimination reaction. Indeed, if the elimination was to furnish the corresponding bromoalkyne species, instead of the desired terminal alkyne **145**, it was envisaged that a subsequent alkoxide-mediated alkynyl debromination reaction would deliver alkyne **145** (**Scheme 137**).[75]



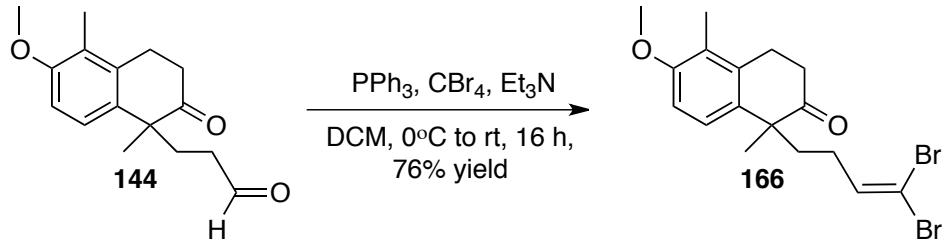
Scheme 137

It was envisaged that dibromo olefin **166** could be accessed *via* a traditional Ramirez reaction. Accordingly, aldehyde **144** was treated with triphenylphosphine and carbon tetrabromide in a bid to introduce the requisite functionality. Frustratingly, the reaction failed to occur and a complex range of products were observed (**Scheme 138**).



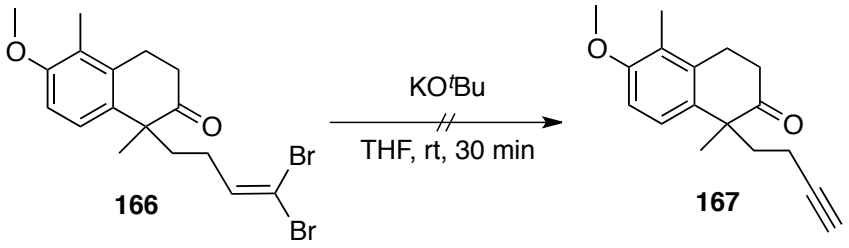
Scheme 138

Upon reviewing the literature it was discovered that the incorporation of triethylamine, within the Ramirez reaction, facilitated access to a range of dibromo olefins, which were not obtainable *via* the standard Ramirez protocol.[76] In this amended protocol, triethylamine acts as a scavenger to neutralise unwanted reactive species that are formed during the course of the reaction. Based on this, triphenylphosphine, carbon tetrabromide, and triethylamine were reacted to form the requisite ylide, which underwent reaction with aldehyde **144** to form the desired olefin **166** in good yield (**Scheme 139**).



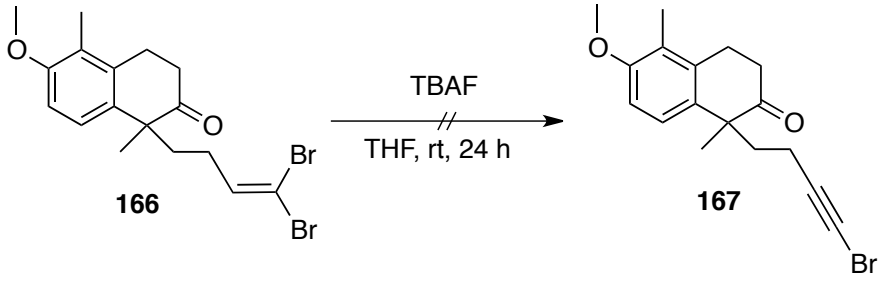
Scheme 139

With dibromoolefin **166** in hand, attention turned to introducing the alkyne moiety. Owing to the success enjoyed by Michel, it was decided to employ potassium *tert*-butoxide in a bid to readily facilitate the desired elimination. Unfortunately, this led to complete degradation of the starting material. It is likely that the ketone functionality complicates the elimination protocol (**Scheme 140**).



Scheme 140

As a result of this disappointing outcome, alternative elimination methods were considered. It was reasoned that the aforementioned TBAF elimination protocol would faciliate access to bromoalkyne **167**. Based on this, olefin **166** was treated with a solution of TBAF and stirred for 24 hours (**Scheme 141**). Disappointingly, the desired alkyne failed to form and an appreciable quantity of the starting material was recovered.



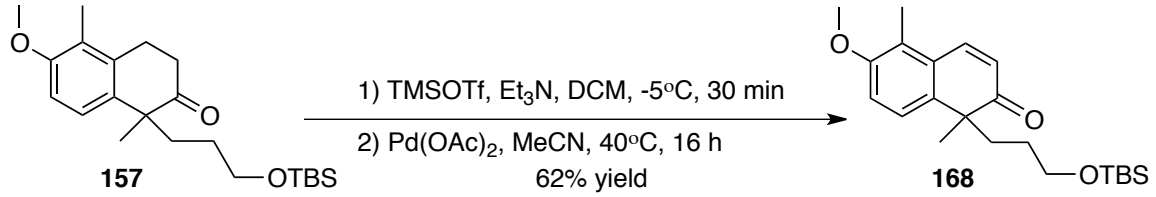
Scheme 141

At this juncture, the synthetic approach was, again, given careful consideration. The above synthetic efforts towards introducing the alkyne species, before attempting the key organometallic addition, had failed to deliver the desired compound, **145**. Installation of the sidechain represented a significant step in this synthetic programme and attention returned to this transformation. As stated previously, the electrophile employed in the preliminary sidechain addition attempts was sterically encumbered. As such, it was rationalised that this attribute was responsible for the modest yields obtained. To date, attempts to introduce the alkyne moiety prior to the organometallic addition have been

met with failure. Having stated this, the homologated chain of the revised substrate could lead to minimised steric hinderance around the carbonyl electrophile.

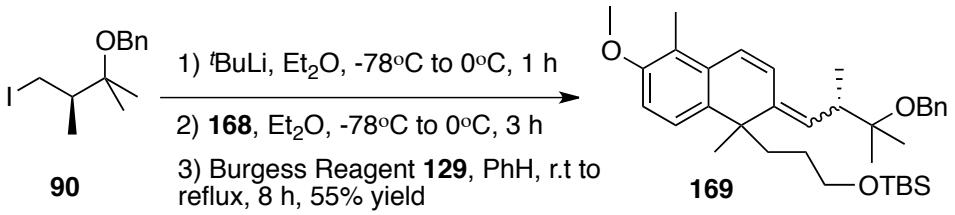
3.5.2 1,2-Organometallic Addition Chemistry

Before the organometallic addition could be attempted, it was necessary to access the requisite enone electrophile **168**. In this regard, ketone **157** was transformed to the analogous enone species, **168**, *via* a Saegusa-Ito oxidation. The telescoped procedure furnished enone **168** in a pleasinging 62% yield (**Scheme 142**).



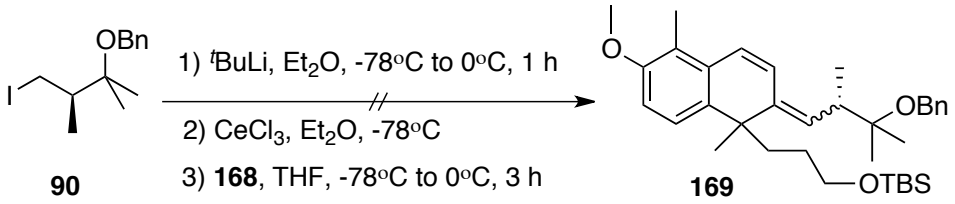
Scheme 142

In a similar manner to that employed previously, alkyl iodide **90** was lithiated under reverse addition conditions before introducing the requisite enone moiety **168**. Owing to the difficulty associated with the unstable nature of allylic alcohol **114** it was decided that the crude reaction mixture would be expedited to the elimination step in a bid to circumvent this issue (**Scheme 143**). Based on this, the crude mixture was subjected to an elimination reaction mediated by Burgess's reagent.[64] Gratifyingly, the reaction proceeded in a pleasing 55% yield (based over two steps). This synthetic approach granted access to the homologated diene, **169**, in an improved yield, relative to the previous addition elimination sequence with substrate **4**, and the alkyne could now potentially be introduced by traditional alkynlation means.



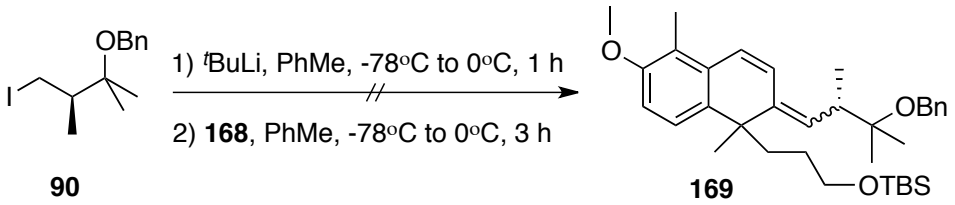
Scheme 143

Before progressing with the synthesis there remained scope for further optimisation of the addition protocol. Previously, the organocerium-mediated addition attempts had been met with failure. However, with a more robust and efficient metallation strategy in hand, attention turned to accessing an organocerium species from the analogous organolithium moiety. As such, the lithiated material was transferred *via* cannula to a stirred solution of $CeCl_3$, before the addition of enone **168** (**Scheme 144**). Disappointingly, this strategy failed to afford diene **169** and instead resulted in a complex mixture of products.



Scheme 144

In a final effort to improve upon the addition protocol it was decided to investigate the employment of toluene as the reaction solvent. It was theorized that the non-coordinating nature of a hydrocarbon solvent could lead to enhanced reactivity of the organolithium species. Accordingly, the standard reverse addition reaction was conducted in toluene (**Scheme 145**). Unfortunately, this led to a complex mixture of reaction products. Based on this, and the disappointing cerium-mediated addition protocol, it was decided to employ the standard reverse addition lithiation approach in future experiments.

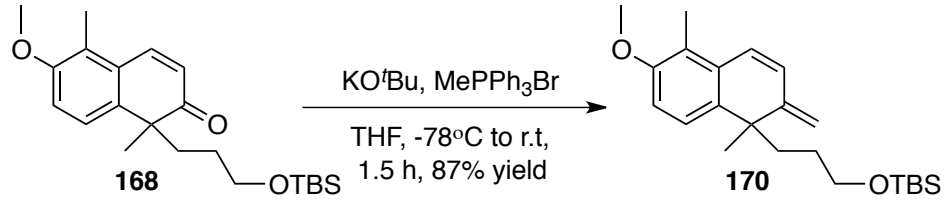


90 169

Scheme 145

3.6 Stereochemical Elucidation of Diene 169

With diene **169** in hand, attention turned to confirming the stereochemistry of the olefin unit. Before initiating NMR studies of diene **169** it was decided that analysing the analogous disubstituted diene **170** species would offer a suitable foundation upon which to build a stereochemical rationale. More specidfically, it was envisaged that the protons of the exocyclic alkene would interact with the other protons present in the molecule. As such, the absence, or enhancement, of these signals in the NOESY spectrum of **169** could give important information regarding the stereochemistry. Based on this, a Wittig methylation was employed to access diene **170** in an 87% yield (**Scheme 146**).



168 170

Scheme 146

With diene **170** in hand, attention turned to performing nuclear Overhauser effect spectroscopy (NOESY) studies; the resulting spectrum can be found in the appendix. The results of these experiments proved integral to understanding the nature of species **169**. The 2D NMR experiments illustrated that H^a and H^b interact, and, as such, exhibit the *syn*

geometry illustrated below (**Figure 5**). In addition, H^c interacts with the H^d protons of the methyl group of the quaternary carbon, giving further diagnostic information.

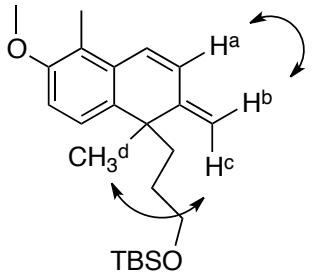


Figure 5

Pleased with the results of the preliminary NOESY investigation, diene **169** was subjected to the same class of NMR experiments. Gratifyingly, the NOESY data indicated that the desired (*E*)-diene species had formed exclusively; again the resulting spectrum can be found in the appendix. It was found that, H^c correlated strongly with the H^d protons of the methyl group of the quaternary carbon, as experienced previously (**Figure 6**). More importantly, H^a failed to interact with the proton(s) of the exocyclic sp^2 carbon (previously H^b), which is strongly indicative of the exclusive formation of the desired (*E*)-olefin.

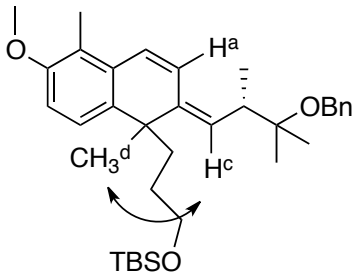
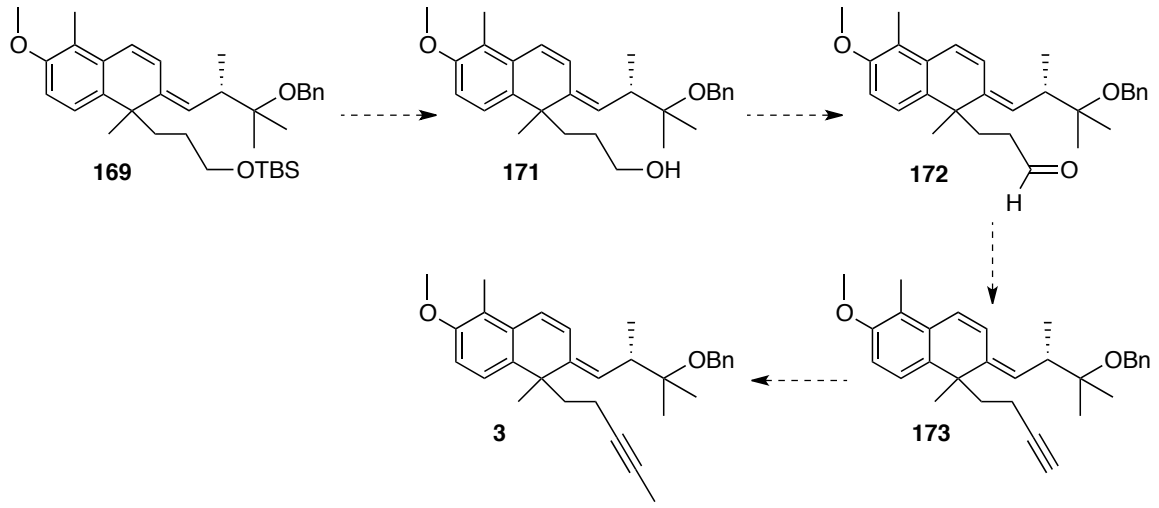


Figure 6

It is important to highlight that the installation of the sidechain moiety results in the formation of two diastereomers. This arises from the presence of a stereogenic centre on the sidechain unit, and also, the quaternary carbon at the benzylic position of the bicyclic core. As such, this leads to 1:1 isomeric splitting of the protons recorded in the ^1H NMR.

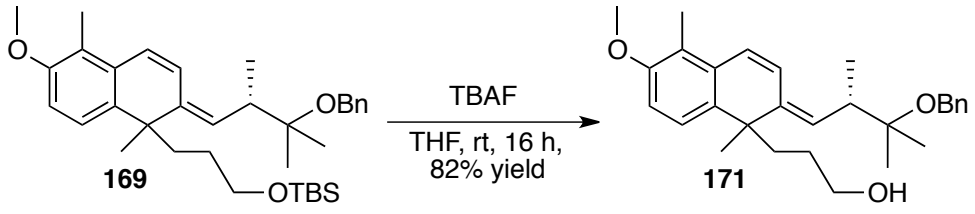
3.7 Accessing the Pauson-Khand Precursor 3

With diene **169** in hand attention was turned to introducing the previously elusive alkyne moiety. It was envisaged that liberation of the free alcohol followed by oxidation would furnish aldehyde **172**, which could undergo an Ohira-Bestmann reaction (**Scheme 147**). Methylation of the terminal alkyne species would generate the key Pauson-Khand precursor alkyne **3**.



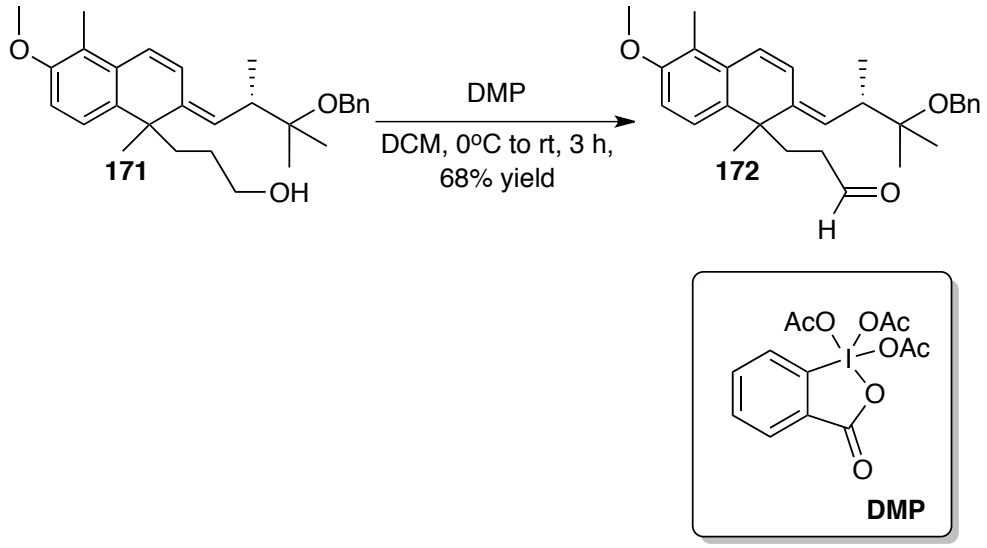
Scheme 147

The silicon protecting group of the primary alcohol was removed using TBAF which delivered the free alcohol, **171**, in an 82% yield (**Scheme 148**).



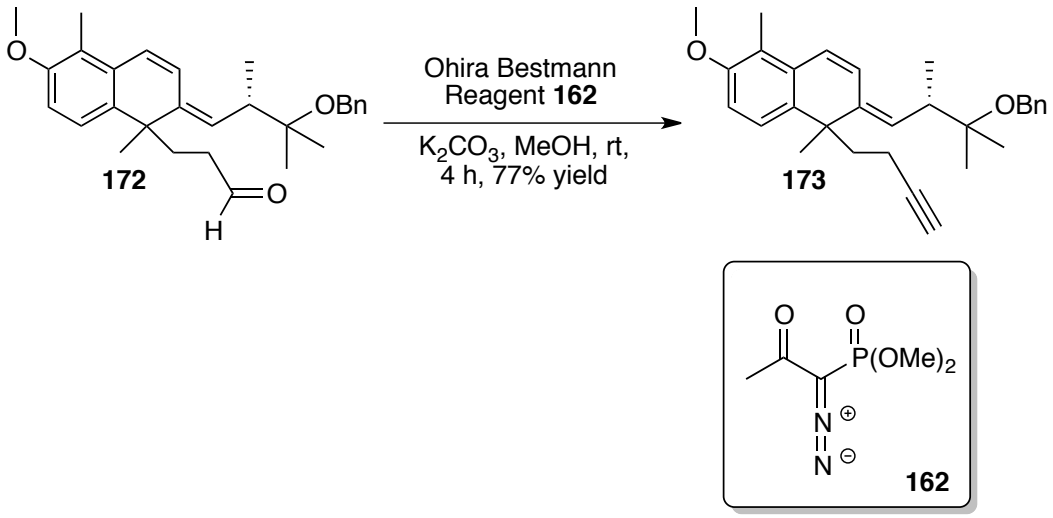
Scheme 148

The oxidation of the primary alcohol to the analogous aldehyde species underpinned this synthetic approach. Judicious choice of oxidation technique was of paramount importance. It was reasoned that diene functionality of **171** could potentially react with electrophilic reagents leading to degradation of the diene functionality. Accordingly, Dess Martin Periodinane (DMP) was selected as a potential oxidant as a result of its relatively benign reaction conditions.[77] Upon treating alcohol **171** with DMP the desired aldehyde, **172**, was formed in a gratifying 68% yield (**Scheme 149**).



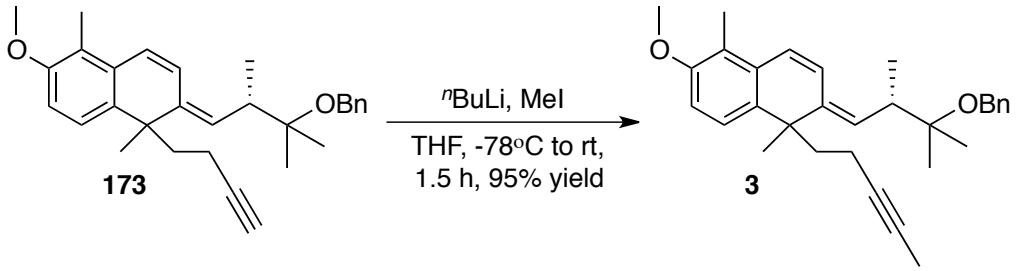
Scheme 149

The freshly installed aldehyde component presented an excellent functional handle for installing the requisite alkyne moiety. It was decided that the Ohira Bestmann reaction would serve to facilitate this transformation. Pleasingly, the reaction proceeded in a respectable 77% yield to furnish terminal alkyne **173** (**Scheme 150**).



Scheme 150

Following this, terminal alkyne **173** was treated with ^{n}BuLi and methyl iodide to deliver the analogous methylated alkyne **3** in an excellent 95% yield (**Scheme 151**).



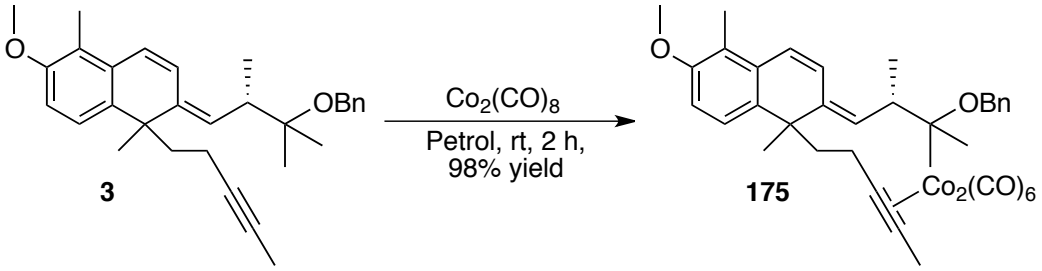
Scheme 151

After a sustained synthetic endeavor, the desired Pauson-Khand precursor, **3**, had been accessed. This represented a significant milestone within the research programme as the formation of Agariblazeispirol C could, theoretically, be achieved in a further two synthetic steps.

3.8 The Pauson-Khand Reaction

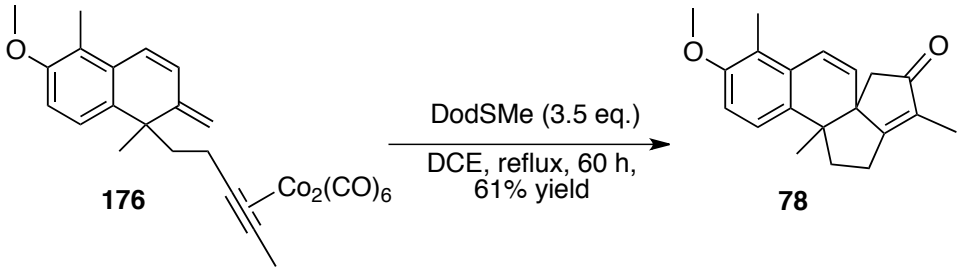
Following the successful isolation of the key Pauson-Khand precursor attention could now turn to promotion of the integral cyclisation. As stated previously, dienyne **3** represents a challenging substrate within the annulation protocol due to the presence of a trisubstituted conjugated diene and an internal alkyne. Undeterred however, it was decided to employ a two-step strategy within the Pauson-Khand reaction, firstly the substrate would be complexed to the cobalt species in order to access precursor **175**. This strategy would allow purification of the cobalt species, **175**, prior to attempting the key cyclisation.

With the above strategy in mind, the cobalt-alkyne complex, **175**, was prepared by stirring dienyne **3** with dicobalt octacarbonyl. Pleasingly, following purification, the desired species was obtained in near quantitative yield (**Scheme 152**).



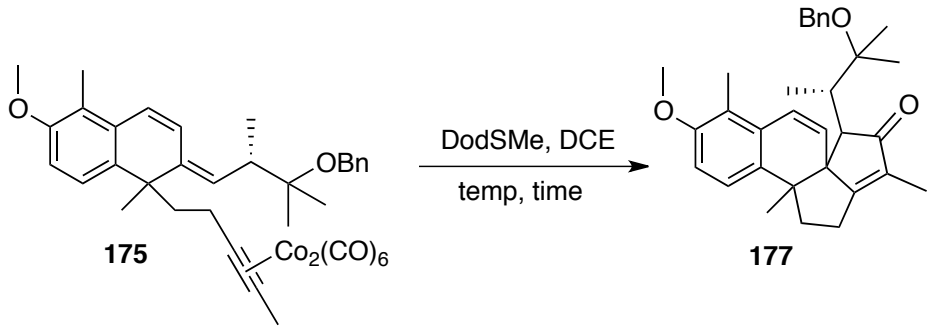
Scheme 152

Preliminary studies carried out within our laboratory identified that a DodSMe promoted annulation protocol was effective in transforming the simple conjugated alkene **176** to the tetracyclic species **78** (**Scheme 153**).[34]



Scheme 153

Based on this, it was reasoned that transposing the optimal conditions to the more elaborate diene, **175**, may result in the formation of the fully functionalised core of the molecule, **177** (**Scheme 154**, **Table 1**). With a grounded sense of optimism, diene **175** was subjected to the DodSMe promoted reaction conditions, whereby 3.5 equivalents of the promoter were added and the resulting mixture heated to reflux for 5 days (**Entry 1**). Unfortunately, the desired product failed to form and a mixture of starting material and decomplexed alkyne **3** were recovered from the reaction. In an effort to enhance the reactivity of the organocobalt species, an increased loading of DodSMe additive was employed (**Entry 2**). In a similar fashion, a mixture of unreacted starting material and free alkyne were observed after a lengthy 5-day period. Following these initial results, it was proposed that employing microwave irradiation could potentially facilitate the annulation protocol (**Entry 3**). In this regard, organocobalt diene **175** was treated with DodSMe and heated at 90°C for 10 minutes in the microwave. After this time, analysis of the reaction mixture indicated that the starting material remained unreacted. In relation to this, it was reasoned that more forcing reaction conditions may be required to promote the cyclisation of the densely functionalised diene **175**. As such, microwave irradiation was employed and the reaction mixture subjected to 150°C for 10 minutes (**Entry 4**). Disappointingly, this failed to promote the reaction and led to decomplexation of the starting material.

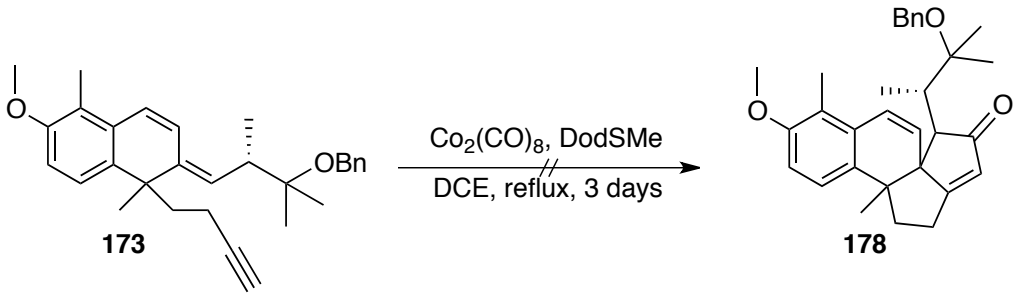


Scheme 154

Entry	*DodSMe (eq)*	*Promotion*	*Temp*	*Time*	*Yield*
1	3.5	Thermal	r.t	5 days	-
2	6	Thermal	r.t	5 days	-
3	3.5	Microwave	90°C	10 min	-
4	3.5	Microwave	150°C	10 min	-

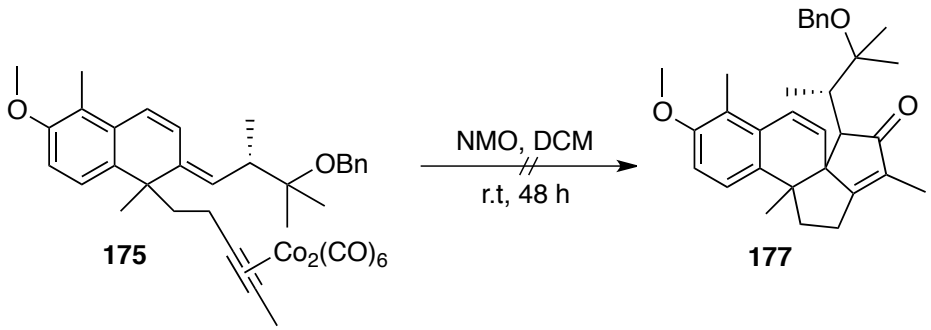
Table 1

In an effort to simplify the Pauson-Khand substrate, it was decided to employ a terminal alkyne species **173**. It was reasoned that this substrate should prove more reactive under the reaction conditions. As such, terminal alkyne **173** was treated with $Co_2(CO)_8$ and DodSMe, and the resulting mixture stirred in 1,2-dichloroethane (DCE) at reflux for 3 days (**Scheme 155**). It should be noted that the *in-situ* formation of the complex is frequently encountered within Pauson-Khand chemistry. Unfortunately, this failed to promote the PKR and a mixture of unreacted starting material and complexed material was recovered from the reaction mixture.



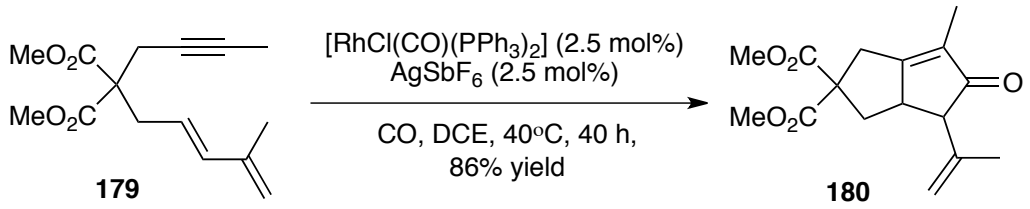
Scheme 155

Despite the above results, it was rationalised that an alternative reaction promoter may offer access to the desired compound. With this in mind, NMO was employed as an additive in the key Pauson-Khand cyclisation (**Scheme 156**). Regrettably, this failed to furnish tetracycle **177** and instead resulted in decomplexation of the alkyne starting material. Based on this, it was decided to return to investigating the promotion of the previously encountered and uncomplexed precursor **3**.



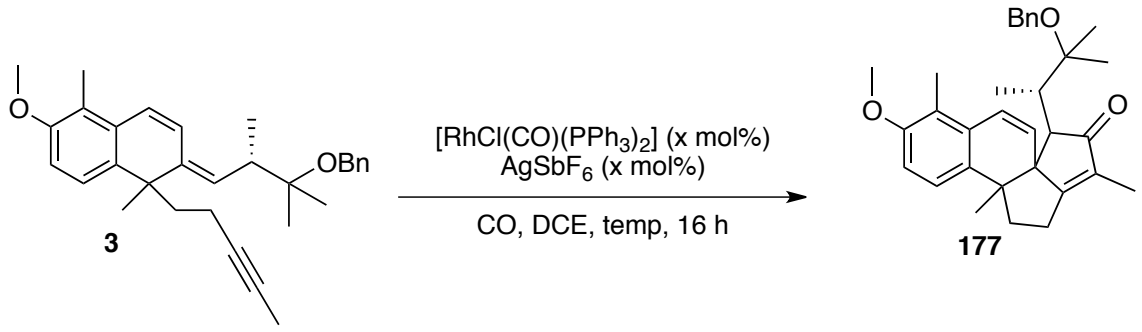
Scheme 156

Given the above failures in promoting the annulation of dienyne **3**, alternative Pauson-Khand reaction conditions were considered. As described previously, diene substrates represent difficult substrates within the Pauson-Khand reaction. Having stated this, Wender and coworkers disclosed a rhodium-promoted strategy that facilitated the PKR of dienyl substrates (**Scheme 157**).[78]



Scheme 157

Based on this, the conditions developed by Wender were employed in an attempt to facilitate access to tetracycle **177** (**Scheme 158**, **Table 2**). In this regard, dienyl **3** was treated with 2.5 mol% of rhodium catalyst and the resulting mixture stirred at room temperature for 16 hours (**Entry 1**). Unfortunately, the alkyne failed to react under these conditions. It was reasoned that increasing the catalyst loading may offer access to the desired product, and, as such, 5 mol% of the rhodium catalyst was employed (**Entry 2**). However, as observed previously, the starting material failed to undergo any conversion. Due to the unreactive nature of dienyl **3**, more forcing conditions were investigated. Accordingly, the above reactions were repeated at a slightly elevated temperature of 40°C (**Entries 3** and **4**). Disappointingly, this led to a complex mixture of products, which failed to contain the desired tetracyclic species.

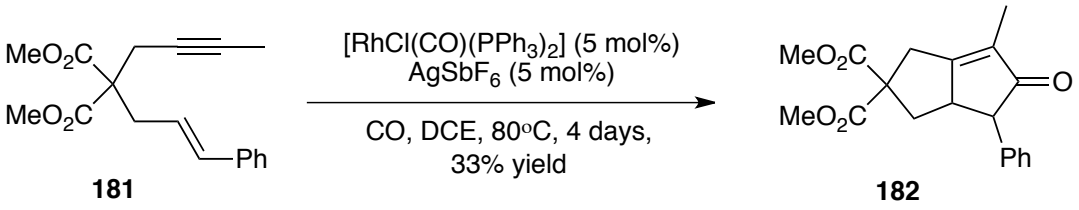


Scheme 158

Entry	*Catalyst Loading (mol%)*	*Temp*	*Yield*
1	2.5	r.t	-
2	5	r.t	-
3	2.5	40°C	-
4	5	40°C	-

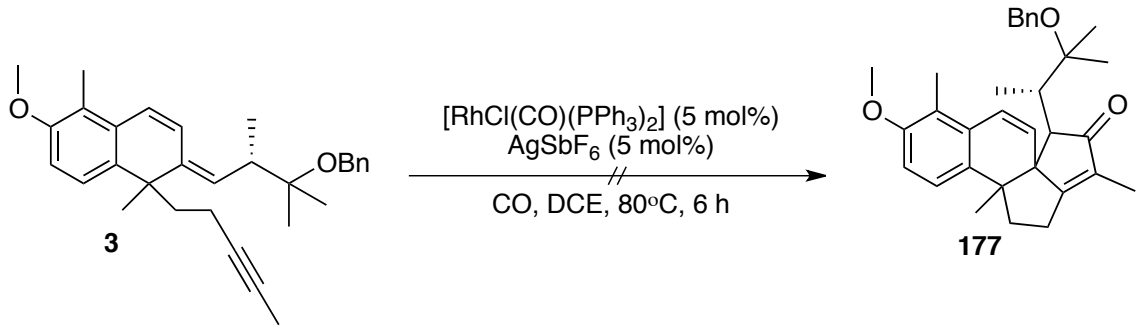
Table 2

It was apparent that the conjugated alkene species **3** was a poor substrate in the rhodium-promoted Pauson-Khand reaction. Wender reported that, although diene containing moieties proved to be good substrates, the same cannot be said for conjugated alkenes in general. This is illustrated by the poor reactivity of styrene **180** that formed the desired PKR product in low yield (**Scheme 159**).[78]



Scheme 159

In a final attempt to access tetracycle **177**, it was decided to transpose the forcing reaction conditions Wender employed on styrene **181**. Based on this, dienyl **3** was treated with 5 mol% of the catalyst and the resulting material heated to 80°C and stirred for 6 hours under an atmosphere of CO (**Scheme 160**). Regrettably, this failed to furnish the desired product and a complex mixture was observed.



Scheme 160

Sadly, due to time constaints, further optimisation studies could not be completed as part of this research project. The following sections summarise the synthesis of the advanced intermediate **3**, and offer discussion regarding the completion of the total synthesis of Agariblazeispirol C.

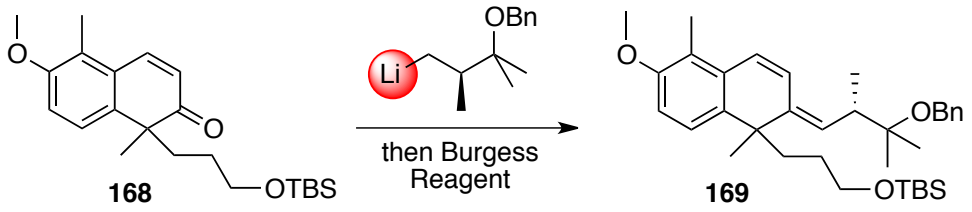
4 Conclusion

Substantial efforts towards the total synthesis of Agariblazeispirol C have been conducted. A variety of advanced intermediates have been accessed as a result of careful strategic planning and considerable synthetic effort. The introduction of the oxygenated sidechain represents a significant milestone towards the synthesis of the target natural product. In this regard, suitable coupling partners for the Wittig reaction **81** and **88**, Julia-Kocienski olefination **94**, and organometallic addition, **90**, were accessed in an efficient manner.

After a sustained period of investigation a suitable organometallic addition protocol was developed. The reverse-addition lithiation methodology facilitated the installation of the oxygentated sidechain and suitably advanced the synthetic efforts towards Agariblazeispirol C. In addition, the subsequent elimination of allylic alcohol **114** to diene **59** was investigated and two suitable reaction protocols were identified. The mesylation/elimination methodology proved equally efficient to the concomitantly developed Burgess reagent mediated elimination.

In an effort to enhance the efficiency of the organometallic addition process it was decided to investigate the ability of a modified alkyne bearing enone species, **130**, to undergo the transformation. However, significant difficulties were encountered with respect to introducing the alkyne unit. It was envisaged that employing a homologated enone **168**, would circumvent the issues previously encountered in accessing alkyne **130**, and allow the strategic employment of traditional alkynyl formation reactions. In this regard, several synthetic strategies were extensively investigated but disappointingly failed to deliver alkyne **130**.

The improvement of the organometallic addition/elimination sequence remained at the forefront of the synthetic strategy, and, accordingly, enone **168**, bearing an extended alkyl chain was employed in the above synthetic transformation. This amended substrate, **168**, afforded the diene species, **169**, in an improved yield in comparison to that obtained for diene **59**. Further still, NMR studies concluded that the diene moiety had formed exclusively with the desired (*E*)-olefin stereochemistry (**Scheme 161**).



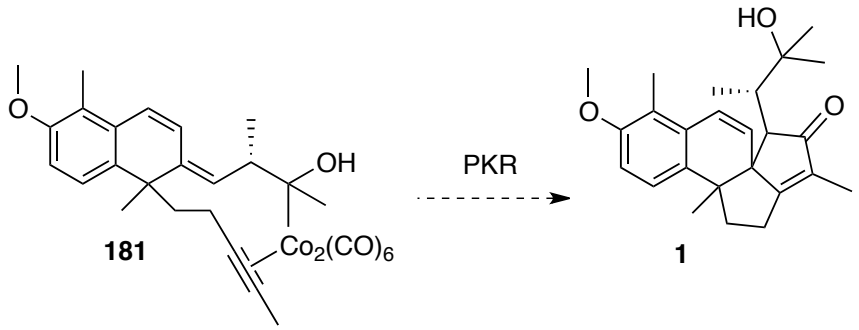
Scheme 161

Following the development of an efficient approach to diene **169**, the next goal was the synthesis of the Pauson-Khand precursor, dienyne **3**. To this end, a robust 4-step synthetic approach featuring: desilyation, oxidation, alkynylation, and methylation granted access to dienyne **3**.

Finally, work towards completing the natural product was carried out and a range of Pauson-Khand reactions were investigated. Disappointingly, efforts towards promoting the cyclisation failed to deliver the desired annulation and the synthesis of the natural product remains elusive. Despite this, with a robust and efficient protocol now in place for the synthesis of the Pauson-Khand precursor **3**, it is envisaged that a comprehensive investigation into promoting the PKR will result in the formation of the desired natural product, Agariblazeispirol C, **1**.

5 Future Work

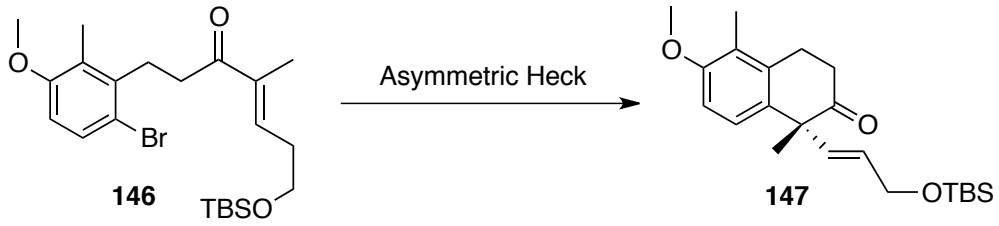
The ultimate goal of the research programme is to complete the total synthesis of Agariblazeispirol C. In this regard, a sustained methodology study of the Pauson-Khand reaction is likely to offer the greatest hope of accessing the desired natural product. Initial efforts investigated commonly used *N*-oxide and sulfide promotion methods, however, there are numerous other methods by which to promote the reaction. Following a successful annulation protocol a final debenzylation reaction would furnish Agariblazeispirol C. Having stated this, an initial debenzylation reaction before the PKR may offer a greater chance of accessing the desired natural product (**Scheme 162**). The reduced steric bulk of the sidechain unit may serve to increase the likelihood of a successful cyclisation occurring. Indeed, *via* this approach, the Pauson-Khand reaction would represent the final step of the reaction and would surely be considered one of the most impressive annulation Pauson-Khand annulations to date.



Scheme 162

In addition to the completion of the racemic natural product, an asymmetric variant would undoubtedly be of significant importance. It is likely that an asymmetric Heck reaction would offer access to the enantio enriched bicyclic species, **147** (**Scheme 163**). Indeed, it follows that this stereocenter would control the selectivity of downstream

processes. There are numerous examples of asymmetric Heck reactions in the chemical literature and it is likely that such a reaction could be applied in this case. Following this, the developed synthetic strategy could presumably facilitate access to the enantiomerically enriched product.



Scheme 163

6 Experimental

6.1 General

Reagents

All reagents were obtained from commercial suppliers and used without further purification, unless otherwise stated. All reactions were carried out under an inert, dry nitrogen atmosphere, unless otherwise stated. Purification was carried out according to standard laboratory methods.[79]

Tetrahydofuran, diethyl ether, toluene, and benzene were dried by heating to reflux over sodium wire, using benzophenone ketyl as an indicator, then distilled under nitrogen. Dichloromethane, 1,2-dichloroethane, acetonitrile, and DodSMe were dried by heating to reflux over calcium hydride then distilled under nitrogen.

^{n}BuLi, ^{t}BuLi, and MeLi were obtained as solutions in hexanes, pentanes, or diethyl ether respectively, and standardised using salicylaldehyde phenylhydrazone.[80]

Triphenylphosphine and tri-*o*-tolylphosphine were recrystallised from ethanol before use.

$CeCl_3.7H_2O$ was dried gradually at 60°C, 80°C and 140°C *in vacuo* over 16 h, then stored under argon.

Instrumentation and Data

Reactions performed under microwave irradiation were carried out in a CEM Discover instrument using sealed glass tubes.

Thin layer chromatography was carried out using Camlab silica plates coated with fluorescent indicator UV_{254}. This was analysed using a Mineralight UVGL-25 lamp or developed using a vanillin or potassium permanganate solution.

Flash column chromatography was carried out using Prolabo silica gel (230-400 mesh).

Melting points were obtained (uncorrected) on a Gallenkamp Griffin melting point apparatus.

FTIR spectra were obtained from neat samples on a Nicolet Impact 400D machine.

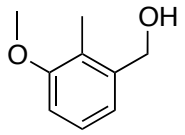
^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer at 400 MHz and 100 MHz, respectively, or a Bruker DRX 500 spectrometer at 500 MHz and 125 MHz, respectively. ^{31}P NMR spectra were recorded on a Bruker DPX 400 spectrometer at 162 MHz. Chemical shifts are reported in ppm. Coupling constants are reported in Hz and refer to $^{3}J_{H\text{-}H}$ interections, unless otherwise stated. Note: $CDCl_3$ solvent signals were used as internal reference points at δ 7.26 and 77.16 ppm in ^{1}H and ^{13}C NMR respectively.

Optical rotation was obtained on Perkin Elmer 341 polarimeter using a cell with a path length of 1 dm. Concentration is expressed in g/100 cm^3.

High resolution mass spectra were recorded on a Finnigan MAT 95 XP instrument at the EPSRC Mass Spectrometry facility at Swansea University, Wales.

6.2 Synthetic Substrates and Procedures

Preparation of (3-methoxy-2-methylphenyl)methanol, ***60***[81]



Scheme 23

To a previously flame dried and nitrogen cooled 3-neck round bottom flask, fitted with a condenser, was added a solution of 3-methoxy-2-methylbenzoic acid (50.0 g, 301.1 mmol) in dry THF (500 ml). The resulting suspension was cooled to 0˚C, followed by dropwise addition of borane dimethylsulfide complex (43.5 ml, 459.5 mmol). An exotherm was observed upon addition of the borane. Upon complete addition, the resulting slurry was warmed to reflux and stirred for 16 h. After this time, the solution was cooled to 0˚C and quenched, carefully, with MeOH (100 ml). Following this, the solution was diluted with ether and washed with water (x 2). The organic solution was dried over sodium sulfate, filtered, and evaporated to give a pale brown oil. Purification by recrystallisation from hexane (x 3) provided **60** (45.8 g, 100% yield) as a white solid.

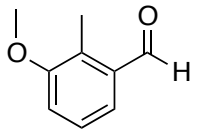
Melting Point: 60-61˚C.

IR: 3284, 1259 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 7.19 (t, *J* = 7.9 Hz, 1H, ArH), 6.99 (d, *J* = 7.4 Hz, 1H, ArH), 6.84 (d, *J* = 8.2 Hz, 1H, ArH), 4.72 (s, 2H, benzylic CH_2), 3.85 (s, 3H, OCH_3), 2.24 (s, 3H, $ArCH_3$) 1.51 ppm (bs, 1H, OH).

^{13}C NMR δ (100 MHz, $CDCl_3$): 157.2, 139.8, 126.5, 124.9, 120.2, 109.4, 63.9, 55.8, 10.9 ppm.

Preparation of 3-methoxy-2-methylbenzaldehyde, ***61***[36]



Scheme 24

A flame dried 3-neck round bottom flask, cooled under nitrogen was charged with oxalyl chloride (30.5 ml, 350 mmol) and dry DCM (500 ml). The solution was cooled to -78˚C prior to the dropwise addition of DMSO (44 ml, 619 mmol). The mixture was stirred at this temperature for 10 minutes prior to the addition of **60** (40 g, 269 mmol) as a solution in dry DCM (60 ml). The mixture was allowed to stir for 15 min followed by the addition of triethylamine (187 ml, 1.34 mol). The cooled mixture was allowed to warm to room temperature and stirred for 16 h. The reaction was quenched with saturated ammonium chloride solution, washed with water (x 2), and brine. The organic solution was dried over sodium sulfate, filtered, and evaporated to yield **61** (39.3 g, 100% yield) as a pale yellow oil.

IR: 1686 cm^{-1}.

^{1}H NMR: δ (400 MHz, $CDCl_3$): 10.35 (s, 1H, aldehyde), 7.44 (d, J = 7.7 Hz, 1H, ArH), 7.33 (t, J = 8.0 Hz, 1H, ArH), 7.10 (d, J = 8.0 Hz, 1H, ArH), 3.89, (s, 3H, OCH_3), 2.56 ppm (s, 3H, $ArCH_3$).

^{13}C NMR δ (100 MHz, $CDCl_3$): 192.2, 157.6, 134.6, 129.2, 126.1, 122.5, 114.8, 55.4, 9.9 ppm.

Preparation of 6-bromo-3-methoxy-2-methylbenzaldehyde, ***62***[36]

Scheme 25

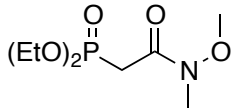
A flame dried, and nitrogen cooled, 1 L round bottom flask was charged with acetic acid (700 ml) and 3-methoxy-2-methylbenzaldehyde **61** (42 g, 280 mmol). The solution was allowed to stir at room temperature, before the dropwise addition of bromine (14.5 ml, 282 mmol). Stirring was continued for 21 h prior to the addition of water (400 ml). The resulting slurry was extracted into DCM, washed with water, and saturated sodium thiosulfate solution. The resulting organic solution was concentrated to a yellow/brown solid and purified by flash column chromatography (petrol), yielding **62** (60.9 g, 95% yield) as a pale yellow oil.

IR: 1683 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 10.47 (s, 1H, aldehyde), 7.46 (d, *J* = 8.7 Hz, 1H, ArH), 6.90 (d, *J* = 8.7 Hz, 1H, ArH), 3.86 (s, 3H, OCH_3), 2.44 ppm (s, 3H, $ArCH_3$).

^{13}C NMR δ (100 MHz, $CDCl_3$): 194.4, 157.1, 132.4, 130.8, 130.7, 116.6, 114.9, 55.5, 11.5 ppm.

Preparation of diethyl (2-(methoxy(methyl)amino)-2-oxoethyl)phosphonate, ***65***[37]



Scheme 26

A flame dried, and nitrogen cooled, 500 ml round bottom flask was charged with dry DCM (300 ml) and *N*,*O*-methoxymethylamine hydrochloride (25 g, 256 mmol). To the stirred suspension was added triethylamine (68.3 ml, 513 mmol) followed by chloroacetylchloride (20.4 ml, 256 mmol) in a dropwise fashion. The reaction was stirred at room temperature for 1 h followed by quenching with an aqueous solution of saturated sodium hydrogen carbonate. The organic portion was washed with 1 M HCl solution and brine. The solution was dried over sodium sulfate, filtered, and evaporated to yield a brown oil. To this was added neat triethylphosphite (30.9 ml, 180 mmol) and the mixture stirred at 80˚C for 24 h. The reaction was allowed to cool to room temperature and concentrated *in vacuo*. The crude product was purified by bulb-to-bulb distillation (150˚C/0.03 mmHg) to yield **65** (41.6 g, 77% yield) as a pale yellow oil.

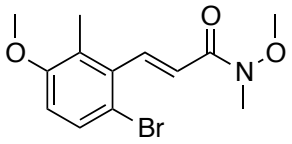
IR: 1656 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 4.03-4.21 (m, 4H, OCH_2), 3.79 (s, 3H, OCH_3), 3.13-3.23 (m, 5H, NCH_3 and PCH_2), 1.37 ppm (t, J = 7.0 Hz, 6H, alkyl CH_3);

^{13}C NMR δ (100 MHz, $CDCl_3$): 166.1, 62.5 (d, $^{2}J_{P\text{-}C}$ = 6.1 Hz), 61.7, 32.1, 31.5 (d, $^{1}J_{P\text{-}C}$ = 138.4 Hz), 16.3 ppm (d, $J_{P\text{-}C}$ = 6.1 Hz).

^{31}P NMR δ (162 MHz, $CDCl_3$): 21.1 ppm.

Preparation of (E)-3-(6-bromo-3-methoxy-2-methylphenyl)-N-methoxy-N-methylacrylamide, ***66***[33]



Scheme 27

A flame dried, and nitrogen cooled, 500 ml 3-neck round bottom flask was charged with dry THF (250 ml) and phosphonate **65** (8.5 g, 35.5 mmol). The solution was cooled to 0˚C, followed by the dropwise addition of ^{n}BuLi (16.1 ml, 2.2 M in hexanes, 35.5 mmol). Aldehyde **62** (7.7 g, 33.8 mmol) was slowly added as a solution in dry THF (20 ml), and upon complete addition the mixture was allowed to warm to room temperature and stir for 1 h. A saturated solution of ammonium chloride was added and the organics were extracted into diethyl ether. The organic phase was washed with water and brine, before drying over sodium sulfate. The suspension was filtered, evaporated to an oil, and purified by flash column chromatography (0-30% diethyl ether in petrol), to yield **66** (10.30 g, 97% yield) as a pale yellow oil.

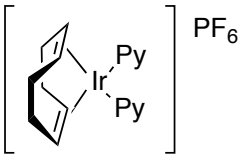
IR: 1656, 1624, 1566 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 7.73 (d, J = 16.1 Hz, 1H, olefinic CH), 7.41 (d, J = 8.8 Hz, 1H, ArH), 6.69-6.73 (m, 2H, ArH and olefinic CH), 3.83 (s, 3H, $ArOCH_3$), 3.74 (s, 3H, $NOCH_3$), 3.33 (s, 3H, NCH_3), 2.26 ppm (s, 3H, $ArCH_3$).

^{13}C NMR δ (100 MHz, $CDCl_3$): 166.2, 157.1, 141.8, 136.8, 130.3, 127.3, 123.7, 114.0, 111.2, 62.0, 55.8, 32.5, 14.0 ppm.

HRMS *m/z* (ESI) Calc. for $C_{13}H_{17}BrNO_3$ (M^+ + H): 316.0366. Found: 316.0370.

Preparation of (η^4-1,5-cyclooctadiene)bis(pyridine)iridium(I) hexafluorophosphate, ***68***[39]



Scheme 28

A flame dried, and nitrogen cooled, 250 ml round bottom flask was charged with degassed acetone/water (50 ml:50 ml) and pyridine (3.4 ml, 41.8 mmol). To the stirred solution was added η^4-cycloocta-1,5-dieneiridium(I) chloride dimer, **67** (2.0 g, 2.97 mmol) and potassium hexafluorophosphate (1.72 g, 9.35 mmol). The yellow slurry was stirred at room temperature for 16 h. The mixture was concentrated *in vacuo*, resulting in a yellow precipitate which was filtered and washed with degassed water. The solid was dried in a vacuum oven, at 40˚C, overnight, yielding the desired product **68** (3.38 g, 90% yield) as a yellow powder.

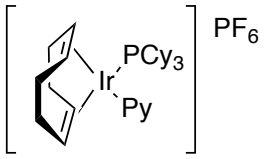
Melting Point: decomposed at > 190˚C.

IR: 1446, 835 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 8.74 (d, *J* = 5.0 Hz, 4H, ArH), 7.77 (t, *J* = 7.7 Hz, 2H, ArH), 7.51 (t, *J* = 7.0 Hz, 4H, ArH), 3.86 (d, *J* = 2.4 Hz, 4H, olefinic CH), 2.51-2.48 (m, 4H, COD CH), 1.86-1.83 ppm (m, 4H, COD CH).

^{31}P NMR δ (162 MHz, $CDCl_3$): -144.2 ppm.

Preparation of Crabtree's Catalyst, ***69***[39]



Scheme 29

A flame dried, and nitrogen cooled, 250 ml round bottom flask was charged with degassed methanol (150 ml) and (η^4-1,5-cyclooctadiene)*bis*(pyridine)iridium(I) hexafluorophosphate, **68** (3.17 g, 5.23 mmol). To the stirred suspension was added tricyclohexylphosphine (1.76 g, 6.28 mmol), which resulted in an immediate colour change from yellow to bright orange. The suspension was allowed to stir for 1 h and reduced to ~ 30 ml *in vacuo*. The resulting slurry was diluted with diethyl ether, the precipitate filtered, washed with diethyl ether, and dried in a vacuum oven at 40˚C overnight. The desired product **69** (3.38 g, 90% yield) was isolated as an orange powder.

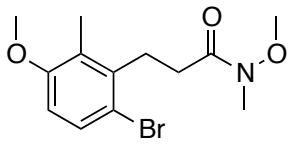
Melting Point: decomposed at > 190˚C.

IR: 1445, 836 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 8.79 (d, *J* = 5.1 Hz, 2H, ArH), 7.90 (t, *J* = 7.7 Hz, 1H, ArH), 7.66 (t, *J* = 7.1 Hz, 2H, ArH), 4.00 (d, *J* = 28.8 Hz, 4H, olefinic CH), 2.39-2.30 (m, 4H, COD CH), 1.95-1.05 ppm (m, 37H, Cy CH and COD CH).

^{31}P NMR δ (162 MHz, $CDCl_3$): 10.2, -144.2 ppm.

Preparation of 3-(6-bromo-3-methoxy-2-methylphenyl)-N-methoxy-N-methylpropanamide, 7[33]



Scheme 30

A flame dried, and nitrogen cooled, 100 ml round bottom flask was charged with Crabtree's catalyst **69** (1.28 g, 1.60 mmol), dry DCM (50 ml), and compound **66** (5 g, 15.97 mmol). The solution was cooled to -78˚C, evacuated and back-filled (x 3) with hydrogen gas *via* a three way tap attached to a vacuum manifold and a hydrogen balloon. The solution was kept under an atmosphere of hydrogen, allowed to warm to room temperature, and stirred for 16 h. The mixture was concentrated *in vacuo*, to give an orange oil, and purified by flash column chromatography (0-50% diethyl ether in petrol). Amide **7** (4.82 g, 97% yield) was isolated as a pale yellow oil.

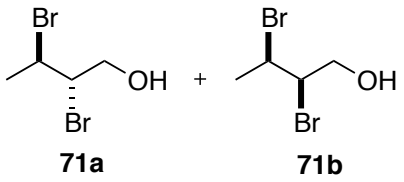
IR: 1656, 1572, 1458 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 7.36 (d, J = 9.0 Hz, 1H, ArH), 6.62 (d, J = 9.0 Hz, 1H, ArH), 3.81 (s, 3H, $ArOCH_3$), 3.67 (s, 3H, $NOCH_3$), 3.22 (s, 3H, NCH_3), 3.16-3.12 (m, 2H, alkyl CH_2), 2.63 (t, J = 6.5 Hz, 2H, alkyl CH_2), 2.26 ppm (s, 3H, $ArCH_3$).

^{13}C NMR δ (100 MHz, $CDCl_3$): 173.5, 157.1, 139.6, 130.1, 127.1, 116.0, 109.9, 61.3, 55.7, 32.2, 30.9, 28.5, 12.3 ppm.

HRMS *m/z* (ESI) Calc. for $C_{13}H_{19}BrNO_3$ (M^+ + H): 318.0522. Found: 318.0520.

Preparation of 2,3-dibromobutan-1-ol, **71a** and **71b**[40]



71a **71b**

Scheme 32

A flame dried, and nitrogen cooled, 3-necked 500 ml round bottom flask was charged with dry DCM (250 ml) and crotyl alcohol (8.5 ml, 100 mmol; *trans:cis* 96:4). The solution was cooled to -78˚C and bromine (5.2 ml, 100 mmol) was added in a dropwise fashion. The solution was stirred at -78˚C for 30 min, allowed to warm to room temperature, and stirred for a further 2 h. The solvent was removed *in vacuo* and the resulting red oil was purified *via* distillation (102-104˚C, 17 mbar) to give a mixture of diastereomers **71a** and **71b** (19.7 g, 86% yield, ratio 96:4) as a colourless oil.

Data for major diastereomer **71a**:

IR: 3363, 1450, 1379 cm^{-1}.

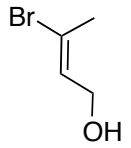
^{1}H NMR δ (400 MHz, $CDCl_3$): 4.42-4.32 (m, 1H, CHBr), 4.30-4.23 (m, 1H, CHBr), 4.16-4.08 (m, 2H, OCH_2), 1.92 ppm (d, J = 6.8 Hz, 3H, CH_3).

^{13}C NMR δ (100 MHz, $CDCl_3$): 66.1, 62.4, 47.6, 25.6 ppm.

Data for minor diastereomer **71b**:

Diagnostic peaks in ^{1}H NMR δ (400 MHz, $CDCl_3$): 1.82 ppm (d, J = 6.8 Hz, CH_3).

Preparation of (E)-3-bromobut-2-en-1-ol, ***72***[40]



Scheme 33

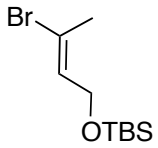
A flame dried, and nitrogen cooled, 3-necked 500 ml round bottom flask was charged with dry THF (170 ml) and di-*iso*-propylamine (35.6 ml, 252 mmol). The solution was cooled to 0˚C, followed by the dropwise addition of ^{n}BuLi (96.6 ml, 2.5 M in hexanes, 241.5 mmol). The mixture was allowed to stir for 10 min before the addition of DMPU (6.28 ml, 52.5 mmol). The solution was cooled to -78˚C and a mixture (96:4) of **71a** and **71b** (24.3 g, 105 mmol), in THF (20 ml), was added. Upon complete addition the mixture was allowed to stir for 30 min before warming to room temperature. Stirring was continued for a further 3 h at this temperature. After this time, the reaction was quenched with water and extracted with diethyl ether (x 2). The organic portions were pooled, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude brown oil was purified by distillation (96-98˚C, 45 mbar) to yield the desired alcohol **72** (11.65 g, 74% yield) as a colourless oil.

IR: 1651, 1429, 1379 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 6.11 (qt, J = 7.2, ^{4}J = 1.3 Hz, 1H, olefinic CH), 4.12 (d, J = 7.2 Hz, 2H, OCH_2), 2.31 ppm (bs, 3H, CH_3).

^{13}C NMR δ (100 MHz, $CDCl_3$): 130.8, 124.2, 59.6, 23.6 ppm.

Preparation of (E)-((3-bromobut-2-en-1-yl)oxy)(tert-butyl)dimethylsilane, ***73***[82]



Scheme 34

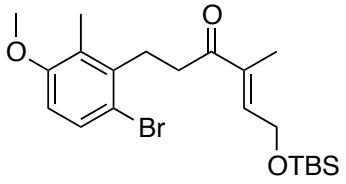
A flame dried, and nitrogen cooled, 3-necked 1 L round bottom flask was charged with dry DCM (500 ml), alcohol **72** (10.00 g, 66.7 mmol), and imidazole (9.08 g, 133.4 mmol). *Tert*-butyldimethylsilyl chloride (12.56 g, 83.38 mmol) was added portionwise and the resulting solution stirred at room temperature for 1 h. The reaction mixture was quenched with saturated sodium bicarbonate solution. The organic portion was washed with brine, dried over sodium sulfate, filtered, and evaporated to an oil. The crude material was purified by flash column chromatography (petrol) to yield **73** (17.08 g, 97% yield) as a colourless oil.

IR: 1653, 1463, 1251 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 6.01 (qt, J = 6.8, ^{4}J = 1.1 Hz, 1H, olefinic CH), 4.14 (d, J = 6.8 Hz, 2H, OCH_2), 2.27 (bs, 3H, CH_3), 0.91 (s, 9H, Si^{t}Bu), 0.08 ppm (s, 6H, $SiCH_3$).

^{13}C NMR δ (100 MHz, $CDCl_3$): 131.7, 121.9, 60.4, 25.9, 23.7, 18.3, -5.2 ppm.

Preparation of (E)-1-(6-bromo-3-methoxy-2-methylphenyl)-6-((tert-butyldimethylsilyl)oxy)-4-methylhex-4-en-3-one, ***6***[32]



Scheme 35

A flame dried, and nitrogen cooled, 3-necked 250 ml round bottom flask was charged with vinyl bromide **73** (5.24 g, 19.8 mmol) and dry diethyl ether (75 ml). The reaction mixture was cooled to -78˚C, followed by the dropwise addition of ^{t}BuLi (23 ml, 1.7 M in pentane, 39.5 mmol) and allowed to stir at this temperature for 1 h.

Simultaneously, a 3-necked 100 ml round bottom flask, fitted with a reflux condenser, was charged with magnesium turnings (960 mg, 39.7 mmol) and flame dried under vacuum. The flask was cooled under nitrogen and charged with dry diethyl ether (30 ml) and dry benzene (10 ml). To the stirred suspension was added dibromoethane (3.36 ml, 39.5 mmol), dropwise, at such a rate as to ensure the mixture refluxed without external heating. Upon complete addition, the reaction mixture was warmed to a gentle reflux (50˚C) and held at this temperature for 1 h. Stirring was discontinued and the solution allowed to settle at room temperature, resulting in a 1 M solution of anhydrous $MgBr_2(OEt_2)$.

The freshly generated anhydrous $MgBr_2(OEt_2)$ solution (20.5 ml, 1 M in Et_2O/benzene, 20.5 mmol) was added to the vinyllithium species at -78˚C. The mixture was stirred at this temperature for 10 min before warming to 0˚C. The solution was allowed to stir at this temperature for 30 min prior to the addition of Weinreb amide **7** (4.5 g, 14.2 mmol) as a solution in dry diethyl ether (10 ml). The mixture was stirred at 0˚C for 30 min prior

to warming to room temperature for a further 30 min. Following this, the reaction was quenched with saturated ammonium chloride solution. The organic phase was washed with water and brine, before drying over sodium sulfate. The mixture was filtered, concentrated *in vacuo*, and purified by flash column chromatography (0-5% diethyl ether in petrol) to yield **6** (5.94 g, 95% yield) as a pale yellow oil.

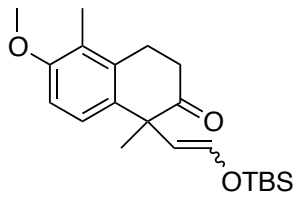
IR: 1670, 1572, 1460 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 7.38 (d, J = 8.8 Hz, 1H, ArH), 6.70-6.67 (m, 1H, olefinic CH), 6.63 (d, J = 8.8 Hz, 1H, ArH), 4.42 (d, J = 5.2 Hz, 2H, OCH_2), 3.82 (s, 3H, $ArOCH_3$), 3.13-3.09 (m, 2H, alkyl CH_2), 2.91-2.87 (m, 2H, alkyl CH_2), 2.24 (s, 3H, $ArCH_3$), 1.78 (s, 3H, vinylic CH_3), 0.93 (s, 9H, Si^{t}Bu), 0.10 ppm (s, 6H, $SiCH_3$).

^{13}C NMR δ (100 MHz, $CDCl_3$): 199.9, 156.6, 142.1, 139.1, 135.0, 129.7, 126.4, 115.4, 109.3, 60.4, 55.2, 35.5, 28.1, 25.5, 17.8, 11.7, 11.0, -5.7 ppm.

HRMS *m/z* (ESI) Calc. for $C_{21}H_{34}BrO_3Si$ (M^+ + H): 443.1435. Found: 443.1430.

Preparation of 1-(2-((tert-butyldimethylsilyl)oxy)vinyl)-6-methoxy-1,5-dimethyl-3,4-dihydronaphthalen-2(1H)-one, ***5***[32]



Scheme 36

A microwave vial was charged with palladium acetate (5 mg, 0.02 mmol), P(*o*-tolyl)$_3$ (27 mg, 0.09 mmol), and acetonitrile (0.5 ml). The resulting mixture was stirred for 5 min, at room temperature, which resulted in a colour change from a brown solution to an opaque yellow suspension. Substrate **6** (100 mg, 0.23 mmol) was added, as a solution in acetonitrile (0.5 ml) before the addition of triethylamine (0.07 ml, 0.45 mmol). The mixture was heated to 100˚C under microwave irradiation, with cooling, for 30 min (15 min x 2). After this time the solution was concentrated *in vacuo* and the resulting residue was filtered through celite (eluent: ethyl acetate). The resulting solution was concentrated *in vacuo* and purified by flash column chromatography* (0-5% diethyl ether in petrol). The desired enol ether, **5**, was obtained as a 50:50 mixture of *E*/*Z* isomers (66 mg, 82 % yield).

* To avoid unwanted hydrolysis of the enol ether product, oven dried silica was employed and approximately 2.5% triethylamine added to the eluent. Optimum yields were obtained with rapid purification.

Scheme 37

A microwave vial was charged with palladium acetate (52 mg, 0.23 mmol), P(*o*-tolyl)$_3$ (274 mg, 0.90 mmol), and acetonitrile (1.5 ml). The resulting mixture was stirred for 5

min, at room temperature, which resulted in a colour change from a brown solution to an opaque yellow suspension. Substrate **6** (1.0 g, 2.25 mmol) was added, as a solution in acetonitrile (0.5 ml) before the addition of triethylamine (0.63 ml, 4.5 mmol). The mixture was heated to 100˚C under microwave irradiation, with cooling, for 30 min (15 min x 2). After this time the solution was concentrated *in vacuo* and the resulting residue was filtered through celite (eluent: ethyl acetate). The resulting solution was concentrated *in vacuo*, solubilised in THF (5 ml) followed by the addition of copper (I) chloride (89 mg, 0.90 mmol) and stirred for 10 min. Following this the resulting suspension was concentrated *in vacuo* and purified by flash column chromatography* (0-5% diethyl ether in petrol). The desired enol ether, **5**, was obtained as a 50:50 mixture of *E*/*Z* isomers (681 mg, 84 % yield).

* To avoid unwanted hydrolysis of the enol ether product, oven dried silica was employed and approximately 2.5% triethylamine added to the eluent. Optimum yields were obtained with rapid purification.

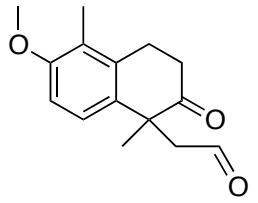
IR: 1714, 1648, 1481, 1463, 1259, 1101 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 7.14-7.11 (m, 1H, ArH), 6.81 (d, *J* = 8.5 Hz, 0.5H, ArH), 6.77 (d, *J* = 8.5 Hz, 0.5Hz, ArH), 6.15 (d, *J* = 6.0 Hz, 0.5H, *Z*-olefinic CH), 5.99 (d, *J* = 12.0 Hz, 0.5H, *E*-olefinic CH), 5.09 (d, *J* = 12.0 Hz, 0.5H, *E*-olefinic CH), 4.47 (d, *J* = 6.0 Hz, 0.5H, *Z*-olefinic CH), 3.85 (s, 1.5H, $ArOCH_3$), 3.83 (s, 1.5H, $ArOCH_3$), 3.22-2.81 (m, 3H, ring CH_2), 2.54-2.45 (m, 1H, ring CH_2), 2.22 (s, 1.5H, $ArCH_3$), 2.20 (s, 1.5H, $ArCH_3$), 1.56 (s, 1.5H, $ArCCH_3$), 1.53 (s, 1.5H, $ArCCH_3$), 0.89 (s, 4.5H, Si^{t}Bu), 0.88 (s, 4.5H, Si^{t}Bu), 0.09 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$).

^{13}C NMR δ (100 MHz, $CDCl_3$): 213.2, 156.0, 139.0, 135.9, 135.8, 124.2, 123.2, 114.1, 108.9, 55.7, 50.9, 36.8, 25.6, 25.4, 25.2, 24.7, 18.0, -5.6.

HRMS *m/z* (ESI) Calc. for $C_{21}H_{33}O_3Si$ (M^+ + H): 361.2193. Found: 361.2197.

Preparation of 2-(6-methoxy-1,5-dimethyl-2-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)acetaldehyde, ***74***



Scheme 39

A microwave vial was charged with palladium acetate (5 mg, 0.02 mmol), P(*o*-tolyl)$_3$ (27 mg, 0.09 mmol), and acetonitrile (0.5 ml). The resulting mixture was stirred for 5 min, at room temperature, which resulted in a colour change from a brown solution to an opaque yellow suspension. Substrate **6** (100 mg, 0.23 mmol) was added, as a solution in acetonitrile (0.5 ml) before the addition of triethylamine (0.07 ml, 0.45 mmol). The mixture was heated to 100˚C under microwave irradiation, with cooling, for 30 min (15 min x 2). After this time the solution was concentrated *in vacuo* and the resulting residue was filtered through celite (eluent: ethyl acetate). The resulting solution was washed with an aqueous solution of 1 M hydrochloric acid, water and brine, before drying over sodium sulfate. The mixture was filtered, concentrated *in vacuo*, and purified by flash column chromatography (0-30% diethyl ether in petrol). The desired aldehyde, **74**, was obtained as a clear yellow oil (44 mg, 77 % yield).

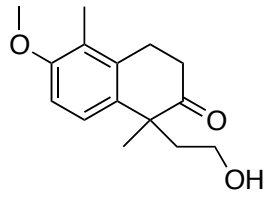
IR: 2975, 2825, 1712, 1479 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 9.42 (d, *J* = 1.6 Hz, 1H, CHO), 7.00 (d, *J* = 8.8 Hz, 1H, ArH), 6.80 (d, *J* = 8.8 Hz, 1H, ArH), 3.81 (s, 3H, $ArOCH_3$), 3.41 (d, ^2J = 17.8 Hz, 1H,

CH_2CHO), 3.20-3.13 (m, 2H, ring CH_2), 3.00 (dd, ^2J = 17.8 Hz, J = 1.6 Hz, 1H, CH_2CHO), 2.88-2.69 (m, 2H, ring CH_2), 2.20 (s, 3H, $ArCH_3$), 1.44 ppm (s, 3H, CCH_3). ^{13}C NMR δ (100 MHz, $CDCl_3$): 213.7, 199.6, 156.0, 135.6, 133.4, 123.9, 123.8, 109.1, 55.6, 53.6, 47.9, 36.9, 29.0, 25.7, 11.6 ppm.

Due to the unstable nature of this compound HRMS data could not be obtained.

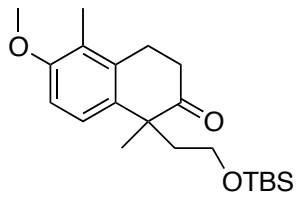
Attempted preparation of 1-(2-hydroxyethyl)-6-methoxy-1,5-dimethyl-3,4-dihydronaphthalen-2(1H)-one, ***75***



Scheme 40

A flame dried, and nitrogen cooled, 50 ml round bottom flask was charged with aldehyde **74** (554 mg, 0.69 mmol), benzene (30 ml), and sodium triacetoxyborohydride (2.5 g, 6.93 mmol). The solution was stirred at room temperature for 1 h. Following this, the mixture was heated to reflux and stirred for 1 h. After this time, the mixture was cooled to room temperature and analysed by TLC and ^{1}H NMR. A complex mixture of products was observed and the reaction was abandoned.

Preparation of 1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-6-methoxy-1,5-dimethyl-3,4-dihydronaphthalen-2(1H)-one, ***76***[32]



Scheme 41

A flame dried, and nitrogen cooled, 100 ml round bottom flask was charged with Crabtree's catalyst (554 mg, 0.69 mmol), dry DCM (30 ml), and enol ether **5** (2.5 g, 6.93 mmol). The solution was cooled to -78˚C, evacuated and back-filled (x 3) with hydrogen gas *via* a three way tap attached to a vacuum manifold and a hydrogen balloon. The solution was kept under an atmosphere of hydrogen, allowed to warm to room temperature, and stirred for 16 h. The mixture was concentrated *in vacuo*, to give an orange oil, which was purified by flash column chromatography (0-10% diethyl ether in petrol), to provide **76** (2.36 g, 94% yield) as a colourless oil.

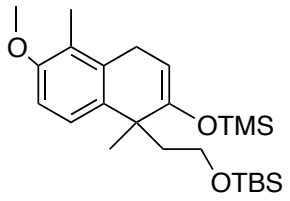
IR: 1713, 1483, 1462, 1261 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 7.11 (d, J = 8.7 Hz, 1H, ArH), 6.81 (d, J = 8.7 Hz, 1H, ArH), 3.84 (s, 3H, $ArOCH_3$), 3.36-3.26 (m, 2H, OCH_2), 3.01 (t, J = 7.5 Hz, 2H, ring CH_2), 2.74-2.60 (m, 2H, ring CH_2), 2.41-2.33 (m, 1H, alkyl CH), 2.20 (s, 3H, $ArCH_3$), 1.92-1.86 (m, 1H, alkyl CH), 1.42 (s, 3H, alkyl CH_3), 0.82 (s, 9H, Si^{t}Bu), -0.04 ppm (d, J = 2.2 Hz, 6H, $SiCH_3$).

^{13}C NMR δ (100 MHz, $CDCl_3$): 214.2, 155.7, 135.8, 134.1, 124.5, 123.4, 109.1, 59.9, 55.6, 49.1, 43.8, 37.6, 28.0, 25.9, 25.3, 18.3, 11.5, -5.5 ppm.

HRMS *m/z* (ESI) Calc. for $C_{21}H_{35}O_3Si$ (M^+ + H): 363.2350. Found: 363.2355.

*Preparation of tert-butyl(2-(6-methoxy-1,5-dimethyl-2-((trimethylsilyl)oxy)-1,4-dihydronaphthalen-1-yl)ethoxy)dimethylsilane, **77**[32]*



Scheme 42

A flame dried, and nitrogen cooled, 100 ml round bottom flask was charged with dry DCM (40 ml), ketone **76** (1.2 g, 3.31 mmol), and triethylamine (1.41 ml, 10.0 mmol). The solution was cooled to -5˚C, before the dropwise addition of trimethylsilyl triflate (1.26 ml, 7.0 mmol). The solution was allowed to stir at this temperature for 30 min before quenching with saturated sodium bicarbonate solution. The mixture was extracted with DCM, the organic portion separated, dried over sodium sulfate, and filtered. The solution was concentrated *in vacuo* and purified by flash column chromatography* (petrol) to yield enol ether **77** (1.25 g, 87% yield) as a colourless oil.

* To avoid unwanted hydrolysis of the enol ether product, oven dried silica was employed and approximately 2.5% triethylamine added to the eluent. Optimum yields were obtained with rapid purification.

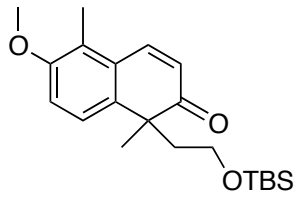
IR: 1687, 1488, 1463, 1254 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 7.19 (d, J = 8.7 Hz, 1H, ArH), 6.79 (d, J = 8.8 Hz, 1H, ArH), 4.93 (t, J = 3.8 Hz, 1H, olefinic CH), 3.82 (s, 3H, $ArOCH_3$), 3.49-3.42 (m, 1H, OCH), 3.26 (t, J = 3.8 Hz, 2H, ring CH_2), 3.13-3.04 (m, 1H, OCH), 2.28-2.20 (m, 1H, alkyl CH), 2.11 (s, 3H, $ArCH_3$), 1.92-1.83 (m, 1H, alkyl CH), 1.36 (s, 3H, alkyl CH_3), 0.82 (s, 9H, Si^{t}Bu), 0.26 (s, 9H, $SiCH_3$), -0.05 ppm (s, 6H, $SiCH_3$).

^{13}C NMR δ (100 MHz, $CDCl_3$): 155.3, 152.1, 134.1, 133.1, 124.6, 123.0, 109.3, 98.8, 61.1, 55.8, 43.5, 40.5, 30.0, 28.2, 26.2, 18.5, 11.3, 0.6, -5.0 ppm.

Due to the unstable nature of this compound HRMS data could not be obtained.

Preparation of tert-butyl(2-(6-methoxy-1,5-dimethyl-2-((trimethylsilyl)oxy)-1,4-dihydronaphthalen-1-yl)ethoxy)dimethylsilane, ***4***[32]



Scheme 43

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with acetonitrile (5 ml), silyl enol ether **77** (500 mg, 1.15 mmol), and palladium acetate (285 mg, 1.27 mmol). The resulting mixture was heated to 40˚C and stirred for 16 h. After this time the solution was concentrated *in vacuo* and purified by flash column chromatography (0-5% diethyl ether in petrol) to yield enone **4** (370 mg, 89% yield).

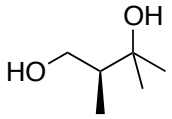
IR: 1575, 1667 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 7.76 (d, J = 10.5 Hz, 1H, olefinic CH), 7.22 (d, J = 8.6 Hz, 1H, ArH), 6.92 (d, J = 8.6 Hz, 1H, ArH), 6.17 (d, J = 10.5 Hz, 1H, olefinic CH), 3.85 (s, 3H, $ArOCH_3$), 3.24-3.21 (m, 2H, OCH_2), 2.57-2.52 (m, 1H, alkyl CH), 2.35 (s, 3H, $ArCH_3$), 2.10-2.04 (m, 1H, alkyl CH), 1.39 (s, 3H, alkyl CH_3), 0.76 (s, 9H, Si^tBu), -0.13 ppm (s, 6H, $SiCH_3$).

^{13}C NMR δ (100 MHz, $CDCl_3$): 203.8, 156.1, 140.5, 138.1, 128.9, 125.4, 125.1, 124.7, 112.1, 59.9, 56.0, 49.1, 44.8, 29.9, 26.0, 18.4, 10.9, -5.3 ppm.

HRMS *m/z* (ESI) Calc. for $C_{21}H_{33}O_3Si$ (M^+ + H): 362.2221. Found: 362.2221.

Preparation of (S)-2,3-dimethylbutane-1,3-diol, ***84***[44]



Scheme 47

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with diethyl ether (2 ml) and methylmagnesium chloride (4.65 ml, 3 M in THF, 13.96 mmol). To this stirred solution was added (*S*)-methyl 3-hydroxy-2-methylpropionoate **85** (500 mg, 4.23 mmol) in diethyl ether (2 ml), dropwise. The reaction temperature was maintained in the region of 20-25˚C (with the aid of an ice bath) in order to minimise the risk of polymerization, and upon complete addition, the mixture was allowed to stir for 2 h at room temperature. After this time, the reaction was quenched with saturated ammonium chloride solution and extracted with diethyl ether (x 5). The organic phases were pooled, washed with brine, dried over sodium sulfate, and concentrated *in vacuo* to yield **84** (355 mg, 71 % yield) as a colourless liquid.

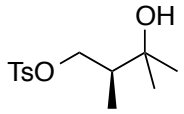
IR: 3325 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 3.77-3.69 (m, 2H, OCH_2), 2.35 (bs, 1H, OH), 1.87-1.79 (m, 1H, CH), 1.29 (s, 3H, CCH_3), 1.21 (s, 3H, CCH_3), 0.88 ppm (d, J = 7.1 Hz, 3H, $CHCH_3$).

^{13}C NMR δ (100 MHz, $CDCl_3$): 74.0, 66.6, 44.4, 30.1, 24.6, 13.3 ppm.

$[\alpha]_D^{24}$ = -2.3˚, c = 0.2 ($CHCl_3$).

Preparation of (S)-3-hydroxy-2,3-dimethylbutyl 4-methylbenzenesulfonate, ***83***[44]



Scheme 48

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with alcohol **84** (250 mg, 2.11 mmol) and pyridine (2.11 ml, 1 M) before cooling to -5˚C. Following this, 4-toluenesulfonyl chloride (402 mg, 2.11 mmol) was added in one portion and the resulting solution transferred to a refrigerator and maintained at 4˚C for 18 h. The mixture was poured into ice water and extracted with diethyl ether (x 2). The resulting organic phases were pooled and washed sequentially with water (x 2), 1 M HCl (x 2), and brine. The mixture was dried over sodium sulfate, filtered, and concentrated *in vacuo*, The resulting crude oil was purified by column chromatography (eluent: 0-50% diethyl ether in petrol) to yield tosylate **83** (448 mg, 79% yield) as a colourless oil.

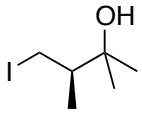
IR: 3534, 2974, 1375, 1174 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 7.80 (d, J = 8.2 Hz, 2H, ArH), 7.36 (d, J = 8.2 Hz, 2H, ArH), 4.25 (dd, ^{2}J = 9.5, J = 4.4 Hz, 1H, OCH_2), 3.94 (dd, ^{2}J = 9.5, J = 2.1 Hz, 1H, OCH_2), 2.46 (s, 3H, $ArCH_3$), 1.86 (ddq, J = 7.0, 4.4, 2.1 Hz, 1H, C$H$$CH_3$), 1.20 (s, 3H, CCH_3), 1.13 (s, 3H, CCH_3), 0.97 ppm (d, J = 7.0 Hz, 3H, CHCH_3).

^{13}C NMR δ (100 MHz, $CDCl_3$): 145.0, 133.2, 130.1, 128.1, 72.8, 72.2, 43.6, 28.9, 26.3, 21.9, 12.9 ppm.

$[\alpha]_D^{24}$ = -13.9˚, c = 1.0 ($CHCl_3$).

Preparation of (R)-4-iodo-2,3-dimethylbutan-2-ol, ***82***[44]



Scheme 49

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with tosylate **83** (170 mg, 0.62 mmol), THF (5 ml), and anhydrous lithium iodide (100 mg, 0.74 mmol). The solution was heated to reflux and stirred for 3 h. After this time, the mixture was allowed to cool to room temperature and quenched by addition of diethyl ether (8 ml). The resulting suspension was filtered and the filtrate was washed with saturated sodium sulfite solution. The organic phase was separated and washed sequentially with water and brine before drying over sodium sulfate. The mixture was filtered, concentrated *in vacuo*, and purified by column chromatography (eluent: 0-80% diethyl ether in petrol) to deliver iodide **82** (139 mg, 98% yield) as a pale yellow oil.

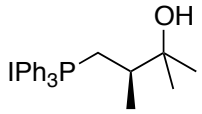
IR: 3362, 1192 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 3.70 (dd, ^{2}J = 9.6, J = 2.8 Hz, 1H, ICH_2), 2.95 (dd, ^{2}J = 9.6, J = 10.7 Hz, 1H, ICH_2), 1.88 (ddq, J = 10.6, 6.8, 2.8 Hz, 1H, C*H*CH_3), 1.28 (s, 3H, CCH_3), 1.19 (s, 3H, CCH_3), 1.14 ppm (d, J = 6.8 Hz, 3H, CHC*H*$_3$).

^{13}C NMR δ (100 MHz, $CDCl_3$): 73.4, 47.9, 28.8, 25.5, 16.3, 11.1 ppm.

$[\alpha]_D^{23}$ = -37.7°, c = 2.0 ($CHCl_3$).

Preparation of (R)-4-(iodotriphenylphosphoranyl)-2,3-dimethylbutan-2-ol, ***81***[44]



Scheme 50

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with iodide **82** (30 mg, 0.13 mmol), MeCN (4 ml), and triphenylphosphine (250 mg, 1.06 mmol). The resulting suspension was warmed to reflux and stirred for 42 h. The mixture was allowed to cool to room temperature and concentrated *in vacuo*. The resulting gum was solubilised in diethyl ether (10 ml), which resulted in the immediate precipitation of a white solid. The suspension was stirred for 20 min and then filtered. The white solid was resolubilised in diethyl ether and allowed to stir for a further 20 min, before a further filtration. The trituration process was repeated a third time and the resulting white solid dried under vacuum for 1 h to yield **81** (46 mg, 72% yield).

Melting point: 165-167˚C

IR: 3417 cm^{-1}.

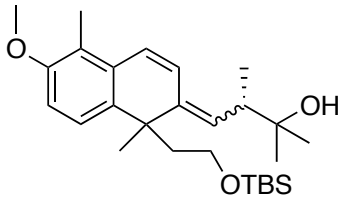
^{1}H NMR δ (400 MHz, $CDCl_3$): 7.99-7.94 (m, 6H, ArH), 7.83-7.78 (m, 3H, ArH), 7.75-7.70 (m, 6H, ArH), 4.72-4.65 (m, 1H, PPh_3CH_2), 2.86-2.77 (m, 1H, PPh_3CH_2), 2.18-2.09 (m, 1H, C*H*CH_3), 1.39 (s, 3H, CCH_3), 1.29 (s, 3H, CCH_3), 0.55 ppm (d, J = 6.9 Hz, 3H, CHCH_3).

^{13}C δ (100 MHz, $CDCl_3$): 135.1 (d, $^{4}J_{P\text{-}C}$ = 3.0 Hz), 134.0 (d, $^{3}J_{P\text{-}C}$ = 9.9 Hz), 130.6, (d, $^{2}J_{P\text{-}C}$ = 12.4 Hz), 119.1 (d, $^{1}J_{P\text{-}C}$ = 85.7 Hz), 73.7 (d, $^{3}J_{P\text{-}C}$ = 12.0 Hz), 39.8 (d, $^{2}J_{P\text{-}C}$ = 4.0 Hz), 29.5, 25.7 (d, $^{1}J_{P\text{-}C}$ = 51.4 Hz), 23.7, 17.2 ppm.

^{31}P NMR δ (162 MHz, $CDCl_3$): 23.7 ppm.

$[\alpha]_D^{24}$ = +6.9˚, c = 1.0 ($CHCl_3$).

Attempted preparation of 4-(1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-6-methoxy-1,5-dimethylnaphthalen-2(1H)-ylidene)-2,3-dimethylbutan-2-ol, ***79***



General Procedure

A flame dried, and nitrogen cooled, Schlenck tube was charged with lithium chloride (0.029 g, previously flame dried) and MeLi (10 ml, 1.6 M in Et_2O). The solution was kept under an inert atmosphere and used immediately in the subsequent reaction(s).

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with phosphonium salt **81** and solvent. The resulting suspension was cooled to -20˚C and charged with the pre-prepared MeLi solution (1.6 M in Et_2O (0.4 wt% LiCl)). The now red solution was allowed to warm to room temperature and stirred for 2 h at this temperature. After this time, the solution was cooled to -20˚C and enone **4** was added a solution in the appropriate solvent. Subsequently, the reaction was allowed to warm to room temperature and stirred for 22 h. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with diethyl ether. The organic phase was washed with water and brine, before drying over sodium sulfate. The mixture was filtered and concentrated *in vacuo*. The resulting residue was analysed by ^1H NMR spectroscopy.

Following the above ***General Procedure***, data are presented as (a) amount of phosphonium salt **81**, (b) solvent, (c) MeLi solution, (d) amount of enone **4** in volume of solvent, (e) reaction outcome.

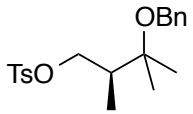
Scheme 52

(a) 230 mg, 0.47 mmol, (b) Et_2O, 6 ml, (c) 0.55 ml, 0.88 mmol, (d) 60 mg, 0.17 mmol in 0.5 ml of Et_2O, (e) desired product failed to form.

Scheme 53

(a) 230 mg, 0.47 mmol, (b) THF, 6 ml, (c) 0.55 ml, 0.88 mmol, (d) 60 mg, 0.17 mmol in 0.5 ml of THF, (e) desired product failed to form.

Preparation of (S)-3-(benzyloxy)-2,3-dimethylbutyl 4-methylbenzenesulfonate, ***89***



Scheme 55

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with alcohol **83** (50 mg, 0.19 mmol), DCM (0.25 ml), and cyclohexane (0.5 ml). The solution was cooled to 0˚C prior to the dropwise addition of benzyl-2,2,2-trichloroacetimidate (0.04 ml, 0.22 mmol) and trifluoromethanesulfonic acid (1.7 µl, 0.019 mmol). The resulting suspension was warmed to room temperature and stirred for 5 h. After this time, the mixture was diluted with DCM and washed with 1 M NaOH solution. The organic phase was separated and washed sequentially with water and brine before drying over sodium sulfate. The mixture was filtered, concentrated *in vacuo*, and purified by column chromatography (eluent: 0-30% diethyl ether in petrol) to deliver **89** (55 mg, 82% yield) as a colourless oil.

IR: 2912, 1454, 1367, 1155, 1026 cm^{-1}.

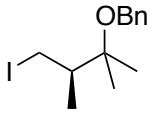
^{1}H NMR δ (400 MHz, $CDCl_3$): 7.78 (d, *J* = 8.2 Hz, 2H, ArH), 7.30-7.18 (m, 7H, ArH), 4.35 (s, 2H, OCH_2), 4.32 (dd, ^{2}J = 9.6, *J* = 3.8 Hz, 1H, $TsOCH_2$), 3.92 (dd, ^{2}J = 9.6, *J* = 8.6 Hz, 1H, $TsOCH_2$), 2.44 (s, 3H, $ArCH_3$), 2.13-2.06 (m, 1H, C*H*CH_3), 1.23 (s, 3H, CCH_3), 1.15 (s, 3H, CCH_3), 1.02 ppm (d, *J* = 6.9 Hz, 3H, CHC*H*$_3$).

^{13}C NMR δ (100 MHz, $CDCl_3$): 144.7, 139.5, 133.2, 129.9, 129.2, 128.1, 127.9, 127.2, 76.6, 72.8, 63.4, 41.7, 24.0, 22.2, 21.8, 12.8 ppm.

HRMS *m/z* (ESI) Calc. for $C_{20}H_{30}NO_4S$ (M^{+}+NH_4): 380.1890. Found: 380.1888.

$[\alpha]_D^{23}$ = -11.4°, c = 0.4 ($CHCl_3$).

Preparation of (R)-(((4-iodo-2,3-dimethylbutan-2-yl)oxy)methyl)benzene, ***90***



Scheme 56

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with tosylate **89** (300 mg, 0.83 mmol), THF (6 ml), and anhydrous lithium iodide (222 mg, 1.66 mmol). The solution was heated to reflux and stirred for 3 h. After this time the mixture was allowed to cool to room temperature and quenched by addition of diethyl ether (15 ml). The resulting suspension was filtered and the filtrate was washed with saturated sodium sulfite solution. The organic phase was separated and washed sequentially with water and brine before drying over sodium sulfate. The mixture was filtered, concentrated *in vacuo* and purified by column chromatography (eluent: 0-20% diethyl ether in petrol) to deliver iodide **90** (254 mg, 96% yield) as a pale yellow oil.

IR: 2963, 1452, 1260 cm^{-1}.

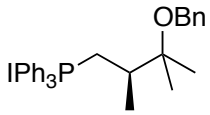
^{1}H NMR δ (400 MHz, $CDCl_3$): 7.38-7.32 (m, 4H, ArH), 7.29-7.26 (m, 1H, ArH), 4.43 (s, 2H, OCH_2), 3.73 (dd, ^{2}J = 9.5 Hz, J = 2.2 Hz, 1H, ICH_2), 2.92 (dd, ^{2}J = 9.5 Hz, J = 11.0 Hz, 1H, ICH_2), 2.16 (ddq, J = 11.0, 6.8, 2.2 Hz, 1H, C*H*CH_3), 1.30 (s, 3H, CCH_3), 1.20 (s, 3H, CCH_3), 1.15 ppm (d, J = 6.8 Hz, 3H, CHC*H*$_3$).

^{13}C NMR δ (100 MHz, $CDCl_3$): 139.4, 128.4, 127.3, 127.3, 77.8, 63.5, 45.6, 23.8, 21.4, 15.8, 11.3 ppm.

HRMS *m/z* (ESI) Calc. for $C_{13}H_{23}ION$ ($M^+ + NH_4^+$): 336.0819. Found: 336.0818.

$[\alpha]_D^{22}$ = +2.2°, c = 1.0 ($CHCl_3$).

Preparation of (R)-(3-(benzyloxy)-2,3-dimethylbutyl)triphenylphosphonium iodide, ***88***



Scheme 57

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with iodide **90** (90 mg, 0.28 mmol), MeCN (4 ml), and triphenylphosphine (584 mg, 2.23 mmol). The resulting suspension was warmed to reflux and stirred for 42 h. The mixture was allowed to cool to room temperature and concentrated *in vacuo*. The resulting gum was solubilised in diethyl ether (10 ml), which resulted in the immediate precipitation of a white solid. The suspension was stirred for 20 min and filtered. The white solid was resolubilised in diethyl ether and allowed to stir for a further 20 min, before a further filtration. The trituration process was repeated a third time and the resulting white solid dried under vacuum for 1 h to yield **88** (117 mg, 72% yield).

Melting point: 174-176˚C

IR: 2970, 1430 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 7.86-7.62 (m, 13H, ArH), 7.56-7.48 (m, 7H, ArH), 4.54 (d, *J* = 10.3 Hz, 1H, OCH_2), 4.45 (d, *J* = 10.3 Hz, 1H, OCH_2), 3.83-3.74 (m, 1H, PCH_2), 3.60-3.48 (m, 1H, PCH_2), 2.18-2.10 (m, 1H, C*H*CH_3), 1.45 (s, 3H, CCH_3), 1.28 (s, 3H, CCH_3), 0.69 ppm (d, *J* = 6.9 Hz, 3H, CHC*H*$_3$).

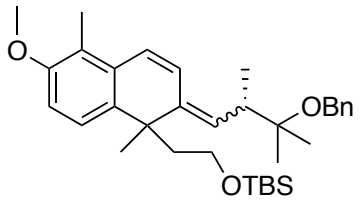
^{13}C NMR δ (100 MHz, $CDCl_3$): 139.0, 135.0 (d, $^{4}J_{P\text{-}C}$ = 3.0 Hz), 134.2 (d, $J_{P\text{-}C}$ = 10.1 Hz), 130.5 (d, $^{2}J_{P\text{-}C}$ = 12.5 Hz), 130.4, 128.8, 127.9, 118.9 (d, $^{1}J_{P\text{-}C}$ = 85.5 Hz), 79.3, 64.6, 39.4 (d, $^{2}J_{P\text{-}C}$ = 4.1 Hz), 24.4 (d, $^{1}J_{P\text{-}C}$ = 51.6 Hz), 23.7, 19.1, 16.6 ppm.

^{31}P NMR δ (162 MHz, $CDCl_3$): 23.8 ppm.

HRMS *m/z* (ESI) Calc. for $C_{31}H_{34}OP$ (M^+ - I^-): 453.2341. Found: 453.2342.

$[\alpha]_D^{25}$ = +4.8˚, c = 1.0 ($CHCl_3$).

Attempted preparation of (2-(2-(3-(benzyloxy)-2,3-dimethylbutylidene)-6-methoxy-1,5-dimethyl-1,2-dihydronaphthalen-1-yl)ethoxy)(tert-butyl)dimethylsilane, ***59***



Scheme 58

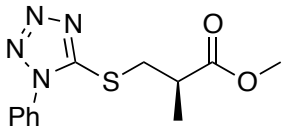
A flame dried, and nitrogen cooled, Schlenck tube was charged with lithium chloride (0.029 g, previously flame dried) and MeLi (10 ml, 1.6 M in Et_2O). The solution was kept under an inert atmosphere and used immediately in the subsequent reaction(s).

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with phosphonium salt **88** (273 mg, 0.47 mmol) and Et_2O (5 ml). The resulting suspension was cooled to -20˚C and charged with the pre-prepared MeLi solution (0.26 ml, 1.6 M in Et_2O (0.4 wt% LiCl, 0.44 mmol). The yellow solution was allowed to warm to room temperature and stirred for 2 h at this temperature. After this time, enone **4** (60 mg, 0.166 mmol) was added as a solution in Et_2O (0.5 ml) and the resulting mixture was stirred at room temperature for 22 h. The reaction mixture was quenched with saturated ammonium chloride solution and the mixture diluted with diethyl ether. The organic layer was separated and washed sequentially with water and brine. The organic phase was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was analysed by ^{1}H NMR spectroscopy, which revealed that the desired compound, **59**, had failed to form.

Scheme 59

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with phosphonium salt **88** (273 mg, 0.47 mmol) and THF (5 ml). The resulting suspension was treated with potassium *tert*-butoxide (45 mg, 0.40 mmol). The yellow solution was allowed to warm to room temperature and stirred for 2 h before the addition of enone **4** (60 mg, 0.17 mmol) as a solution in THF (0.5 ml). The resulting mixture stirred at room temperature for 22 h. The reaction mixture was quenched with saturated ammonium chloride solution and the mixture diluted with diethyl ether. The organic layer was separated and washed sequentially with water and brine. The organic phase was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was analysed by ^{1}H NMR spectroscopy, which revealed that the desired compound, **59**, had failed to form.

Preparation of (R)-methyl 2-methyl-3-((1-phenyl-1H-tetrazol-5-yl)thio)propionoate, ***97***[47]



Scheme 63

A flame dried, and nitrogen cooled, 50 ml round bottom flask was charged with (*S*)-methyl 3-hydroxy-2-methylpropionoate **85** (300 mg, 2.54 mmol), PPh_3 (994 mg, 3.81 mmol), and THF (12 ml). The solution was cooled to 0˚C and stirred for 15 min.

Simultaneously, a flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with diisopropyl azodicarboxylate (710 mg, 3.81 mmol), phenyl tetrazolethiol (620 mg, 3.81 mmol), and THF (12 ml). The mixture was stirred for 5 min before transferring, *via* syringe, to the cooled solution. Upon complete addition, the mixture was stirred for 30 min before warming to room temperature and stirred for a further 3 h. After this time, the reaction was quenched by the addition of water and extracted into diethyl ether. The organic phase was washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude oil was purified by column chromatography (eluent: 0-50% ethyl acetate in petrol) to furnish **97** (685 mg, 97% yield) as a colourless oil.

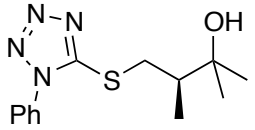
IR: 3068, 2953, 1730, 1597 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 7.58-7.51 (m, 5H, ArH), 3.70 (s, 3H, OCH_3), 3.58 (d, J = 6.9 Hz, 2H, SCH_2), 3.17-3.08 (m, 1H, C*H*CH_3), 1.36 ppm (d, J = 7.2 Hz, 3H, CHC*H*$_3$).

^{13}C NMR δ (100 MHz, $CDCl_3$): 174.5, 154.1, 133.6, 130.2, 129.8, 123.8, 52.1, 39.7, 35.7, 17.1 ppm.

$[\alpha]_D^{22}$ = +86.6˚, c = 1.0 ($CHCl_3$). Lit Data for opposite enantiomer: $[\alpha]_D^{20}$ = -89.5˚, c = 1.0 ($CHCl_3$).

Preparation of (R)-2,3-dimethyl-4-((1-phenyl-1H-tetrazol-5-yl)thio)butan-2-ol, ***96***



Scheme 64

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with diethyl ether (3 ml) and methylmagnesium chloride (1.25 ml, 3 M in THF, 3.73 mmol). To this stirred solution was added **97** (450 mg, 1.62 mmol) in diethyl ether (3 ml), dropwise. The reaction temperature was maintained in the region of 20-25˚C (with the aid of an ice bath) in order to minimise the risk of polymerisation. Upon complete addition the mixture was allowed to stir for 2 h at room temperature. After this time, the reaction was quenched with saturated ammonium chloride solution and extracted with diethyl ether (x 2). The organic phases were pooled, washed with brine, dried over sodium sulfate, and concentrated *in vacuo* to yield **96** (415 mg, 92% yield) as a colourless liquid.

IR: 2972, 2945, 1720, 1550, 1501 cm^{-1}.

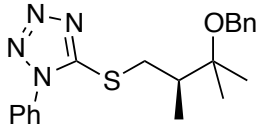
^{1}H NMR δ (400 MHz, $CDCl_3$): 7.63-7.54 (m, 5H, ArH), 4.03 (dd, ^{2}J = 13.2, J = 2.9 Hz, 1H, SCH_2), 2.94 (dd, ^{2}J = 13.2, J = 9.8 Hz, 1H, SCH_2), 2.08-2.01 (m, 1H, C*H*CH_3), 1.99 (bs, 1H, OH), 1.32 (s, 3H, CCH_3), 1.23 (s, 3H, CCH_3), 1.11 ppm (d, J = 7.0 Hz, 3H, CHC*H*$_3$).

^{13}C NMR δ (100 MHz, $CDCl_3$): 154.4, 133.2, 129.6, 129.3, 123.4, 76.2, 44.1, 35.5, 28.5, 23.9, 13.7 ppm.

HRMS *m/z* (ESI) Calc. for $C_{13}H_{19}N_4OS$ (M^+ + H): 279.1274. Found: 279.1279.

$[\alpha]_D^{24}$ = -99.3˚, c = 0.3 ($CHCl_3$).

Preparation of (R)-5-((3-(benzyloxy)-2,3-dimethylbutyl)thio)-1-phenyl-1H-tetrazole, ***95***



Scheme 65

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with alcohol **96** (280 mg, 1.01 mmol) and THF (5 ml) before cooling to 0˚C. To the stirred solution was added sodium hydride (51 mg, 2.00 mmol) portionwise and the resulting suspension was stirred at 0˚C for 30 min. After this time, benzyl bromide (0.24 ml, 2.00 mmol) was added and the resulting solution was stirred for a further 30 min at 0˚C. Following this, the solution was warmed to room temperature and stirred for 48 h. The reaction was quenched with saturated ammonium chloride solution and extracted into diethyl ether. The organic phase was washed sequentially with water and brine before drying over sodium sulfate. The mixture was filtered, concentrated *in vacuo*, and purified by column chromatography (eluent: 0-50% diethyl ether in petrol) to yield **95** (242 mg, 65% yield) as a pale yellow oil.

IR: 1595, 1545, 1505 cm^{-1}.

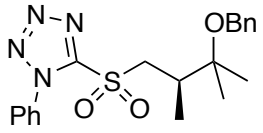
^{1}H NMR δ (400 MHz, $CDCl_3$): 7.64-7.60 (m, 2H, ArH), 7.52-7.48 (m, 2H, ArH), 7.47-7.43 (m, 1H, ArH), 7.26-7.16 (m, 5H, ArH), 3.67 (d, J = 13.5 Hz, 1H, OCH_2), 3.62 (d, J = 13.5 Hz, 1H, OCH_2), 2.69 (dd, ^{2}J = 12.7, J = 2.8 Hz, 1H, SCH_2), 2.61-2.54 (m, 1H, C*H*CH_3), 2.15 (dd, ^{2}J = 12.7, J = 10.6 Hz, 1H, SCH_2), 1.63 (s, 3H, CCH_3), 1.55 (s, 3H, CCH_3), 1.10 ppm (d, J = 7.0 Hz, 3H, CHCH_3).

^{13}C NMR δ (100 MHz, $CDCl_3$): 158.1, 138.0, 133.6, 129.4, 128.9, 128.8, 128.5, 127.0, 92.4, 63.2, 41.3, 36.5, 33.6, 23.5, 22.6, 14.5 ppm.

HRMS *m/z* (ESI) Calc. for $C_{20}H_{25}N_4OS$ (M^+ + H): 369.1744. Found: 369.1747.

$[\alpha]_D^{24}$ = -55.8˚, c = 0.3 ($CHCl_3$).

Preparation of (R)-5-((3-(benzyloxy)-2,3-dimethylbutyl)sulfonyl)-1-phenyl-1H-tetrazole, ***94***



Scheme 66

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with **95** (150 mg, 0.41 mmol) and DCM (10 ml). The solution was cooled to 0˚C followed by the portionwise addition of *m*CPBA (202 mg, 0.82 mmol). The mixture was warmed to room temperature and stirred for 24 h. After this time, saturated sodium bicarbonate solution was added and the mixture was extracted into DCM. The organic phase was separated, washed sequentially with water and brine, dried over sodium sulfate, and filtered, and concentrated *in vacuo* to furnish **94** (118 mg, 72 % yield) as white oil/residue.

IR: 1541, 1502, 1458 cm^{-1}.

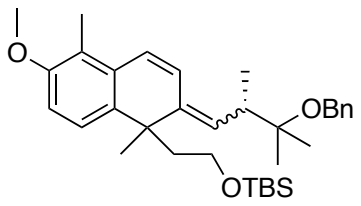
^{1}H NMR δ (400 MHz, $CDCl_3$): 7.66-7.63 (m, 2H, ArH), 7.57-7.53 (m, 2H, ArH), 7.50-7.46 (m, 1H, ArH), 7.36-7.29 (m, 5H, ArH), 4.21 (d, J = 14.2 Hz, 1H, OCH_2), 4.12 (d, J = 14.2 Hz, 1H, OCH_2), 3.19 (bd, ^{2}J = 13.4, 1H, SCH_2), 2.95-2.88 (m, 1H, C*H*CH_3), 2.64 (dd, ^{2}J = 13.4, J = 10.3 Hz, 1H, SCH_2), 1.67 (s, 3H, CCH_3), 1.54 (s, 3H, CCH_3), 1.26 ppm (d, J = 7.3 Hz, 3H, CHC*H*$_3$).

^{13}C NMR δ (100 MHz, $CDCl_3$): 168.9, 130.8, 130.5, 129.5, 129.1, 128.9, 128.0, 122.1, 119.6, 82.0, 60.4, 59.8, 57.2, 37.1, 15.8, 14.2 ppm.

HRMS *m/z* (ESI) Calc. for $C_{20}H_{25}N_4O_3S$ (M^+ + H): 402.1642. Found: 402.1644.

$[\alpha]_D^{24}$ = -14.2˚, c = 0.2 ($CHCl_3$).

Attempted preparation of (2-(2-(3-(benzyloxy)-2,3-dimethylbutylidene)-6-methoxy-1,5-dimethyl-1,2-dihydronaphthalen-1-yl)ethoxy)(tert-butyl)dimethylsilane, ***59***



Scheme 67

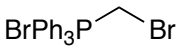
A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with sulfone **94** (140 mg, 0.35 mmol) and THF (5 ml). The resulting suspension was cooled to -78˚C, then LiHMDS (0.3 ml, 1 M in hexanes, 0.30 mmol) was added *via* syringe in a dropwise fashion before stirring for 30 min. After this time, enone **4** (60 mg, 0.17 mmol) was added as a solution in THF (1 ml), the resulting mixture was warmed to room temperature and stirred for 16 h. After this time the mixture was quenched with saturated ammonium chloride solution and diluted with diethyl ether. The organic layer was separated and washed sequentially with water and brine. The organic phase was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was analysed by ^{1}H NMR spectroscopy, which revealed a complex mixture of products.

Scheme 68

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with sulfone **94** (140 mg, 0.35 mmol) and THF (5 ml). The resulting suspension was cooled to -78˚C before LDA (0.2 ml, 1.5 M in hexanes, 0.30 mmol) was added *via* syringe in a dropwise fashion. After stirring for 30 minutes, enone **4** (60 mg, 0.17 mmol) was added as a solution in THF (1 ml). The resulting mixture was warmed to room temperature and stirred for 16 h. TLC analysis indicated that the reaction had failed to occur. In an effort

to promote the reaction the mixture was heated to reflux for 4 h before cooling to room temperature. The reaction mixture was quenched with saturated ammonium chloride solution and the mixture diluted with diethyl ether. The organic layer was separated and washed sequentially with water and brine. The organic phase was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was analysed by ^{1}H NMR spectroscopy, which revealed that the desired compound, **59**, had failed to form.

Preparation of (bromomethyl)triphenylphosphonium bromide, ***104***[83]



Scheme 72

A flame dried, and nitrogen cooled, 500 ml round bottom flask was charged with triphenylphosphine (20.0 g, 76.6 mmol) and dry toluene (160 ml). The resulting suspension was treated with the dropwise addition of dibromomethane (12 ml, 100 mmol), and the resulting solution was stirred at 60 °C for 72 h. The precipitate obtained was filtered, washed with toluene (5 × 100 ml), and dried under vacuum for 12 h to yield **104** (26.4 g, 79% yield) as a white solid.

Melting point 220-222°C.

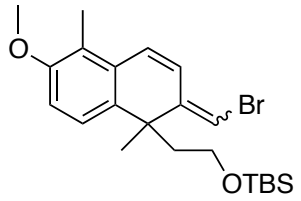
IR: 2884, 1585, 1437, 1107 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 7.99−7.91 (m, 6H, ArH), 7.84−7.79 (m, 3H, ArH), 7.73−7.68 (m, 6H, ArH), 5.87 ppm (d, ^{2}J = 5.4 Hz, 2H, CH_2Br).

^{13}C NMR δ (100 MHz, $CDCl_3$): 135.2 (d, ^{4}J = 2.8 Hz), 133.9 (d, J = 10.5 Hz), 130.0 (d, ^{2}J = 12.8 Hz), 116.9 (d, ^{1}J = 89.2 Hz), 18.3 (d, ^{1}J = 54.6 Hz) ppm.

^{31}P NMR δ (162 MHz, $CDCl_3$): 23.9 ppm.

Attempted preparation of (2-(2-(bromomethylene)-6-methoxy-1,5-dimethyl-1,2-dihydronaphthalen-1-yl)ethoxy)(tert-butyl)dimethylsilane, ***102***



Scheme 73

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with phosphonium salt **104** (610 mg, 1.40 mmol) and THF (12 ml). The resulting suspension was cooled to -78˚C, then potassium *tert*-butoxide (145 mg, 1.30 mmol) was added as a single portion before stirring for 50 min. After this time, enone **4** (100 mg, 0.28 mmol) was added as a solution in THF (2 ml) and the resulting mixture was stirred for 3 h, at -78˚C. After this time, the mixture was warmed to -40˚C and stirred for 1 h, prior to being warmed to room temperature and stirred for a further 16 h. The reaction mixture was quenched with saturated sodium bicarbonate solution and diluted with diethyl ether. The organic layer was separated and washed sequentially with water and brine. The organic phase was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was analysed by TLC and ^{1}H NMR spectroscopy, which revealed that the desired reaction had failed to occur.

Scheme 74

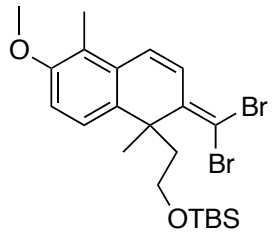
A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with phosphonium salt **104** (288 mg, 0.66 mmol) and THF (10 ml) before cooling to -60˚C. NaHMDS (0.6 ml, 1 M in THF, 0.60 mmol) was added dropwise *via* syringe and the

resulting solution was stirred for 2 h at this temperature. Following this, enone **4** (80 mg, 0.22 mmol) was added as a solution in THF (2 ml) and the resulting reaction mixture was stirred for 3 h at -60˚C, then 2 h at -40˚C, and for 12 h at -5˚C. The reaction mixture was warmed to room temperature and stirred for a further 5 h before being quenched with saturated sodium bicarbonate solution. The organic layer was separated and washed sequentially with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was analysed by ^{1}H NMR spectroscopy, which revealed that the desired compound, **102**, had failed to form.

Scheme 76

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with piperidine (0.15 ml, 1.50 mmol) and THF (6 ml) before cooling to 0˚C. ^{n}BuLi (0.91 ml, 1.6 M in hexanes, 1.45 mmol) was added dropwise *via* syringe and the resulting solution stirred for 30 min at this temperature. After this time, the solution was added dropwise *via* syringe to a stirred suspension of phosphonium salt **104** (662 mg, 1.52 mmol) and THF (10 ml). The resulting mixture was stirred for 30 min at 0˚C, before the dropwise addition of a THF (2 ml) solution of enone **4** (110 mg, 0.31 mmol). After stirring at 0˚C for 3 h, the reaction mixture was diluted with diethyl ether, and quenched with water. The organic layer was separated and washed sequentially with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was analysed by ^{1}H NMR spectroscopy, which revealed that the desired compound, **102**, had failed to form.

Attempted preparation of tert-butyl(2-(2-(dibromomethylene)-6-methoxy-1,5-dimethyl-1,2-dihydronaphthalen-1-yl)ethoxy)dimethylsilane, ***107***



Scheme 77

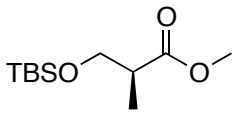
A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with triphenylphosphine (290 mg, 1.10 mmol) and DCM (10 ml), before adding carbon tetrabromide (182 mg, 0.55 mmol) at 0˚C. The resulting bright yellow solution was stirred for 10 min at this temperature. Enone **4** (100 mg, 0.27 mmol) was added as a solution in DCM (2 ml), and the resulting mixture was warmed to room temperature and stirred for 16 h. After this time, hexane (6 ml) was added and the reaction mixture was filtered through celite (eluent: 20% ether in hexane) and the filtrate concentrated *in vacuo*. The resulting residue was analysed by ^{1}H NMR spectroscopy and GC-MS, which revealed that the desired compound, **107**, had failed to form.

Scheme 80

A flame dried, and nitrogen cooled, 50 ml round bottom flask was charged with phosphonium salt **104** (1,221 mg, 2.8 mmol) and THF (15 ml), followed by the portionwise addition of potassium *tert*-butoxide (315 mg, 2.8 mmol). The resulting solution was stirred for 6 h, before the addition of a THF solution of enone **4** (100 mg, 0.28 mmol). The reaction mixture was heated to reflux and stirred for 16 h before being quenched with water and extracted into hexane. The suspension was filtered and the filtrate extracted with diethyl ether. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting

residue was analysed by TLC and ^{1}H NMR spectroscopy, which indicated that the desired product had failed to form.

Preparation of (S)-methyl 3-((tert-butyldimethylsilyl)oxy)-2-methylpropionoate, ***115***[84]



Scheme 83

A flame dried, and nitrogen cooled, 250 ml round bottom flask was charged with dry DCM (100 ml) and alcohol **85** (2.5 g, 21.15 mmol). The resulting solution was cooled to -78˚C and triethylamine (7.66 ml, 55 mmol) was added slowly, followed by the dropwise addition of *tert*-butyldimethylsilyl triflate (6.32 ml, 27.5 mmol), the resulting mixture was stirred at -78˚C for 30 min. After this time, the solution was warmed to room temperature and stirred for 1 h. The reaction mixture was quenched with saturated sodium bicarbonate solution, the resulting organic layer separated, washed with brine, and dried over sodium sulfate. The resulting suspension was filtered, concentrated *in vacuo* and purified by column chromatography (eluent: petrol) to yield **115** (4.78 g, 98% yield) as a colourless liquid.

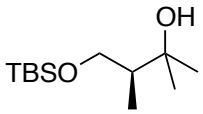
IR: 2953, 1740, 1462, 1091 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 3.79 (dd, ^2J = 9.8 Hz, J = 6.8 Hz, 1H, OCH_2), 3.70 (s, 3H, OCH_3), 3.67 (dd, ^2J = 9.8 Hz, J = 6.1 Hz, 1H, OCH_2), 2.71-2.64 (m, 1H, C*H*CH_3), 1.16 (d, J = 7.0 Hz, 3H, CHC*H*$_3$), 0.90 (s, 9H, Si^{t}Bu), 0.06 ppm (s, 6H, $SiCH_3$).

^{13}C NMR δ (100 MHz, $CDCl_3$): 175.5, 65.2, 51.5, 42.5, 25.7, 18.2, 13.4, -5.5, -5.6 ppm.

$[\alpha]_D^{24}$ = +19.1˚, c = 1.0 ($CHCl_3$).

Preparation of (S)-4-((tert-butyldimethylsilyl)oxy)-2,3-dimethylbutan-2-ol, ***116***



Scheme 84

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with diethyl ether (9 ml) and methylmagnesium chloride (23.0 ml, 3 M in THF, 69.9 mmol). To this stirred solution was added protected alcohol **115** (4.9 g, 21.12 mmol) in diethyl ether (9 ml), dropwise. The reaction temperature was maintained in the region of 20-25˚C (with the aid of an ice bath) in order to minimise the risk of polymerisation. Upon complete addition the mixture was allowed to stir for 2 h at room temperature. After this time, the reaction was quenched with saturated ammonium chloride solution and extracted with diethyl ether (x 2). The organic phases were pooled, washed with brine, dried over sodium sulfate, and concentrated *in vacuo* to yield **116** (4.72 g, 96% yield) as a colourless liquid.

IR: 3468, 2956, 1471, 1256 cm^{-1}.

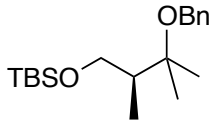
^{1}H NMR δ (400 MHz, $CDCl_3$): 3.79 (dd, ^{2}J = 10.2 Hz, J = 4.5 Hz, 1H, OCH_2), 3.66 (dd, ^{2}J = 10.2 Hz, J = 8.2 Hz, 1H, OCH_2), 1.82-1.79 (m, 1H, C*H*CH_3), 1.23 (s, 3H, CCH_3), 1.17 (s, 3H, CCH_3), 0.93 (s, 9H, Si^{t}Bu), 0.87 (d, J = 7.0 Hz, 3H, CHC*H*$_3$), 0.11 ppm (s, 6H, $SiCH_3$).

^{13}C NMR δ (100 MHz, $CDCl_3$): 73.2, 67.1, 43.5, 29.2, 25.8, 24.4, 18.0, 12.8, -5.8 ppm.

HRMS *m/z* (ESI) Calc. for $C_{12}H_{29}O_2Si$ (M^+ + H): 233.1931. Found: 233.1928.

$[\alpha]_D^{22}$ = +6.1˚, c = 1.0 ($CHCl_3$).

Preparation of (S)-(3-(benzyloxy)-2,3-dimethylbutoxy)(tert-butyl)dimethylsilane, ***117***



Scheme 85

A flame dried, and nitrogen cooled, 50 ml round bottom flask was charged with alcohol **116** (1.0 g, 4.3 mmol), THF (25 ml), and DMF (5 ml), before cooling to 0˚C. To the stirred solution was added sodium hydride (126 mg, 5.0 mmol) portionwise and the resulting suspension was stirred at 0˚C for 30 min. After this time, benzyl bromide (0.71 ml, 6.0 mmol) was added and the solution stirred for 30 min at 0˚C. Following this, the solution was warmed to room temperature and stirred for 48 h. The reaction was quenched with saturated ammonium chloride solution and extracted into diethyl ether. The organic phase was washed sequentially with water and brine before drying over sodium sulfate. The mixture was filtered, concentrated *in vacuo*, and purified by column chromatography (eluent: 0-50% diethyl ether in petrol) to yield **117** (919 mg, 66% yield) as a pale yellow oil.

Scheme 86

A flame dried, and nitrogen cooled, 50 ml round bottom flask was charged with alcohol **116** (1.0 g, 4.3 mmol), THF (25 ml), and DMF (5 ml), before cooling to 0˚C. To the stirred solution was added sodium hydride (126 mg, 5.0 mmol) portionwise and the resulting suspension was stirred at 0˚C for 30 min. After this time, benzyl bromide (0.71 ml, 6.0 mmol) was added, followed by TBAI (238 mg, 0.65 mmol) and the resulting solution was stirred for 30 min at 0˚C. Following this, the solution was warmed to room temperature and stirred for 26 h. The reaction was quenched with saturated ammonium chloride solution and extracted into diethyl ether. The organic phase was washed

sequentially with water and brine before drying over sodium sulfate. The mixture was filtered, concentrated *in vacuo*, and purified by column chromatography (eluent: 0-50% diethyl ether in petrol) to yield **117** (1.13 g, 81% yield) as a pale yellow oil.

IR: 1167, 1028 cm^{-1}.

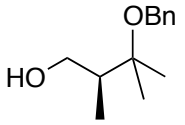
^{1}H NMR δ (400 MHz, $CDCl_3$): 7.34-7.28 (m, 5H, ArH), 4.52 (d, J = 12.0 Hz, 1H, OCH_2), 4.47 (d, J = 12.0 Hz, 1H, OCH_2), 3.72 (dd, ^{2}J = 9.1 Hz, J = 4.0 Hz, 1H, OCH_2), 3.29-3.21 (m, 1H, OCH_2), 1.82-1.74 (m, 1H, C*H*CH_3), 1.25 (s, 3H, CCH_3), 1.17 (s, 3H, CCH_3), 1.00 (d, J = 7.0 Hz, 3H, CHC*H*$_3$), 0.85 (s, 9H, Si^{t}Bu), 0.07 ppm (s, 6H, $SiCH_3$).

^{13}C NMR δ (100 MHz, $CDCl_3$): 140.9, 130.4, 129.7, 129.4, 77.1, 75.1, 74.2, 47.5, 31.2, 28.0, 24.7, 20.3, 13.5, 0.0 ppm.

HRMS *m/z* (ESI) Calc. for $C_{19}H_{33}O_2Si$ (M^+ - H): 321.2244. Found: 321.2237.

$[\alpha]_D^{24}$ = -10.6°, c = 1.0 ($CHCl_3$).

Preparation of (S)-3-(benzyloxy)-2,3-dimethylbutan-1-ol, ***118***[85]



Scheme 87

A flame dried, and nitrogen cooled, 50 ml round bottom flask was charged with **117** (1.0 g, 3.1 mmol) and THF (20 ml), before cooling to 0˚C. TBAF (10.86 ml, 1 M in THF, 10.86 mmol) was added dropwise to the reaction mixture and the resulting solution stirred for 24 h at room temperature. The reaction was quenched with saturated sodium bicarbonate solution and extracted into diethyl ether. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: 0-100% diethyl ether in petrol) to yield **118** (425 mg, 68% yield) as a pale yellow oil.

Scheme 88

A flame dried, and nitrogen cooled, 50 ml round bottom flask was charged with **117** (1.0 g, 3.1 mmol) and dry MeOH (30 ml), before cooling to 0˚C. Acetyl chloride (33 µl, 0.15 mmol) was added dropwise to the reaction mixture and the resulting solution stirred for 15 min at 0˚C. After this time, the mixture was extracted into DCM and quenched with saturated sodium bicarbonate solution. The organic phase was separated, washed with brine, and dried over sodium sulfate. The solution was filtered, concentrated *in vacuo*, and purified by column chromatography (eluent: 0-100% diethyl ether in petrol) to yield **118** (601 mg, 96% yield) as a pale yellow oil.

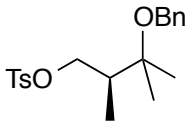
IR: 2912, 1454, 1367, 1155, 1026 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 7.39-7.30 (m, 5H, ArH), 4.53 (d, *J* = 11.0 Hz, 1H, OCH_2), 4.50 (d, *J* = 11.0 Hz, 1H, OCH_2), 3.78-3.72 (m, 1H, HOC*H*$_2$), 3.66-3.58 (m, 1H, HOC*H*$_2$), 3.44 (bs, 1H, OH), 2.02-1.99 (m, 1H, C*H*CH_3), 1.36 (s, 3H, CCH_3), 1.29 (s, 3H, CCH_3), 0.95 ppm (d, *J* = 7.0 Hz, 3H, CHC*H*$_3$).

^{13}C NMR δ (100 MHz, $CDCl_3$): 138.5, 128.0, 126.93, 126.88, 79.7, 65.5, 63.2, 43.3, 24.0, 19.8, 12.5 ppm.

$[\alpha]_D^{23}$ = -11.4˚, c = 0.4 ($CHCl_3$).

Preparation of (S)-3-(benzyloxy)-2,3-dimethylbutyl 4-methylbenzenesulfonate, ***89***



Scheme 89

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with alcohol **118** (350 mg, 1.68 mmol) and pyridine (1.68 ml, 1 M) before cooling to -5˚C. Following this, 4-toluenesulfonyl chloride (321 mg, 1.68 mmol) was added in one portion and the resulting solution transferred to a refrigerator and maintained at 4˚C for 18 h. The mixture was poured into ice water and extracted with diethyl ether (x 2). The resulting organic phases were pooled and washed sequentially with water (x 2), 1 M HCl (x 2), and brine. The mixture was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting crude oil was purified by column chromatography (eluent: 0-30% diethyl ether in petrol) to yield tosylate **89** (258 mg, 71% yield) as a colourless oil.

IR: 2978, 1358, 1175 cm^{-1}.

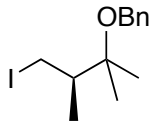
^{1}H NMR δ (400 MHz, $CDCl_3$): 7.78 (d, *J* = 8.2 Hz, 2H, ArH), 7.31-7.28 (m, 4H, ArH), 7.26-7.20 (m, 3H, ArH), 4.35 (s, 2H, OCH_2Ph), 4.32 (dd, ^{2}J = 9.6 Hz, *J* = 3.8 Hz, 1H, CH_2OTs), 3.93-3.90 (m, 1H, CH_2OTs), 2.44 (s, 3H, $ArCH_3$), 2.12–2.06 (m, 1H, C*H*CH_3), 1.23 (s, 3H, CCH_3), 1.15 (s, 3H, CCH_3), 1.02 ppm (d, *J* = 6.9 Hz, 3H, CHC*H*$_3$).

^{13}C NMR δ (100 MHz, $CDCl_3$): 144.8, 139.3, 133.1, 129.8, 128.3, 127.9, 127.14, 127.07, 76.4, 72.7, 63.3, 41.5, 23.8, 22.1, 21.6, 12.7 ppm.

HRMS *m/z* (ESI) Calc. for $C_{20}H_{30}O_4SN$ ($M^+ + NH_4^+$): 380.1890. Found 380.1896.

$[\alpha]_D^{23}$ = -27.7°, c = 1.0 ($CHCl_3$).

Preparation of (R)-(((4-iodo-2,3-dimethylbutan-2-yl)oxy)methyl)benzene, ***90***

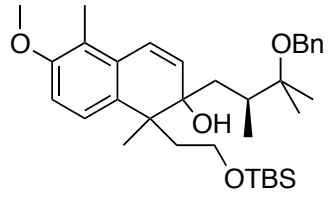


Scheme 90

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with tosylate **89** (300 mg, 0.83 mmol), THF (6 ml), and anhydrous lithium iodide (222mg, 1.66 mmol). The solution was heated to reflux and stirred for 3 h. After this time, the mixture was allowed to cool to room temperature and quenched by addition of diethyl ether (15 ml). The resulting suspension was filtered and the filtrate was washed with saturated sodium sulfite solution. The organic phase was separated and washed sequentially with water and brine before drying over sodium sulfate. The mixture was filtered, concentrated *in vacuo* and purified by column chromatography (eluent: 0-20% diethyl ether in petrol) to deliver iodide **90** (254 mg, 96% yield) as a pale yellow oil.

Full analysis for compound **90** can be found on page 353.

Preparation of 2-((S)-3-(benzyloxy)-2,3-dimethylbutyl)-1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-6-methoxy-1,5-dimethyl-1,2-dihydronaphthalen-2-ol, ***114***



Scheme 91

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with alkyl iodide **90** (92 mg, 0.29 mmol) and Et_2O (4 ml) before being cooled to -78˚C. *Tert*-butyllithium (0.34 ml, 1.7 M in pentane, 0.58 mmol) was added dropwise and the resulting solution stirred at this temperature for 1 h. After this time, the lithiated material was transferred *via* cannula to a stirred solution of enone **4** (80 mg, 0.22 mmol) in Et_2O (2 ml) at -78˚C. The mixture was stirred at this temperature for 3 hours before warming to room temperature and stirred for a further 14 h. Following this, the reaction was quenched with a saturated ammonium chloride solution. The organic phase was separated, washed with water, and brine, before drying over sodium sulfate. The mixture was filtered, concentrated *in vacuo*, and analysed by ^1H NMR. Unfortunately, allylic alcohol **114**, and/or diene **59**, had failed to form and a complex mixture of products was observed. Alkyl iodide **90** (63 mg, 68% yield) was isolated from the mixture.

Scheme 92

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with alkyl iodide **90** (92 mg, 0.29 mmol) and Et_2O (4 ml) before being cooled to -78˚C. *Tert*-butyllithium (0.34 ml, 1.7 M in pentane, 0.58 mmol) was added dropwise and the

resulting solution warmed to 0˚C over the course of 30 minutes and stirred for a further 10 minutes upon reaching this temperature. After this time, the lithiated material was cooled to -78˚C and transferred *via* cannula to a stirred solution of enone **4** (80 mg, 0.22 mmol) in Et_2O (2 ml) at -78˚C. The mixture was stirred at this temperature for 2 hours before warming to room temperature and stirred for a further 14 h. Following this, the reaction was quenched with a saturated ammonium chloride solution. The organic phase was separated, washed with water, and brine, before drying over sodium sulfate. The mixture was filtered, concentrated *in vacuo*, and analysed by ^1H NMR. Unfortunately, allylic alcohol **114**, and/or diene **59**, had failed to form and a complex mixture of products was observed.

Scheme 93

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with alkyl iodide **90** (92 mg, 0.29 mmol) and Et_2O (4 ml) before being cooled to -78˚C. *Tert*-butyllithium (0.34 ml, 1.7 M in pentane, 0.58 mmol) was added dropwise and the resulting solution warmed to -40˚C and stirred at this temperature for 1 h. After this time, the lithiated material was cooled to -78˚C and transferred *via* cannula to a stirred solution of enone **4** (80 mg, 0.22 mmol) in Et_2O (2 ml) at -78˚C. The mixture was stirred at this temperature for 2 hours before warming to room temperature and stirred for a further 14 h. Following this, the reaction was quenched with a saturated ammonium chloride solution. The organic phase was separated, washed with water, and brine, before drying over sodium sulfate. The mixture was filtered, concentrated *in vacuo*, and analysed by ^1H NMR. Unfortunately, allylic alcohol **114**, and/or diene **59**, had failed to form and a complex mixture of products was observed.

Scheme 94

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with alkyl iodide **90** (92 mg, 0.29 mmol) and Et_2O (4 ml) before being cooled to -78˚C. *Tert*-butyllithium (0.34 ml, 1.7 M in pentane, 0.58 mmol) was added dropwise and the

resulting solution warmed to -40˚C and stirred at this temperature for 1 h. After this time, the lithiated material was cooled to -78˚C and transferred *via* cannula to a stirred solution of enone **4** (80 mg, 0.22 mmol) in Et_2O (2 ml) at -78˚C. The mixture was warmed to -40˚C over the course of 3 h. Following this, the reaction was quenched with a saturated ammonium chloride solution. The organic phase was separated, washed with water, and brine, before drying over sodium sulfate. The mixture was filtered, concentrated *in vacuo*, and analysed by ^{1}H NMR. Unfortunately, allylic alcohol **114**, and/or diene **59**, had failed to form and a complex mixture of products was observed.

Scheme 95

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with alkyl iodide **90** (92 mg, 0.29 mmol) and Et_2O (4 ml) before being cooled to -78˚C. *Tert*-butyllithium (0.34 ml, 1.7 M in pentane, 0.58 mmol) was added dropwise and the resulting solution warmed to -40˚C and stirred at this temperature for 1 h. After this time, the lithiated material was cooled to -78˚C and transferred *via* cannula to a stirred solution of enone **4** (80 mg, 0.22 mmol) in Et_2O (2 ml) at -78˚C. The mixture was stirred at this temperature for 7 h. Following this, the reaction was quenched with a saturated ammonium chloride solution. The organic phase was separated, washed with water, and brine, before drying over sodium sulfate. The mixture was filtered, concentrated *in vacuo*, and analysed by ^{1}H NMR. Unfortunately, allylic alcohol **114**, and/or diene **59**, had failed to form and a complex mixture of products was observed.

Scheme 96

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with alkyl iodide **90** (92 mg, 0.29 mmol) and Et_2O (4 ml) before being cooled to -78˚C. *Tert*-butyllithium (0.34 ml, 1.7 M in pentane, 0.58 mmol) was added dropwise and the resulting solution warmed to -40˚C and stirred at this temperature for 1 h. After this time, the lithiated material was cooled to -78˚C and transferred *via* cannula to a stirred solution of $CeCl_3$ (72 mg, 0.29 mmol) in THF (3 ml) at -78˚C. Following this, a solution of enone

4 (80 mg, 0.22 mmol) in THF (2 ml) was added and the mixture stirred at -78˚C for 4 h before being warmed to room temperature and stirred for a further 14 h. After this time, the reaction was quenched with a saturated ammonium chloride solution. The organic phase was separated, washed with water, and brine, before drying over sodium sulfate. The mixture was filtered, concentrated *in vacuo*, and analysed by ^{1}H NMR. Unfortunately, allylic alcohol **114**, and/or diene **59**, had failed to form and a complex mixture of products was observed.

Scheme 97

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with alkyl iodide **90** (92 mg, 0.29 mmol) and Et_2O (4 ml) before being cooled to -78˚C. *Tert*-butyllithium (0.34 ml, 1.7 M in pentane, 0.58 mmol) was added dropwise and the resulting solution warmed to -40˚C and stirred at this temperature for 1 h. After this time, the lithiated material was cooled to -78˚C and transferred *via* cannula to a stirred solution of $CeCl_3$ (72 mg, 0.29 mmol) in THF (3 ml) at -78˚C. Following this, a solution of enone **4** (80 mg, 0.22 mmol) in THF (2 ml) was added and the mixture stirred at -78˚C for 1 h before being warmed to -40˚C and stirred for a further 7 h. After this time, the reaction was quenched with a saturated ammonium chloride solution. The organic phase was separated, washed with water, and brine, before drying over sodium sulfate. The mixture was filtered, concentrated *in vacuo* and analysed by ^{1}H NMR. Unfortunately, allylic alcohol **114**, and/or diene **59**, had failed to form and a complex mixture of products was observed.

Scheme 98

A flame dried, and nitrogen cooled, 3-necked 100 ml round bottom flask, fitted with a reflux condenser, was charged with magnesium turnings (240 mg, 10 mmol) and flame dried under vacuum. The flask was cooled under nitrogen and charged with dry diethyl ether (7.5 ml) and dry benzene (2.5 ml). To the stirred suspension was added dibromoethane (0.84 ml, 10 mmol), dropwise, at such a rate as to ensure the mixture

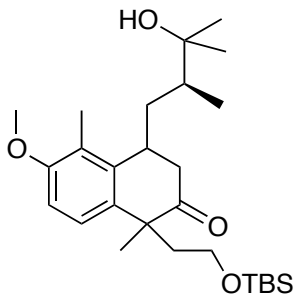
refluxed without external heating. Upon complete addition, the reaction mixture was warmed to a gentle reflux (50˚C) and held at this temperature for 1 h. Stirring was discontinued and the solution allowed to settle at room temperature, resulting in a 1 M solution of anhydrous $MgBr_2(OEt_2)$.

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with alkyl iodide **90** (92 mg, 0.29 mmol) and Et_2O (4 ml) before being cooled to -78˚C. A solution of $MgBr_2(OEt_2)$ (0.29 ml, 1 M in Et_2O/benzene, 0.29 mmol) was added dropwise and the resulting solution warmed to room temperature over the course of 3 h. After this time, a small aliquot of the reaction mixture was removed and quenched with acetone. Analysis of this material revealed that the Grignard reagent had failed to form and alkyl iodide, **90**, was recovered from the reaction mixture (71 mg, 77% yield).

Scheme 100

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with alkyl iodide **82** (41 mg, 0.18 mmol) and THF (3 ml) before being cooled to -78˚C. *Iso*-propylmagnesium chlordie (0.15 ml, 1.3 M in THF, 0.20 mmol) was added dropwise and the resulting solution stirred at this temperature for 5 min. After this time, *n*-BuLi (0.24 ml, 1.6 M in hexanes, 0.38 mmol) was added and the resulting mixture stirred for 20 min. Following this, a solution of enone **4** (80 mg, 0.22 mmol) in THF (2 ml) was added and the mixture stirred at -78˚C for 1 h. After this time, the reaction was quenched with a saturated ammonium chloride solution. The organic phase was separated, washed with water, and brine, before drying over sodium sulfate. The mixture was filtered, concentrated *in vacuo*, and analysed by ^{1}H NMR. Unfortunately, allylic alcohol **124**, and/or diene **79**, had failed to form and compound **125** was identified as the major product.

Data for compound **125**:



IR: 1260 cm^{-1}.

The ^1H NMR spectrum for **125** can be found in the appendix.

Scheme 102

A flame dried, and nitrogen cooled, 100 ml Schlenck tube was charged with alkyl iodide **90** (92 mg, 0.92 mmol) and $ZnEt_2$ (4.6 ml, 1 M in hexanes, 4.6 mmol) before being heated to 50˚C for 12 h. After this time, the low boiling materials were removed under reduced pressure, and the residue diluted with PhMe (0.9 ml). Following this, an aliquot of the material removed, hydrolysed and analysed by TLC and ^1H NMR. Unfortunately, the desired organozinc species failed to form and the reaction was abandoned.

Scheme 103

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with alkyl iodide **90** (92 mg, 0.29 mmol), enone **4** (80 mg, 0.22 mmol), and Et_2O (4 ml) before being cooled to -78˚C. *Tert*-butyllithium (0.34 ml, 1.7 M in pentane, 0.58 mmol) was added dropwise and the resulting solution stirred at this temperature for 4 h. After this time, the reaction mixture was warmed to room temperature and stirred for 14 h. Following this, the reaction was quenched with a saturated ammonium chloride solution. The organic phase was separated, washed with water, and brine, before drying over

sodium sulfate. The mixture was filtered, concentrated *in vacuo* and analysed by ^{1}H NMR. Unfortunately, allylic alcohol **114**, and/or diene **59**, had failed to form and a complex mixture of products was observed.

Scheme 104

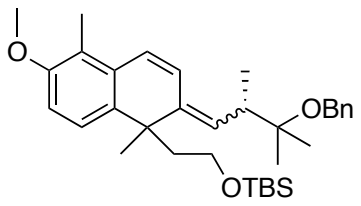
A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with *tert*-butyllithium (0.34 ml, 1.7 M in pentane, 0.58 mmol) and Et_2O (4 ml) before being cooled to -78˚C. Alkyl iodide **90** (92 mg, 0.29 mmol) was added as a solution in Et_2O (2 ml) and the resulting solution warmed to 0˚C over the course of 1 h. After this time, the reaction mixture was cooled to -78˚C and enone **4** (80 mg, 0.22 mmol) was added as a solution in Et_2O (2 ml). The mixture was warmed to 0˚C over the course of 3 h. Following this, the reaction was quenched with a saturated ammonium chloride solution. The organic phase was separated, washed with water, and brine, before drying over sodium sulfate. The mixture was filtered, concentrated *in vacuo*, and purified by flash column chromatography (eluent: 0-50% diethyl ether in petrol) to furnish allylic alcohol **114** as a pale yellow oil (52 mg, 43% yield).

Alcohol **114** rapidly degraded upon isolation and as a result full data was unobtainable. Having stated this, IR data is presented below and a ^{1}H NMR spectrum is attached in the appendix. Based on the instability of alcohol **114**, it was used immediately in further reactions.

IR: 3416, 1463, 1258, 1101 cm^{-1}.

The ^{1}H NMR spectrum for **114** can be found in the appendix.

Preparation of (2-(2-(3-(benzyloxy)-2,3-dimethylbutylidene)-6-methoxy-1,5-dimethyl-1,2-dihydronaphthalen-1-yl)ethoxy)(tert-butyl)dimethylsilane, ***59***



Scheme 106

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with *tert*-butyllithium (0.34 ml, 1.7 M in pentane, 0.58 mmol) and Et_2O (4 ml) before being cooled to -78˚C. Alkyl iodide **90** (92 mg, 0.29 mmol) was added as a solution in Et_2O (2 ml) and the resulting solution warmed to 0˚C over the course of 1 h. After this time, the reaction mixture was cooled to -78˚C and enone **4** (80 mg, 0.22 mmol) was added as a solution in Et_2O (2 ml). The mixture was warmed to 0˚C over the course of 3 h. Following this, the reaction was quenched with a saturated ammonium chloride solution. The organic phase was separated, washed with water, and brine, before drying over sodium sulfate. The mixture was filtered, concentrated *in vacuo* and solubilised in petrol (10 ml) before the addition of silica gel (1 g). The suspension was stirred at room temperature for 1 h. After this time, the mixture was filtered, concentrated *in vacuo* and purified by flash column chromatography (eluent: 0-30% diethyl ether in petrol) to furnish diene **59** as a pale yellow oil (21 mg, 18% yield).

Scheme 107

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with *tert*-butyllithium (0.34 ml, 1.7 M in pentane, 0.58 mmol) and Et_2O (4 ml) before being cooled to -78˚C. Alkyl iodide **90** (92 mg, 0.29 mmol) was added as a solution in Et_2O (2 ml) and the resulting solution warmed to 0˚C over the course of 1 h. After this time, the reaction mixture was cooled to -78˚C and enone **4** (80 mg, 0.22 mmol) added as a solution in Et_2O (2 ml). The mixture was warmed to 0˚C over the course of 3 h. Following this, the reaction was quenched with a saturated ammonium chloride solution. The organic phase was separated, washed with water, and brine, before drying over sodium sulfate. The mixture was filtered, concentrated *in vacuo*, and solubilised in DCM (10 ml), before cooling to 0˚C. Following this, Et_3N (0.17 ml, 1.20 mmol) and MsCl (0.05 ml, 0.60 mmol) were added. The resulting mixture was allowed to warm to room temperature and stirred for 16 h. After this time, the mixture was quenched with water, the organic phase was separated and washed with brine, before drying over sodium sulfate. The mixture was filtered, concentrated *in vacuo*, and purified by flash column chromatography (eluent: 0-30% diethyl ether in petrol) to furnish diene **59** as a pale yellow oil (44 mg, 37% yield).

Scheme 108

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with *tert*-butyllithium (0.34 ml, 1.7 M in pentane, 0.58 mmol) and Et_2O (4 ml) before being cooled to -78˚C. Alkyl iodide **90** (92 mg, 0.29 mmol) was added as a solution in Et_2O (2 ml) and the resulting solution warmed to 0˚C over the course of 1 h. After this time, the reaction mixture was cooled to -78˚C and enone **4** (80 mg, 0.22 mmol) added as a solution in Et_2O (2 ml). The mixture was warmed to 0˚C over the course of 3 h. Following this, the reaction was quenched with a saturated ammonium chloride solution. The organic phase was separated, washed with water, and brine, before drying over sodium sulfate. The mixture was filtered, concentrated *in vacuo* and solubilised in PhH (20 ml), before the addition of Burgess's reagent, **129**, (262 mg, 1.10 mmol). The suspension was stirred at room temperature for 2 h, followed by heating to reflux and stirring for 6 h. After this

time, the mixture was concentrated *in vacuo* and purified by flash column chromatography (eluent: 0-30% diethyl ether in petrol) to furnish diene **59** as a pale yellow oil (47 mg, 39% yield).

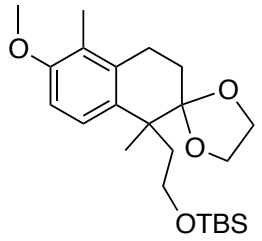
IR: 1479, 1259 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 7.39-7.20 (m, 7H, ArH & olefinic CH), 6.75-6.68 (m, 2H, ArH, olefinic CH), 5.63 (d, J = 10.2 Hz, 0.5H, olefinic CH), 5.61 (d, J = 10.2 Hz, 0.5H, olefinic CH), 4.50 (s, 1H, OCH_2Ph), 4.48 (s, 1H, OCH_2Ph), 3.82 (s, 3H, $ArOCH_3$), 3.48-3.39 (m, 1H, CH_2OTBS), 3.29-3.17 (m, 1H, CH_2OTBS), 3.03-2.94 (m, 1H, $CHCH_3$), 2.25 (s, 1.5H, $ArCH_3$), 2.24 (s, 1.5H, $ArCH_3$), 2.19-2.08 (m, 1H, CH_2CH_2OTBS), 2.01-1.91 (m, 1H, CH_2CH_2OTBS), 1.45 (s, 1.5H, $ArCCH_3$), 1.43 (s, 1.5H, $ArCCH_3$), 1.31-1.23 (m, 6H, CCH_3), 1.10-1.05 (m, 3H, $CHCH_3$), 0.83 (s, 4.5H, Si^{t}Bu), 0.81 (s, 4.5H, Si^{t}Bu), -0.05 (s, 3H, $SiCH_3$) -0.10 ppm (s, 3H, $SiCH_3$).

^{13}C NMR δ (125 MHz, $CDCl_3$): 155.3, 139.9, 139.5, 131.4, 130.5, 127.8, 126.7, 126.6, 123.8, 123.3, 123.0, 121.8, 117.8, 109.0, 76.3, 63.0, 62.7, 55.1, 35.4, 28.2, 28.0, 25.7, 23.9, 23.5, 21.9, 17.3, 15.3, 10.2, -5.8 ppm.

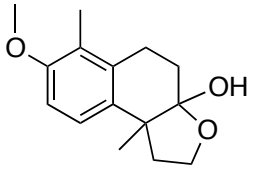
HRMS *m/z* (ESI) Calc. for $C_{34}H_{54}O_3SiN$ ($M^+ + NH_4$): 552.3867. Found: 552.3860.

Attempted preparation of tert-butyl(2-(6'-methoxy-1',5'-dimethyl-3',4'-dihydro-1'H-spiro[[1,3]dioxolane-2,2'-naphthalen]-1'-yl)ethoxy)dimethylsilane, ***132***



Scheme 111

A flame dried, and nitrogen cooled, 25 ml round bottom flask fitted with a Dean Stark apparatus before the addition of ketone **76** (100 mg, 0.28 mmol), benzene (14 ml), ethylene glycol (0.03 ml, 0.56 mmol), and tosic acid (5 mg, 0.03 mmol). The reaction was heated at reflux for 16 h. After this time, the reaction mixture was cooled to room temperature and the solvent removed under reduced pressure. The crude residue was analysed by ^{1}H NMR, which showed that the desired product had failed to form. The major product appeared to be lactol **136**. In addition, the IR spectrum did not feature a carbonyl stretch.



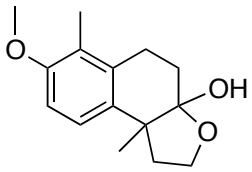
IR: 3212 cm^{-1}.

The ^{1}H NMR featuring the proposed lactol species, **136**, is included in the appendix.

Scheme 113

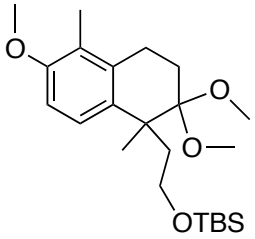
A flame dried, and nitrogen cooled, 50 ml round bottom flask fitted with a Dean Stark apparatus before the addition of ketone **76** (100 mg, 0.28 mmol), benzene (14 ml), ethylene glycol (0.03 ml, 0.56 mmol), and indium triflate (5 mg, 0.01 mmol). The reaction was heated at reflux for 16 h. After this time, the reaction mixture was cooled to room temperature and the solvent removed under reduced pressure. The crude residue was analysed by ^{1}H NMR, which showed that the desired product had failed to form.

The major product appeared to be lactol **136**.



The ^{1}H NMR featuring the proposed lactol species, **136**, is included in the appendix.

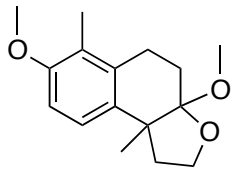
Attempted preparation of tert-butyldimethyl(2-(2,2,6-trimethoxy-1,5-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)ethoxy)silane, ***139***



Scheme 114

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with ketone **76** (100 mg, 0.28 mmol), trimethyl orthoformate (0.06 ml, 0.56 mmol), and indium triflate (5 mg, 0.01 mmol) in dichloromethane (10 ml). The reaction mixture was stirred for 16 h. The reaction mixture was passed through a plug of neutral alumina which was then washed with additional DCM. Following this, the mixture was concentrated *in vacuo* and analysed by ^{1}H NMR, which showed that the desired ketal, **139**, had failed to form.

^{1}H NMR and IR analysis suggested the formation of lactol **140**. Within the ^{1}H NMR spectrum many of the characteristic signals were present, including a methyl signal of the methoxy ketal component. Also, the IR spectrum did not feature a carbonyl stretch.



IR: 1210 cm^{-1}.

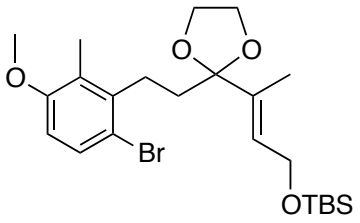
The ^{1}H NMR featuring the proposed lactol species, **140**, is included in the appendix.

Scheme 115

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with ketone **76** (100 mg, 0.28 mmol), indium triflate (5 mg, 0.01 mmol), and methanol (14 ml). The reaction mixture was stirred at room temperature for 16 h before being concentrated under reduced pressure. The crude products were analysed by ^{1}H NMR which showed that the desired product, **139**, had failed to form. It appeared that lactol **140** had formed as the major product.

The ^{1}H NMR featuring the proposed lactol species, **140**, is included in the appendix.

Preparation of (E)-((3-(2-(6-bromo-3-methoxy-2-methylphenethyl)-1,3-dioxolan-2-yl)but-2-en-1-yl)oxy)(tert-butyl)dimethylsilane, ***141***



Scheme 116

A flame dried, and nitrogen cooled, 25 ml round bottom flask fitted with a Dean-Stark apparatus, was charged with enone **6** (250 mg, 0.57 mmol), benzene (20 ml), ethylene glycol (0.1 ml, 1.78 mmol), and indium triflate (17 mg, 0.03 mmol). The stirred suspension was heated to reflux and maintained at this temperature for 16 h. After this time, the solution was allowed to cool and concentrated *in vacuo*. The crude residue was purified by column chromatography (eluent: 0-40% diethyl ether in petrol) to yield **141** (252 mg, 92% yield) as a pale yellow oil.

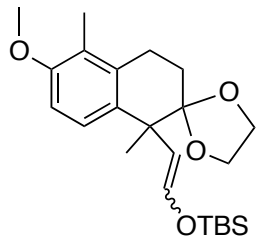
IR: 1458, 1258, 1099 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 7.37 (d, J = 8.7 Hz, 1H, ArH), 6.63 (d, J = 8.7 Hz, 1H, ArH), 5.66 (t, J = 6.3 Hz, 1H, olefin CH), 4.07-3.95 (m, 6H, CH_2OTBS & ketal CH_2), 3.82 (s, 3H, ArOMe), 3.14-3.09 (m, 2H, alkyl CH_2), 2.93-2.88 (m, 2H, alkyl CH_2), 2.23 (s, 3H, $ArCH_3$), 1.97-1.95 (m, 3H, olefin CH_3), 0.93 (s, 9H, Si^{t}Bu), 0.10 ppm (s, 6H, $SiCH_3$).

^{13}C NMR δ (100 MHz, $CDCl_3$): 174.9, 156.6, 140.7, 135.0, 129.7, 126.4, 120.8, 115.3, 109.4, 64.8, 63.6, 55.2, 35.9, 28.6, 25.4, 18.3, 13.8, 11.4, -5.8 ppm.

HRMS *m/z* (ESI) Calc. for $C_{23}H_{38}BrO_4Si$ (M^+ + H): 485.1717. Found: 485.1713.

Attempted preparation of tert-butyl((2-(6'-methoxy-1',5'-dimethyl-3',4'-dihydro-1'H-spiro[[1,3]dioxolane-2,2'-naphthalen]-1'-yl)vinyl)oxy)dimethylsilane, ***142***

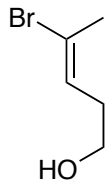


Scheme 117

A microwave vial was charged with palladium acetate (5 mg, 0.02 mmol), P(*o*-tolyl)$_3$ (24 mg, 0.08 mmol), and acetonitrile (0.5 ml). The resulting mixture was stirred for 5 min, at room temperature, which resulted in a colour change from a brown solution to an opaque yellow suspension. Substrate **141** (100 mg, 0.21 mmol) was added, as a solution in acetonitrile (0.5 ml) before the addition of triethylamine (0.07 ml, 0.53 mmol). The mixture was heated to 100˚C under microwave irradiation, with cooling, for 30 min (15 min x 2). After this time the solution was concentrated *in vacuo* and the resulting residue was filtered through celite (eluent: ethyl acetate). The resulting solution was concentrated *in vacuo*, and solubilised in THF (5 ml) followed by the addition of copper (I) chloride (10 mg, 0.1 mmol) and stirred for 10 min. The resulting suspension was concentrated *in vacuo* and purified by flash column chromatography (0-5% diethyl ether in petrol). The desired product, **142**, failed to form and compound **5** was obtained as the major product (54 mg, 72% yield).

Full analysis for compound **5** can be found on page 340.

Preparation of (E)-4-bromopent-3-en-1-ol, ***150***[68]



Scheme 120

A flame dried, and nitrogen cooled, 250 ml round bottom flask was charged with copper cyanide (3.84 g, 42.95 mmol), THF (55 ml), and diethyl ether (90 ml). The resulting solution was cooled to -40˚C and stirred at this temperature for 5 min before the dropwise addition of ^{n}BuLi (39.0 ml, 2.2 M in hexanes, 85.9 mmol). Upon complete addition the solution was warmed to room temperature and stirred for 15 min before cooling to -40˚C. Tributyltin hydride (23.1 ml, 85.9 mmol) was added and the resulting solution stirred for 70 min.

Simultaneously, a flame dried, and nitrogen cooled, 250 ml round bottom flask was charged with 2,3-dihydrofuran (3.25 ml, 42.95 mmol) and THF (40 ml) before cooling to -60˚C. Following this, ^{t}BuLi (33.3 ml, 1.55 M in pentane, 51.54 mmol) was added dropwise. Upon complete addition the mixture was allowed to warm to 0˚C and stirred at this temperature for 1 h. After this time, the lithiated material was transferred *via* cannula to the previously prepared cuprate solution, which was stirred at -40˚C throughout. Upon complete addition, the mixture was warmed to 0˚C and stirred for 90 min. Methyl iodide (18.5 ml, 296.4 mmol) was added dropwise and the resulting solution was warmed to room temperature over 1 h and stirred for a further 3 h. The reaction mixture was poured into a mixture of saturated ammonium chloride solution (500 ml) and sodium hydroxide solution (125 ml) at 0˚C. The resulting suspension was stirred vigorously for 30 min, the aqueous layer was separated, extracted with diethyl ether, and the organic portions combined. The organic solution was dried over sodium sulfate, filtered, and concentrated

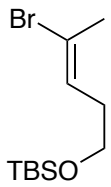
in vacuo. The colourless oil was solubilised in DCM (40 ml) and cooled to 0˚C. A solution of bromine (2.34 ml, 46.4 mmol) in DCM (100 ml) was added dropwise until the brown colour persisted. The reaction mixture was quenched with a saturated sodium thiosulfite solution and extracted with DCM. The organic phase was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude oil was purified by column chromatography (eluent: 0-80% diethyl ether in petrol) to furnish **150** (6.24 g, 88% yield) as colourless oil.

IR: 3333, 1651, 1043 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 5.90 (t, *J* = 7.7 Hz, 1H, olefinic CH), 3.68 (t, *J* = 6.3 Hz, 2H, OCH_2), 2.38-2.25 ppm (m, 5H, vinyl CH_3 & allylic CH_2).

^{13}C δ (100 MHz, $CDCl_3$): 127.7, 121.3, 61.0, 32.5, 22.9 ppm.

Preparation of (E)-((4-bromopent-3-en-1-yl)oxy)(tert-butyl)dimethylsilane, ***156***[33]



Scheme 123

A flame dried, and nitrogen cooled, 250 ml round bottom flask was charged with **150** (9.00 g, 54.50 mmol) and DCM (200 ml). To the stirred mixture was added imidazole (8.61 g, 126.50 mmol) and *tert*-butyldimethylsilyl chloride (12.32 g, 81.75 mmol). The resulting solution was stirred at room temperature for 1 h. After this time, the reaction was quenched by the addition of a saturated sodium bicarbonate solution and extracted

into DCM. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (eluent: 0-10% diethyl ether in petrol) to furnish **156** (14.61 g, 96% yield) as a colourless oil.

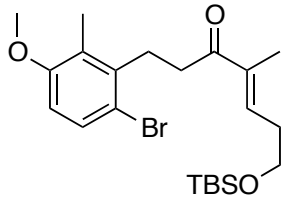
IR: 1256, 1098 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 5.86 (t, *J* = 6.6 Hz, 1H, olefinic CH), 3.63 (t, *J* = 6.6 Hz, 2H, OCH_2), 2.27-2.21 (m, 5H, vinyl CH_3 & allylic CH_2), 0.86 (s, 9H, Si^tBu), 0.06 ppm (s, 6H, $SiCH_3$).

^{13}C δ (100 MHz, $CDCl_3$): 128.8, 120.9, 61.9, 33.3, 25.9, 23.4, 18.3, -5.3 ppm.

HRMS *m/z* (ESI) Calc. for $C_{11}H_{24}BrOSi$ (M^+ + H): 279.0774. Found: 279.0771.

Preparation of (E)-7-((tert-butyldimethylsilyl)oxy)-1-(3-methoxy-2-methylphenyl)-4-methylhept-4-en-3-one, ***146***[33]



Scheme 124

A flame dried, and nitrogen cooled, 3-necked 250 ml round bottom flask was charged with vinyl bromide **156** (5.52 g, 19.76 mmol) and dry diethyl ether (75 ml). The reaction mixture was cooled to -78˚C, followed by the dropwise addition of ^{t}BuLi (24.5 ml, 1.6 M in pentane, 39.5 mmol) and allowed to stir at this temperature for 1 h.

Simultaneously, a 3-necked 100 ml round bottom flask, fitted with a reflux condenser, was charged with magnesium turnings (0.96 g. 24.3 mmol) and flame dried under vacuum. The flask was cooled under nitrogen and charged with dry diethyl ether (30 ml) and dry benzene (10 ml). To the stirred suspension was added dibromoethane (3.36 ml, 39.5 mmol), dropwise, at such a rate as to ensure the mixture refluxed without external heating. Upon complete addition, the reaction mixture was warmed to a gentle reflux (50˚C) and held at this temperature for 1 h. Stirring was discontinued and the solution allowed to settle at room temperature, resulting in a 1 M solution of anhydrous $MgBr_2(OEt_2)$.

The freshly generated anhydrous $MgBr_2(OEt_2)$ solution (20.5 ml, 1 M in Et_2O/benzene, 20.5 mmol) was added to the vinyllithium species at -78˚C. The mixture was stirred at this temperature for 10 min before warming to 0˚C. The solution was allowed to stir at this temperature for 30 min prior to the addition of Weinreb amide **7** (5.00 g, 15.81 mmol) as a solution in dry diethyl ether (10 ml). The mixture was stirred at 0˚C for 30 min prior to warming to room temperature for a further 30 min. Following this, the reaction was quenched with saturated ammonium chloride solution. The organic phase was washed with water, and brine, before drying over sodium sulfate. The mixture was filtered, concentrated *in vacuo*, and purified by flash column chromatography (0-5% diethyl ether in petrol) to yield **146** (6.70 g, 93% yield) as a pale yellow oil.

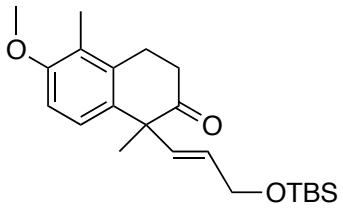
IR: 1668, 1460 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 7.37 (d, J = 8.8 Hz, 1H, ArH), 6.72-6.68 (m, 1H, olefinic CH), 6.63 (d, J = 8.8 Hz, 1H, ArH), 3.81 (s, 3H, $ArOCH_3$), 3.72 (t, J = 6.5 Hz, 2H, OCH_2), 3.13-3.10 (m, 2H, alkyl CH_2), 2.89-2.85 (m, 2H, alkyl CH_2), 2.48-2.44 (m, 2H, allylic CH_2), 2.24 (s, 3H, $ArCH_3$), 1.84 (s, 3H, vinylic CH_3), 0.89 (s, 9H, Si^tBu), 0.06 ppm (s, 6H, $SiCH_3$).

^{13}C δ (100 MHz, $CDCl_3$): 200.7, 157.1, 139.8, 139.4, 138.3, 130.1, 127.0, 116.0, 109.8, 61.7, 55.7, 36.1, 32.8, 28.7, 25.9, 18.3, 12.4, 11.6, -5.3 ppm.

HRMS *m/z* (ESI) Calc. for $C_{22}H_{36}BrO_3Si$ (M^+ + H): 455.1612. Found: 455.1609.

Preparation of (E)-1-(3-((tert-butyldimethylsilyl)oxy)prop-1-en-1-yl)-6-methoxy-1,5-dimethyl-3,4-dihydronaphthalen-2(1H)-one, ***147***[33]



Scheme 125

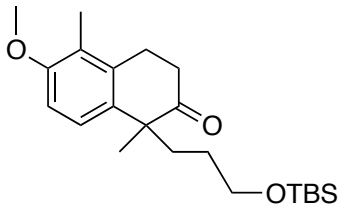
A microwave vial was charged with palladium acetate (34 mg, 0.15 mmol), P(*o*-tolyl)$_3$ (182 mg, 0.60 mmol), and acetonitrile (1.5 ml). The resulting mixture was stirred for 5 min, at room temperature, which resulted in a colour change from a brown solution to an opaque yellow suspension. Substrate **146** (680 mg, 1.49 mmol) was added, as a solution in acetonitrile (0.6 ml) before the addition of triethylamine (0.42 ml, 2.98 mmol). The mixture was heated to 100˚C under microwave irradiation, with cooling, for 30 min (15 min x 2). After this time the solution was concentrated *in vacuo* and the resulting residue was filtered through celite (eluent: ethyl acetate). The resulting solution was concentrated *in vacuo* and purified by flash column chromatography (0-5% diethyl ether in petrol) to furnish **147** (513 mg, 92% yield).

IR: 1717, 1483, 1260 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 7.09 (d, J = 8.7 Hz, 1H, ArH), 6.80 (d, J = 8.7 Hz, 1H, ArH), 5.69 (dt, J = 15.5, ^4J = 1.8 Hz, 1H, olefinic CH), 5.35 (dt, J = 15.5 and 5.0 Hz, 1H, olefinic CH), 4.13 (d, J = 4.7 Hz, 2H, OCH_2), 3.83 (s, 3H, $ArOCH_3$), 3.02 (q, J = 6.8 Hz, 2H, ring CH_2), 2.81-2.74 (m, 1H, ring CH_2), 2.53-2.46 (m, 1H, ring CH_2), 2.21 (s, 3H, $ArCH_3$), 1.54 (d, ^4J = 1.8 Hz, 3H, alkyl CH_3), 0.89 (s, 9H, Si^{t}Bu), 0.03 ppm (s, 6H, $SiCH_3$).

^{13}C δ (100 MHz, $CDCl_3$): 211.9, 156.9, 136.0, 134.0, 133.2, 130.5, 125.6, 123.9, 108.9, 63.4, 55.6, 54.5, 36.7, 25.9, 25.6, 25.0, 18.5, 11.5, -5.2 ppm.
HRMS *m/z* (ESI) Calc. for $C_{22}H_{35}O_3Si$ (M^+ + H): 375.2350. Found: 375.2355.

Preparation of 1-(3-((tert-butyldimethylsilyl)oxy)propyl)-6-methoxy-1,5-dimethyl-3,4-dihydronaphthalen-2(1H)-one, ***157***[33]



Scheme 126

A flame dried, and nitrogen cooled, 100 ml round bottom flask was charged with Crabtree's catalyst (105 mg, 0.13 mmol), DCM (30 ml), and olefin **147** (500 mg, 1.33 mmol). The solution was cooled to -78˚C, evacuated and back-filled (x 3) with hydrogen gas *via* a three way tap attached to a vacuum manifold and a hydrogen balloon. The solution was kept under an atmosphere of hydrogen, allowed to warm to room temperature, and stirred for 16 h. The mixture was concentrated *in vacuo* and subsequently purified by column chromatography (0-10% diethyl ether in petrol). The desired product, **157**, was obtained as a colourless oil (471 mg, 94% yield).

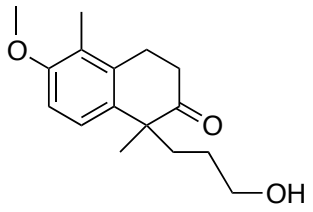
IR: 1713, 1263, 1209 cm^{-1}.
^1H NMR δ (400 MHz, $CDCl_3$): 7.11 (d, *J* = 8.7 Hz, 1H, ArH), 6.81 (d, *J* = 8.7 Hz, 1H, ArH), 3.83 (s, 3H, $ArOCH_3$), 3.48-3.41 (m, 2H, OCH_2), 3.05-2.97 (m, 2H, ring CH_2), 2.69-2.60 (m, 2H, ring CH_2), 2.19 (s, 3H, $ArCH_3$), 2.06 (dt, ^2J = 12.5, *J* = 4.8 Hz, 1H,

CCH_2), 1.73 (dt, ^2J = 12.5, J = 4.8 Hz, 1H, CCH_2), 1.40 (s, 3H, alkyl CH_3), 1.23-1.12 (m, 2H, CH_2CH_2O), 0.86 (s, 9H, Si^tBu), -0.02 ppm (s, 6H, $SiCH_3$).

^{13}C NMR δ (100 MHz, $CDCl_3$): 215.1, 155.7, 135.6, 134.4, 124.6, 123.4, 109.2, 63.2, 55.6, 51.0, 37.9, 36.8, 28.5, 27.5, 26.0, 25.3, 18.3, 11.6, -5.3 ppm.

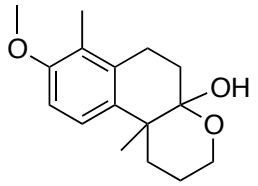
HRMS *m/z* (ESI) Calc. for $C_{22}H_{37}O_3Si$ (M^+ + H): 377.2506. Found: 377.2511.

Attempted preparation of 1-(3-hydroxypropyl)-6-methoxy-1,5-dimethyl-3,4-dihydronaphthalen-2(1H)-one, ***158***



Scheme 127

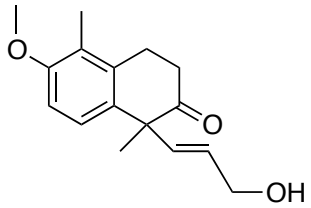
A flame dried, and nitrogen cooled, 50 ml round bottom flask was charged with **157** (400 mg, 1.06 mmol) and THF (20 ml), before cooling to 0˚C. TBAF (3.0 ml, 1M in THF, 3.00 mmol) was added dropwise to the reaction mixture and the resulting solution stirred for 24 h at room temperature. The reaction was quenched with saturated sodium bicarbonate solution and extracted into diethyl ether. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was analysed by ^1H NMR which indicated that lactol **159** formed as the major product.



IR: 3473, 1458, 1263 cm^{-1}.

The ^{1}H NMR featuring the proposed lactol species, **159**, is included in the appendix.

Preparation of (E)-1-(3-hydroxyprop-1-en-1-yl)-6-methoxy-1,5-dimethyl-3,4-dihydronaphthalen-2(1H)-one, ***160***



Scheme 129

A flame dried, and nitrogen cooled, 50 ml round bottom flask was charged with **147** (396 mg, 1.06 mmol) and THF (20 ml), before cooling to 0˚C. TBAF (3.0 ml, 1M in THF, 3.00 mmol) was added dropwise to the reaction mixture and the resulting solution stirred for 24 h at room temperature. The reaction was quenched with saturated sodium bicarbonate solution and extracted into diethyl ether. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: 0-100% diethyl ether in petrol) to yield **160** (251 mg, 91% yield) as a pale yellow oil.

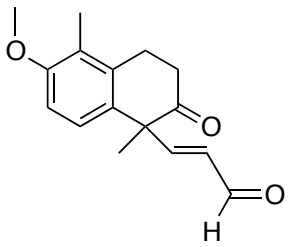
IR: 3454, 1707, 1481, 1261, 1101 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 7.09 (d, *J* = 8.7 Hz, 1H, ArH), 6.82 (d, *J* = 8.7 Hz, 1H, ArH), 5.76 (dt, *J* = 15.4, ^{4}J = 1.5 Hz, 1H, olefinic CH), 5.49 (dt, *J* = 15.4 and 5.5 Hz, 1H, olefinic CH), 4.13 (dd, *J* = 5.6, ^{4}J = 1.5 Hz, 2H, OCH_2), 3.86 (s, 3H, $ArOCH_3$), 3.08-3.04 (m, 2H, ring CH_2), 2.80 (dt, ^{2}J = 15.8, *J* = 6.5 Hz, 1H, ring CH_2), 2.56 (dt, ^{2}J = 15.8, *J* = 6.9 Hz, 1H, ring CH_2), 2.22 (s, 3H, $ArCH_3$), 1.57 ppm (s, 3H, alkyl CH_3).

^{13}C NMR δ (100 MHz, $CDCl_3$): 212.2, 156.3, 135.9, 135.6, 132.9, 130.0, 125.6, 123.6, 109.0, 63.2, 55.6, 54.3, 36.8, 23.7, 22.6, 11.5 ppm.

HRMS *m/z* (ESI) Calc. for $C_{16}H_{20}O_3Na$ (M^+ + Na): 283.1305. Found: 283.1307.

Preparation of (E)-3-(6-methoxy-1,5-dimethyl-2-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)acrylaldehyde, ***161***



Scheme 130

A flame dried, and nitrogen cooled, 50 ml round bottom flask was charged with **160** (650 mg, 2.5 mmol), MnO_2 (2.2 g, 25.0 mmol), and DCM (20 ml). The resulting suspension was stirred at room temperature for 16 h. After this time the mixture was filtered through a pad of celite (eluent: DCM) and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: 0-50% diethyl ether in petrol) to yield **161** (568 mg, 88% yield) as a pale yellow oil.

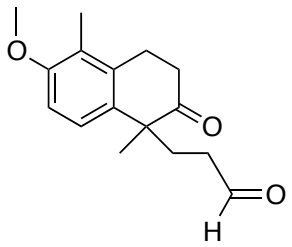
IR: 1717, 1684, 1261 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 9.55 (d, *J* = 7.7 Hz, 1H, CHO), 7.03 (d, *J* = 8.5 Hz, 1H, ArH), 6.85 (d, *J* = 15.8 Hz, 1H, olefinic CH), 6.84 (d, *J* = 8.5 Hz, 1H, ArH), 5.93 (dd, *J* = 15.8, 7.7 Hz, 1H, olefinic CH), 3.87 (s, 3H, $ArOCH_3$), 3.18-3.09 (m, 1H, alkyl CH), 3.04-2.94 (m, 1H, alkyl CH), 2.83-2.74 (m, 1H, alkyl CH), 2.73-2.64 (m, 1H, alkyl CH), 2.23 (s, 3H, $ArCH_3$), 1.68 ppm (s, 3H, alkyl CH_3).

^{13}C NMR δ (100 MHz, $CDCl_3$): 210.2, 193.4, 159.9, 135.7, 130.2, 132.0, 130.8, 125.7, 124.2, 109.3, 55.6, 55.3, 37.1, 25.0, 23.8, 11.5 ppm.

HRMS *m/z* (ESI) Calc. for $C_{16}H_{19}O_3$ (M^+ + H): 259.1329. Found: 259.1332.

Preparation of 3-(6-methoxy-1,5-dimethyl-2-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)propanal, ***144***



General Procedure

A flame dried, and nitrogen cooled, 50 ml round bottom flask was charged with **161**, 10% palladium on carbon catalyst, and solvent. The suspension was cooled to -78˚C, evacuated and back-filled (x 3) with hydrogen gas *via* a three way tap attached to a vacuum manifold and a hydrogen balloon. The solution was kept under an atmosphere of hydrogen, allowed to warm to room temperature, and stirred for 16 h. After this time the slurry was filtered through a pad of celite and concentrated *in vacuo*. The resulting oil

was purified by flash column chromatography (0-20% diethyl ether in petrol) to provide **144** as a colourless oil.

Following the ***General Procedure***, data are presented as (a) amount of **161**, (b) solvent, (c) amount of Pd/C, and (d) outcome.

Scheme 131 - MeOH

(a) 300 mg, 1.16 mmol, (b) MeOH, 10 ml, (c) 127 mg, and (d) degradation of starting material.

Scheme 131 - EtOAc

(a) 300 mg, 1.16 mmol, (b) EtOAc, 10 ml, (c) 127 g, and (d) 233 mg, 77% yield.

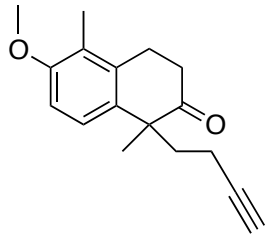
IR: 1714, 1483, 1265 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 9.56 (s, 1H, CHO), 7.09 (d, J = 8.6 Hz, 1H, ArH), 6.82 (d, J = 8.6 Hz, 1H, ArH), 3.84 (s, 3H, $ArOCH_3$), 3.17-3.11 (dt, ^{2}J = 16.3, J = 5.8 Hz, 1H, alkyl CH_2), 2.99-2.89 (m, 1H, alkyl CH_2), 2.79-2.73 (m, 1H, alkyl CH_2), 2.60 (dt, ^{2}J = 14.6, J = 5.5 Hz, 1H, alkyl CH_2), 2.47-2.40 (m, 1H, alkyl CH_2), 2.20 (s, 3H, $ArCH_3$), 2.18-2.11 (m, 1H, alkyl CH_2), 2.01-1.93 (m, 2H, alkyl CH_2), 1.45 ppm (s, 3H, alkyl CH_3).

^{13}C NMR δ (100 MHz, $CDCl_3$): 214.4, 201.6, 155.4, 135.7, 133.2, 124.5, 123.7, 109.4, 55.6, 50.5, 40.1, 37.5, 31.9, 28.2, 25.5, 11.6 ppm.

HRMS *m/z* (ESI) Calc. for $C_{16}H_{21}O_3$ (M^+ + H): 261.1485. Found: 261.1484.

Attempted preparation of 1-(but-3-yn-1-yl)-6-methoxy-1,5-dimethyl-3,4-dihydronaphthalen-2(1H)-one, ***145***



Scheme 132

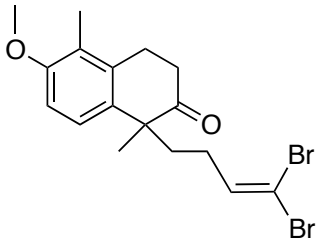
A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with **144** (80 mg, 0.19 mmol), potassium carbonate (51 mg, 0.37 mmol), and MeOH (15 ml). Ohira Bestmann reagent **162** (46 mg, 0.24 mmol) was added and the resulting solution stirred for 4 h at room temperature. After this time, the mixture was diluted with saturated sodium bicarbonate and the organic layer separated. The organic phase was washed with water, brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was analysed by ^{1}H NMR, which indicated that the desired product had failed to form and a complex mixture of products was observed.

Scheme 135

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with phosphonium salt **104** (420 mg, 0.96 mmol) and THF (12 ml). The resulting suspension was cooled to -78˚C, then potassium *tert*-butoxide (130 mg, 0.94 mmol) was added as a single portion before stirring for 50 min. After this time, aldehyde **144** (100 mg, 0.38 mmol) was added as a solution in THF (2 ml), and the resulting mixture was stirred for 3 h, at -78˚C. After this time, the mixture was warmed to -40˚C, stirred for 1 h, following this the solution was warmed to room temperature and stirred for 16 h. The reaction

mixture was quenched with saturated sodium bicarbonate solution and diluted with diethyl ether. The organic layer was separated and washed sequentially with water and brine. The organic phase was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was analysed by ^{1}H NMR spectroscopy, which revealed that the desired vinyl bromide, **163**, was present (see appendix). The crude material was solubilised in THF (10 ml) before the addition of TBAF (1.9 ml, 1 M in THF, 1.9 mmol) dropwise. The resulting solution stirred for 16 h at room temperature. Unfortunately, ^{1}H NMR indicated that the desired product failed to form and a complex mixture of products was observed.

Preparation of 1-(4,4-dibromobut-3-en-1-yl)-6-methoxy-1,5-dimethyl-3,4-dihydronaphthalen-2(1H)-one, ***166***



Scheme 138

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with triphenylphosphine (202 mg, 0.77 mmol) and DCM (6 ml), before adding carbon tetrabromide (133 mg, 0.40 mmol) at 0˚C. The resulting bright yellow solution was stirred for 10 min at this temperature. Aldehyde **144** (100 mg, 0.38 mmol) was added as a solution in DCM (2 ml), and the resulting mixture was warmed to room temperature and stirred for 16 h. After this time, hexane (6 ml) was added, the reaction mixture was

filtered through celite (eluent: 20% ether in hexane), and the filtrate was concentrated *in vacuo*. The resulting residue was analysed by ^{1}H NMR, which revealed that the desired compound, **166**, had failed to form.

Scheme 139

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with triphenylphosphine (202 mg, 0.77 mmol) and DCM (6 ml), before adding carbon tetrabromide (133 mg, 0.40 mmol) at 0˚C. The resulting bright yellow solution was stirred for 10 min at this temperature. Aldehyde **144** (100 mg, 0.38 mmol) and Et_3N (0.05 ml, 0.38 mmol) were added as a solution in DCM (2 ml), and the resulting mixture was warmed to room temperature and stirred for 16 h. After this time, hexane (6 ml) was added, the reaction mixture was filtered through celite (eluent: 20% ether in hexane), and the filtrate concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (0-40% diethyl ether in petrol) to yield dibromo olefin, **166**, as a yellow oil (120 mg, 76% yield).

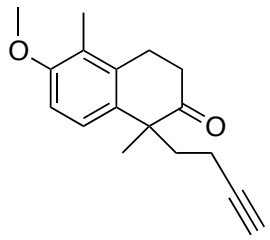
IR: 1711, 1483, 1263, 1101 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 7.12 (d, *J* = 8.7 Hz, 1H, ArH), 6.84 (d, *J* = 8.7 Hz, 1H, ArH), 6.18 (t, *J* = 7.1 Hz, 1H, olefinic CH), 3.85 (s, 3H $ArOCH_3$), 3.33-3.21 (m, 1H, alkyl CH_2), 3.13-3.04 (m, 1H, alkyl CH_2), 2.98-2.90 (m, 1H, alkyl CH_2), 2.78-2.70 (m, 1H, alkyl CH_2), 2.64-2.57 (m, 1H, alkyl CH_2), 2.31-2.25 (m, 1H, alkyl CH_2), 2.20 (s, 3H, $ArCH_3$), 1.85-1.68 (m, 2H, alkyl CH_2), 1.42 ppm (s, 3H, alkyl CH_3).

^{13}C NMR δ (100 MHz, $CDCl_3$): 214.5, 155.9, 138.1, 135.7, 133.4, 124.6, 123.7, 109.4, 88.9, 55.6, 50.9, 41.4, 37.8, 37.2, 25.4, 19.4, 11.6 ppm.

HRMS *m/z* (ESI) Calc. for $C_{17}H_{21}Br_2O_2$ (M^+ + H): 416.9882. Found: 416.9874.

Attempted preparation of 1-(but-3-yn-1-yl)-6-methoxy-1,5-dimethyl-3,4-dihydronaphthalen-2(1H)-one, ***145***



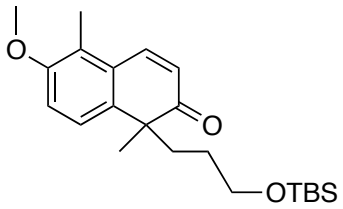
Scheme 140

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with dibromo olefin **166** (100 mg, 0.24 mmol) and THF (10 ml). Following this, potassium *tert*-butoxide (66 mg, 0.48 mmol) was added in one portion and the mixture was stirred at room temperature for 30 min. The reaction was quenched with water, the organic portion separated, washed with brine, dried over sodium sulfate, and filtered. The solution was concentrated *in vacuo* and analysed by ^{1}H NMR. Unfortunately, the desired product failed to form and a complex mixture of products was observed.

Scheme 141

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with dibromo olefin **166** (100 mg, 0.24 mmol) and THF (10 ml). Following this, TBAF (1.21 ml, 1 M in THF, 1.21 mmol) was added and the mixture was stirred at room temperature for 24 h. The reaction was quenched with water and diluted with Et_2O, the organic portion separated, washed with brine, dried over sodium sulfate and filtered. The solution was concentrated *in vacuo* and analysed by ^{1}H NMR. Unfortunately, the desired product failed to form and an appreciable quantity of starting material (82 mg) was recovered.

Preparation of 1-(3-((tert-butyldimethylsilyl)oxy)propyl)-6-methoxy-1,5-dimethylnaphthalen-2(1H)-one, ***168***[33]



Scheme 142

A flame dried, and nitrogen cooled, 100 ml round bottom flask was charged with dry DCM (30 ml), ketone **157** (300 mg, 0.80 mmol), and triethylamine (0.33 ml, 2.40 mmol). The solution was cooled to -5˚C, before the dropwise addition of trimethylsilyl triflate (0.173 ml, 1.00 mmol). The solution was allowed to stir at this temperature for 30 min before quenching with saturated sodium bicarbonate solution. The mixture was extracted with DCM, the organic portion separated, dried over sodium sulfate and filtered through celite (eluent: DCM). The solution was concentrated *in vacuo* before solubilising in acetonitrile (30 ml). Following the addition of palladium acetate (200 mg, 0.88 mmol), the resulting mixture was heated to 40˚C and stirred for 16 h. After this time, the solution was concentrated *in vacuo* and purified by flash column chromatography (0-5% diethyl ether in petrol) to yield enone **168** (186 mg, 62% yield).

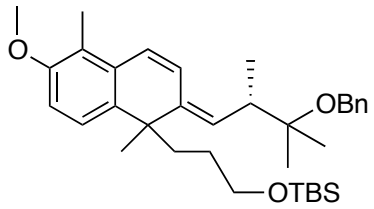
IR: 1657, 1570, 1263, 1092 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 7.81 (d, J = 10.2 Hz, 1H, olefinic CH), 7.22 (d, J = 8.7 Hz, 1H, ArH), 6.93 (d, J = 8.7 Hz, 1H, ArH), 6.19 (d, J = 10.2 Hz, 1H, olefinic CH), 3.86 (s, 3H, $ArOCH_3$), 3.47-3.35 (m, 2H, CH_2OTBS), 2.36 (s, 3H, $ArCH_3$), 2.19-2.11 (m, 1H, alkyl CH_2), 1.92-1.84 (m, 1H, alkyl CH_2), 1.41 (s, 3H, alkyl CH_3), 1.21-0.99 (m, 2H, alkyl CH_2), 0.85 (s, 9H, Si^{t}Bu), -0.02 (s, 3H, $SiCH_3$), -0.04 ppm (s, 3H, $SiCH_3$).

^{13}C NMR δ (100 MHz, $CDCl_3$): 204.7, 155.9, 141.0, 138.5, 128.9, 125.2, 125.0, 124.5, 112.1, 63.1, 55.8, 50.8, 38.8, 28.8, 28.3, 25.9, 18.3, 10.7, -5.3, -5.4 ppm.

HRMS *m/z* (ESI) Calc. for $C_{22}H_{35}O_3Si$ (M^+ + H): 375.2350. Found: 375.2351.

Preparation of (3-((E)-2-((S)-3-(benzyloxy)-2,3-dimethylbutylidene)-6-methoxy-1,5-dimethyl-1,2-dihydronaphthalen-1-yl)propoxy)(tert-butyl)dimethylsilane, ***169***



Scheme 143

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with *tert*-butyllithium (0.33 ml, 1.7 M in pentane 0.56 mmol) and Et_2O (4 ml) before being cooled to -78˚C. Alkyl iodide **90** (88 mg, 0.28 mmol) was added as a solution in Et_2O (2 ml) and the resulting mixture was warmed to 0˚C over the course of 1 h. After this time, the reaction mixture was cooled to -78˚C and enone **168** (80 mg, 0.21 mmol) was added as a solution in Et_2O (2 ml). The mixture was warmed to 0˚C over the course of 3 h. Following this, the reaction was quenched with a saturated ammonium chloride solution. The organic phase was separated, washed with water, and brine, before drying over sodium sulfate. The mixture was filtered, concentrated *in vacuo* and solubilised in PhH (15 ml), before the addition of Burgess's reagent (250 mg, 1.05 mmol). The suspension was stirred at room temperature for 2 h, followed by heating to reflux and stirring for 6 h. After this time, the mixture was concentrated *in vacuo* and purified by flash column chromatography (eluent: 0-30% diethyl ether in petrol) to furnish diene **169** as a pale yellow oil (63 mg, 55% yield).

Scheme 144

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with *tert*-butyllithium (0.33 ml, 1.7 M in pentane 0.56 mmol) and Et_2O (4 ml) before being cooled to -78˚C. Alkyl iodide **90** (88 mg, 0.28 mmol) was added as a solution in THF (2 ml) and

the resulting mixture was warmed to 0˚C over the course of 1 h. After this time, the reaction mixture was cooled to -78˚C and transferred *via* cannula to a stirred solution of $CeCl_3$ (69 mg, 0.28 mmol) in Et_2O (3 ml). A solution of enone **168** (80 mg, 0.21 mmol) in THF (2 ml) was added to the stirred suspension and the resulting mixture allowed to warm to 0˚C over the course of 3 h. After this time, the reaction was quenched with a saturated ammonium chloride solution. The organic phase was separated, washed with water, and brine, before drying over sodium sulfate. The mixture was filtered, concentrated *in vacuo* and analysed by TLC and ^{1}H NMR. Unfortunately, the desired product had failed to form and a complex mixture was observed.

Scheme 145

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with *tert*-butyllithium (0.33 ml, 1.7 M in pentane 0.56 mmol) and PhMe (4 ml) before being cooled to -78˚C. Alkyl iodide **90** (88 mg, 0.28 mmol) was added as a solution in PhMe (2 ml) and the resulting solution warmed to 0˚C over the course of 1 h. After this time, the reaction mixture was cooled to -78˚C and enone **168** (80 mg, 0.21 mmol) added as a solution in PhMe (2 ml). The mixture was warmed to 0˚C over the course of 3 h. Following this, the reaction was quenched with a saturated ammonium chloride solution. The organic phase was separated, washed with water, and brine, before drying over sodium sulfate. The mixture was filtered, concentrated *in vacuo* and analysed by TLC and ^{1}H NMR. Unfortunately, the desired product had failed to form and a complex mixture was observed.

IR: 1466, 1261, 1103 cm^{-1}.

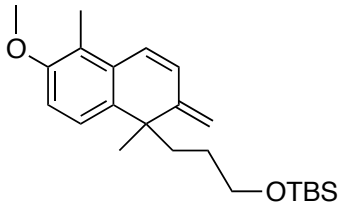
^{1}H NMR δ (400 MHz, $CDCl_3$): 7.39-7.18 (m, 6H, ArH and olefinic CH), 6.76-6.65 (m, 3H, ArH and olefinic CH), 5.57 (d, J = 10.1 Hz, 0.5 H, olefinic CH), 5.56 (d, J = 10.1 Hz, 0.5 H, olefinic CH), 4.46 (s, 1H, CH_2OPh), 4.44 (s, 1H, CH_2OPh), 3.83 (s, 3H, $ArOCH_3$), 3.48-3.41 (m, 2H, CH_2OTBS), 3.07-2.97 (m, 1H, C*H*CH_3), 2.26 (s, 3H, $ArCH_3$), 2.00-1.65 (m, 4H, alkyl CH_2), 1.43 (s, 1.5H, $ArCCH_3$), 1.41 (s, 1.5H, $ArCCH_3$), 1.29-1.23 (m,

6H, CCH_3), 1.13-1.07 (m, 3H, $CHCH_3$), 0.88 (s, 4.5H, Si^{t}Bu), 0.87 (s, 4.5H, Si^{t}Bu), 0.00 (s, 3H, $SiCH_3$), -0.02 ppm (s, 3H, $SiCH_3$).

^{13}C NMR δ (100 MHz, $CDCl_3$): 155.1, 139.7, 139.2, 131.3, 130.1, 127.7, 126.7, 126.6, 123.7, 123.0, 122.9, 121.7, 117.8, 108.7, 76.2, 63.1, 62.9, 62.6, 55.1, 35.4, 31.1, 28.2, 28.0, 25.5, 23.7, 23.4, 21.7, 17.1, 15.3, 10.2, -5.8 ppm.

HRMS *m/z* (ESI) Calc. for $C_{35}H_{56}O_3SiN$ ($M^+ + NH_4$): 566.4024. Found: 566.4016.

Preparation of tert-butyl(3-(6-methoxy-1,5-dimethyl-2-methylene-1,2-dihydronaphthalen-1-yl)propoxy)dimethylsilane, ***170***[33]



Scheme 146

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with methyltriphenylphosphonium bromide (107 mg, 0.30 mmol) and THF (12 ml) before cooling to -78˚C. Potassium *tert*-butoxide (30 mg, 0.26 mmol) was added and the resulting yellow solution stirred for 30 min at this temperature. After this time, enone **168** (30 mg, 0.08 mmol) was added as a solution in THF (2 ml) and the reaction mixture stirred for 30 min. The reaction mixture was warmed to room temperature and stirred for 1 h before being quenched with saturated ammonium chloride solution. The mixture was diluted with diethyl ether, the organic layer was separated and washed sequentially with water and brine. The organic phase was dried over sodium sulfate, filtered, and

concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: 0-10% diethyl ether in petrol) to yield **170** (26 mg, 87% yield) as a colourless oil.

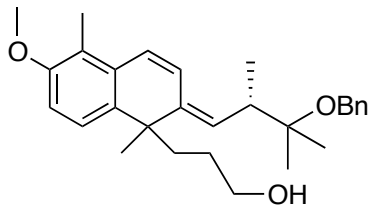
IR: 1464, 1261, 1099 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 7.18 (d, J = 8.7 Hz, 1H, ArH), 6.74 (d, J = 8.7 Hz, 1H, ArH), 6.65 (d, J = 10.0 Hz, 1H, olefinic CH), 6.38 (d, J = 10.0 Hz, 1H, olefinic CH), 5.17 (s, 1H, olefinic CH_2), 5.15 (s, 1H, olefinic CH_2), 3.83 (s, 3H, $ArOCH_3$), 3.46 (t, J = 6.5 Hz, 2H, OCH_2), 2.26 (s, 3H, $ArCH_3$), 1.92 (dt, ^{2}J = 12.2, J = 4.5 Hz, 1H, alkyl CH_2), 1.73 (dt, ^{2}J = 12.2, J = 4.5 Hz, 1H, alkyl CH_2), 1.43 (s, 3H, $ArCCH_3$), 1.38-1.30 (m, 1H, alkyl CH_2), 1.18-1.09 (m, 1H, alkyl CH_2), 0.88 (s, 9H, Si^{t}Bu), 0.00 ppm (s, 6H, $SiCH_3$).

^{13}C NMR δ (100 MHz, $CDCl_3$): 155.1, 150.0, 135.2, 131.2, 129.5, 122.9, 121.8, 121.2, 112.7, 108.8, 63.0, 55.1, 41.7, 41.5, 32.0, 27.9, 25.5, 17.8, 10.2, -5.8 ppm.

HRMS *m/z* (ESI) Calc. for $C_{23}H_{37}O_2Si$ (M^+ + H): 373.2557. Found: 373.2558.

Preparation of 3-(2-(3-(benzyloxy)-2,3-dimethylbutylidene)-6-methoxy-1,5-dimethyl-1,2-dihydronaphthalen-1-yl)propan-1-ol, ***171***



Scheme 148

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with **169** (60 mg, 0.11 mmol) and THF (6 ml). TBAF (0.2 ml, 1 M in THF, 0.20 mmol) was added

dropwise to the reaction mixture and the resulting solution stirred for 16 h at room temperature. The reaction was quenched with saturated sodium bicarbonate solution and extracted into diethyl ether. The organic layer was separated, washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: 0-100% diethyl ether in petrol) to yield **171** (39 mg, 82% yield) as a pale yellow oil.

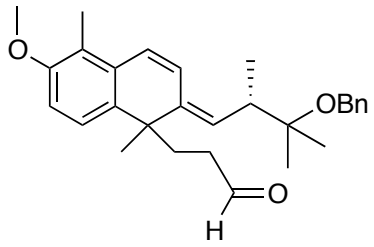
IR: 3726, 1261, 1103 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 7.39-7.16 (m, 6H, ArH and olefinic CH), 6.77-6.65 (m, 3H, ArH and olefinic CH), 5.64-5.57 (m, 1H, olefinic CH), 4.53-4.47 (m, 2H, CH_2OPh), 3.83 (bs, 3H, $ArOCH_3$), 3.50-3.46 (m, 1H, CH_2OH), 3.36-3.31 (m, 1H, CH_2OH), 3.07-2.97 (m, 1H, C*H*CH_3), 2.27 (s, 1.5H, $ArCH_3$), 2.26 (s, 1.5H, $ArCH_3$), 1.95-1.53 (m, 4H, alkyl CH_2), 1.46 (s, 1.5H, $ArCCH_3$), 1.44 (s, 1.5H, $ArCCH_3$), 1.31 (s, 3H, CCH_3), 1.29 (s, 3H, CCH_3), 1.10-1.07 ppm (m, 3H, CHC*H*$_3$).

^{13}C NMR δ (100 MHz, $CDCl_3$): 155.2, 139.4, 138.9, 135.6, 131.3, 130.1, 127.7, 126.64, 126.60, 126.53, 126.47, 123.6, 122.9, 121.7, 121.4, 108.7, 77.3, 65.3, 62.8, 55.1, 41.8, 40.8, 39.9, 28.7, 28.3, 20.3, 14.8, 13.6 ppm.

HRMS *m/z* (ESI) Calc. for $C_{29}H_{39}O_3$ (M^+ + H): 435.2894. Found: 435.2889.

Preparation of 3-((E)-2-((S)-3-(benzyloxy)-2,3-dimethylbutylidene)-6-methoxy-1,5-dimethyl-1,2-dihydronaphthalen-1-yl)propanal, ***172***



Scheme 149

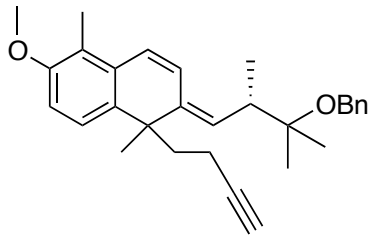
A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with **171** (150 mg, 0.35 mmol) and DCM (15 ml), before cooling to 0˚C. DMP (165 mg, 0.39 mmol) was added to the reaction mixture and the resulting solution allowed to warm to room temperature and stirred for 3 h. The reaction mixture was diluted with diethyl ether and DCM was removed *in vacuo*. The mixture was further diluted with diethyl ether and a 1:1 mixture of 10% sodium thiosulfite and saturated aqueous solution of sodium bicarbonate added. The organic layer was separated, washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: 0-30% diethyl ether in petrol) to yield **172** (103 mg, 68% yield) as a colourless oil.

IR: 1720, 1456, 1261 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 9.60 (s, 0.5H, CHO), 9.43 (s, 0.5H, CHO), 7.38-7.14 (m, 6H, ArH and olefinic CH), 6.76-6.68 (m, 3H, ArH and olefinic CH), 5.62-5.59 (m, 1H, olefinic CH), 4.49 (s, 1H, CH_2OPh), 4.48 (s, 1H, CH_2OPh), 3.84 (s, 1.5H, $ArOCH_3$), 3.83 (s, 1.5H, $ArOCH_3$), 3.02-2.98 (m, 1H, C*H*CH_3), 2.27 (s, 3H, $ArCH_3$), 2.23-1.89 (m, 4H, alkyl CH_2), 1.46 (s, 1.5H, $ArCCH_3$), 1.44 (s, 1.5H, $ArCCH_3$), 1.28-1.26 (m, 3H, CCH_3), 1.25-1.23 (m, 3H, CCH_3), 1.11-1.06 ppm (m, 3H, CHC*H*$_3$).

^{13}C NMR δ (100 MHz, $CDCl_3$): 202.7, 202.6, 155.9, 138.8, 138.7, 134.9, 131.8, 131.4, 131.1, 128.2, 127.11, 127.05, 124.1, 123.5, 123.4, 123.3, 109.34, 109.30, 77.5, 63.4, 55.6, 40.8, 40.6, 40.4, 37.9, 37.2, 31.3, 23.8, 23.4, 22.7, 22.4, 16.0, 15.8, 10.7 ppm.
HRMS *m/z* (ESI) Calc. for $C_{29}H_{37}O_3$ (M^+ + H): 433.2737. Found: 433.2740.

Preparation of (E)-2-((S)-3-(benzyloxy)-2,3-dimethylbutylidene)-1-(but-3-yn-1-yl)-6-methoxy-1,5-dimethyl-1,2-dihydronaphthalene, ***173***



Scheme 150

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with **172** (80 mg, 0.19 mmol), potassium carbonate (51 mg, 0.37 mmol), and MeOH (15 ml). Ohira Bestmann reagent **162** (46 mg, 0.24 mmol) was added and the resulting solution stirred for 4 h at room temperature. After this time, the mixture was diluted with saturated sodium bicarbonate and the organic layer separated. The organic phase was washed with water, brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: 0-20% diethyl ether in petrol) to yield **173** (63 mg, 77% yield) as a colourless oil.

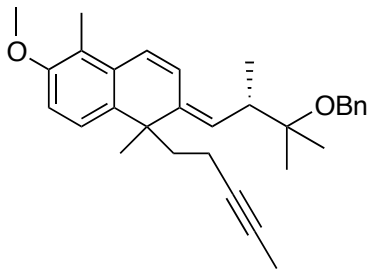
IR: 3306, 2364, 1466, 1263 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 7.40-7.17 (m, 6H, ArH and olefinic CH), 6.77-6.66 (m, 3H, ArH and olefinic CH), 5.64-5.60 (m, 1H, olefinic CH), 4.51 (s, 1H, CH_2OPh), 4.49 (s, 1H, CH_2OPh), 3.84 (s, 1.5H, $ArOCH_3$), 3.83 (s, 1.5H, $ArOCH_3$), 3.05-2.95 (1H, m, C*H*CH_3), 2.26 (s, 3H, $ArCH_3$), 2.18-2.08 (m, 1H, alkyl CH_2), 2.00-1.91 (m, 2H, alkyl CH_2), 1.88-1.84 (m, 1H, alkynyl CH), 1.82-1.71 (m, 1H, alkyl CH_2), 1.44 (s, 1.5H, $ArCCH_3$), 1.42 (s, 1.5H, $ArCCH_3$), 1.30 (s, 1.5H, CCH_3), 1.28 (s, 1.5H, CCH_3), 1.25 (s, 1.5H, CCH_3), 1.24 (s, 1.5H, CCH_3), 1.13 (d, *J* = 6.9 Hz, 1.5H, CHC*H*$_3$), 1.08 ppm (d, *J* = 6.9 Hz, 1.5H, CHC*H*$_3$).

^{13}C NMR δ (100 MHz, $CDCl_3$): 156.0, 140.0, 135.0, 131.9, 131.0, 128.23, 128.20, 127.2, 127.1, 127.0, 125.5, 124.0, 123.9, 123.34, 123.27, 122.3, 109.3, 77.2, 67.6, 63.5, 55.6, 44.8, 44.3, 42.4, 40.8, 40.5, 31.2, 30.7, 30.3, 23.9, 22.44, 22.40, 15.8, 14.6, 14.3, 10.7 ppm.

HRMS *m/z* (ESI) Calc. for $C_{30}H_{36}O_2Na$ (M^+ + Na): 451.2608. Found: 451.2603.

Preparation of (E)-2-((S)-3-(benzyloxy)-2,3-dimethylbutylidene)-6-methoxy-1,5-dimethyl-1-(pent-3-yn-1-yl)-1,2-dihydronaphthalene, ***3***



Scheme 151

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with alkyne **173** (22 mg, 0.05 mmol) and THF (5 ml) before cooling to -78˚C. ^{n}BuLi (0.05 ml, 1.6 M

in hexanes, 0.08 mmol) was added dropwise *via* syringe and the resulting solution stirred for 30 min at this temperature. After this time, methyl iodide (10 mg, 0.08 mmol) was added and the reaction mixture stirred for 30 min. The reaction mixture was warmed to room temperature and stirred for 1 h before being quenched with saturated ammonium chloride solution. The mixture was diluted with diethyl ether, the organic layer was separated and washed sequentially with water and brine. The organic phase was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: 0%-10% diethyl ether in petrol) to yield **3** (21 mg, 95% yield) as a colourless oil.

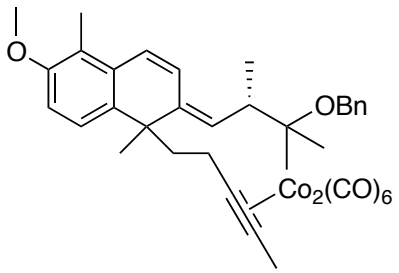
IR: 2964, 1464, 1261, 1103 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 7.41-7.18 (m, 6H, ArH and olefinic CH), 6.75-6.65 (m, 3H, ArH and olefinic CH), 5.63-5.59 (m, 1H, olefinic CH), 4.52 (s, 1H, CH_2OPh), 4.49 (s, 1H, CH_2OPh), 3.84 (s, 1.5H, $ArOCH_3$), 3.83 (s, 1.5H, $ArOCH_3$), 3.06-2.95 (m, 1H, C*H*CH_3), 2.26 (s, 3H, $ArCH_3$), 2.15-2.03 (m, 1H, alkyl CH_2), 1.96-1.83 (m, 2H, alkyl CH_2), 1.81-1.68 (m, 4H, alkyl CH_2 & alkynyl CH_3), 1.43 (s, 1.5H, $ArCCH_3$), 1.41 (s, 1.5H, $ArCCH_3$), 1.30 (s, 1.5H, CCH_3), 1.28 (s, 1.5H, CCH_3), 1.25 (s, 1.5H, CCH_3), 1.24 (s, 1.5H, CCH_3), 1.13 (d, J = 6.8 Hz, 1.5H, CHC*H*$_3$), 1.09 ppm (d, J = 6.8 Hz, 1.5H, CHC*H*$_3$).

^{13}C NMR δ (100 MHz, $CDCl_3$): 155.3, 139.5, 138.4, 138.0, 134.8, 134.7, 131.3, 130.5, 130.4, 127.72, 127.70, 126.7, 126.6, 126.5, 123.53, 123.47, 122.9, 122.8, 121.80, 121.77, 121.5, 121.4, 108.8, 79.3, 79.1, 74.4, 63.0, 62.9, 55.1, 44.8, 44.1, 41.9, 41.7, 40.2, 40.0, 30.6, 30.2, 29.8, 23.5, 23.4, 21.92, 21.88, 15.3, 14.4, 14.1, 10.2, 3.0 ppm.

HRMS *m/z* (ESI) Calc. for $C_{31}H_{42}O_2N$ ($M^+ + NH_4$): 460.3210. Found: 460.3215.

Preparation of (E)-2-((S)-3-(benzyloxy)-2,3-dimethylbutylidene)-6-methoxy-1,5-dimethyl-1-(pent-3-yn-1-yl)-1,2-dihydronaphthalene dicobalt hexacarbonyl, ***175***



Scheme 152

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with **3** (25 mg, 0.06 mmol) and petroleum ether (2 ml). Dicobalt octacarbonyl (24 mg, 0.07 mmol) was added and the resulting solution stirred for 2 h at room temperature. After this time, the solution was concentrated *in vacuo* and the crude product purified by column chromatography (eluent: 0-5% diethyl ether in petrol) to yield **175** (44 mg, 98% yield) as a dark red oil.

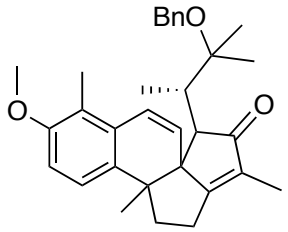
IR: 2044, 2008, 1456, 1263, 1101 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 7.39-7.18 (m, 6H, ArH and olefinic CH), 6.80-6.69 (m, 3H, ArH and olefinic CH), 5.69-5.60 (m, 1H, olefinic CH), 4.50 (s, 2H, CH_2OPh), 3.84 (s, 1.5H, $ArOCH_3$), 3.83 (s, 1.5H, $ArOCH_3$), 3.09-3.00 (m, 1H, C*H*CH_3), 2.57 (s, 1.5H, alkynyl CH_3), 2.54 (s, 1.5H, alkynyl CH_3), 2.41-2.01 (m, 7H, alkyl CH_2 & $ArCH_3$), 1.45 (s, 3H, $ArCCH_3$), 1.28 (s, 3H, CCH_3), 1.26 (s, 1.5H, CCH_3), 1.25 (s, 1.5H, CCH_3), 1.13-1.09 ppm (m, 3H, CHC*H*$_3$).

^{13}C NMR δ (100 MHz, $CDCl_3$): 200.2, 155.8, 140.0, 139.3, 138.9, 135.2, 135.1, 131.7, 131.0, 130.8, 128.2, 127.12, 127.08, 127.0, 123.8, 123.3, 123.2, 122.4, 109.5, 100.4, 93.8, 77.5, 63.4, 55.6, 46.5, 46.4, 42.3, 42.2, 40.7, 40.5, 33.7, 33.3, 29.1, 28.6, 24.2, 23.8, 22.3, 22.0, 20.3, 15.7, 15.6, 10.7 ppm.

HRMS *m/z* (ESI) Calc. for $C_{37}H_{39}Co_2O_8$ (M^+ + H): 729.1303. Found: 729.1302.

Attempted preparation of 5-((S)-3-(benzyloxy)-3-methylbutan-2-yl)-9-methoxy-3,8,11b-trimethyl-5,11b-dihydro-1H-pentaleno[1,6a-a]naphthalen-4(2H)-one, ***177***



General Procedure – Thermal Promotion

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with cobalt complex **175**, DodSMe, and 1,2-DCE. The reaction mixture was heated to reflux and stirred for the allotted time. Following this, the mixture was cooled to room temperature and concentrated *in vacuo*. The crude oil was subsequently analysed by TLC and ^{1}H NMR.

Following the *General Procedure*, data are reported as (a) amount of cobalt complex **175**, (b) amount of DodSMe, (c) amount of 1,2-DCE, (d) reaction time, and (e) reaction outcome.

Scheme 154, Table 1, Entry 1

(a) 35 mg, 0.05 mmol, (b) 35 mg, 0.16 mmol, (c) 3 ml, (d) 5 days, and (e) unreacted starting material and decomplexed alkyne.

Scheme 154, Table 1, Entry 2

(a) 35 mg, 0.05 mmol, (b) 65 mg, 0.30 mmol, (c) 3 ml, (d) 5 days, and (e) unreacted starting material and decomplexed alkyne.

General Procedure – Microwave Promotion

An oven-dried sealed tube was charged with cobalt complex **175**, DodSMe, and 1,2-DCE. The reaction mixture was subjected to microwave irradiation at the appropriate temperature and stirred for the allotted time. Following this, the mixture was cooled to room temperature and concentrated *in vacuo*. The crude oil was subsequently analysed by TLC and ^{1}H NMR.

Following the *General Procedure*, data are reported as (a) amount of cobalt complex **175**, (b) amount of DodSMe, (c) amount of 1,2-DCE, (d) reaction temperature, (e) reaction time, and (f) reaction outcome.

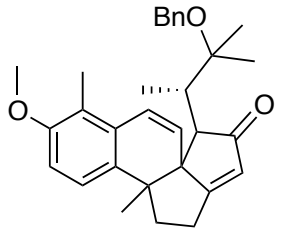
Scheme 154, Table 1, Entry 3

(a) 35 mg, 0.05 mmol, (b) 35 mg, 0.16 mmol, (c) 2 ml, (d) 90˚C (e) 10 min, and (f) unreacted starting material.

Scheme 154, Table 1, Entry 4

(a) 35 mg, 0.05 mmol, (b) 35 mg, 0.16 mmol, (c) 2 ml, (d) 150˚C, (e) 10 min, and (f) decomplexed alkyne.

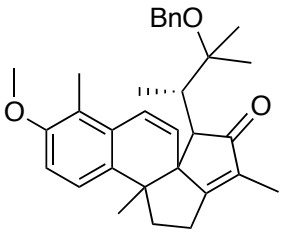
Attempted preparation of 5-((S)-3-(benzyloxy)-3-methylbutan-2-yl)-9-methoxy-8,11b-dimethyl-5,11b-dihydro-1H-pentaleno[1,6a-a]naphthalen-4(2H)-one, ***178***



Scheme 155

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with alkyne **173** (40 mg, 0.09 mmol), dicobalt octacarbonyl (34 mg, 0.10 mmol), DodSMe (69 mg, 0.32 mmol), and 1,2-DCE (3 ml). The reaction mixture was heated to reflux and stirred for 3 days. Following this, the mixture was cooled to room temperature and concentrated *in vacuo*. The crude oil was subsequently analysed by TLC and ^{1}H NMR, which indicated that the desired product had failed to form.

Attempted preparation of 5-((S)-3-(benzyloxy)-3-methylbutan-2-yl)-9-methoxy-3,8,11b-trimethyl-5,11b-dihydro-1H-pentaleno[1,6a-a]naphthalen-4(2H)-one, ***177***



Scheme 156

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with cobalt complex **175** (35 mg, 0.05 mmol), NMO (9 mg, 0.07 mmol), and DCM (3 ml). The reaction mixture was stirred for 48 h prior to analysis by TLC and ^{1}H NMR. Unfortunately, the desired product failed to form and an appreciable quantity of decomplexed starting material, **3**, was observed.

Scheme 158

Catalyst activation:

An oven-dried sealed tube was charged with $[RhCl(CO)PPh_3)_2]$ (4 mg, 0.056 mmol), $AgSbF_6$ (20 mg 0.058 mmol), and 1,2-DCE (5.6 ml). CO gas was bubbled through the suspension before the mixture was stirred for 15 min under an atmosphere of CO (1 atm.). This provided a 0.01 M solution of the active catalyst.

General Procedure

An oven-dried sealed tube was charged with alkyne **3** and 1,2-DCE (0.11 M) and stirred under a CO atmosphere for 5 min. Following this a solution of the catalyst was added in one portion and the resulting mixture stirred at room temperature under a CO atmosphere (1 atm.) for 16 h. After this time, the mixture was filtered through a pad of silica (eluent: EtOAc) and concentrated *in vacuo*. The crude residue was analysed by TLC and ^{1}H NMR.

Following the *General Procedure*, data are reported as (a) amount of alkyne **3**, (b) amount of 1,2-DCE, (c) amount of catalyst solution, and (d) reaction outcome.

Table 2, Entry 1

(a) 40 mg, 0.09 mmol, (b) 0.8 ml, (c) 0.23 ml, 2.5 mol%, and (d) unreacted starting material.

Table 2, Entry 2

(a) 40 mg, 0.09 mmol, (b) 0.8 ml, (c) 0.45 ml, 5 mol%, and (d) unreacted starting material.

General Procedure

A flame dried, and nitrogen cooled, 25 ml round bottom flask was charged with alkyne **3** and 1,2-DCE (0.11 M) and stirred under a CO atmosphere for 5 min. Following this, a solution of the catalyst was added in one portion and the resulting mixture stirred at the specified temperature under a CO atmosphere (1 atm.) for the allotted time. After this time, the mixture was filtered through a pad of silica (eluent: EtOAc) and concentrated *in vacuo*. The crude residue was analysed by TLC and ^{1}H NMR.

Following the *General Procedure*, data are reported as (a) amount of alkyne **3**, (b) amount of 1,2-DCE, (c) amount of catalyst solution, (d) reaction temperature, (e) reaction time, and (f) reaction outcome.

Table 2, Entry 3

(a) 40 mg, 0.09 mmol, (b) 0.8 ml, (c) 0.23 ml, 2.5 mol%, (d) 40˚C (e) 16 h, and (f) desired product not obtained; complex mixture of products observed.

Table 2, Entry 4

(a) 40 mg, 0.09 mmol, (b) 0.8 ml, (c) 0.45 ml, 5 mol% (d) 40˚C, (e) 16 h, and (f) desired product not obtained; complex mixture of products observed.

Scheme 160

(a) 40 mg, 0.09 mmol, (b) 0.8 ml, (c) 0.45 ml, 5 mol% (d) 80˚C, (e) 6 h, and (f) desired product not obtained; complex mixture of products observed.

7 References

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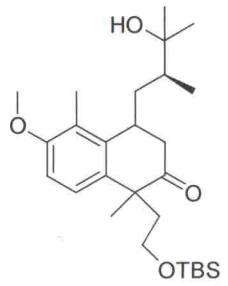
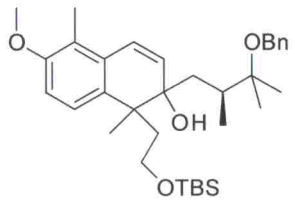
Appendix

Data for Compound 125



Data for Compound 114



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7.362
6.982
6.961
6.654
6.633
6.572
6.546
6.043
6.018
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4.536
4.493
4.465
3.823
3.454
3.197
3.184
2.194
1.970
1.962
1.950
1.936
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1.252
1.076
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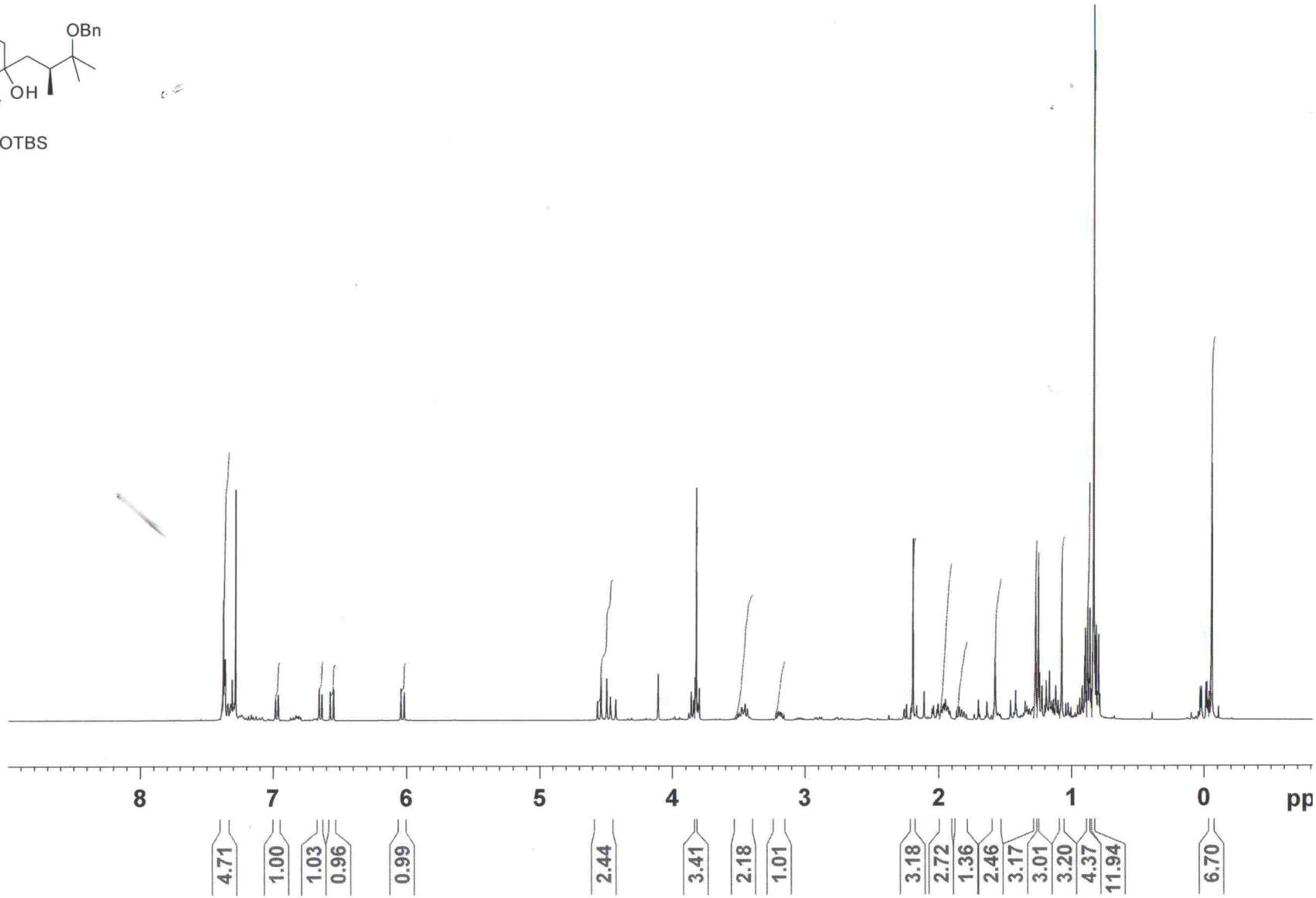
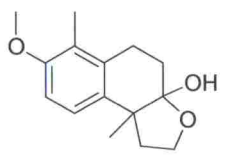
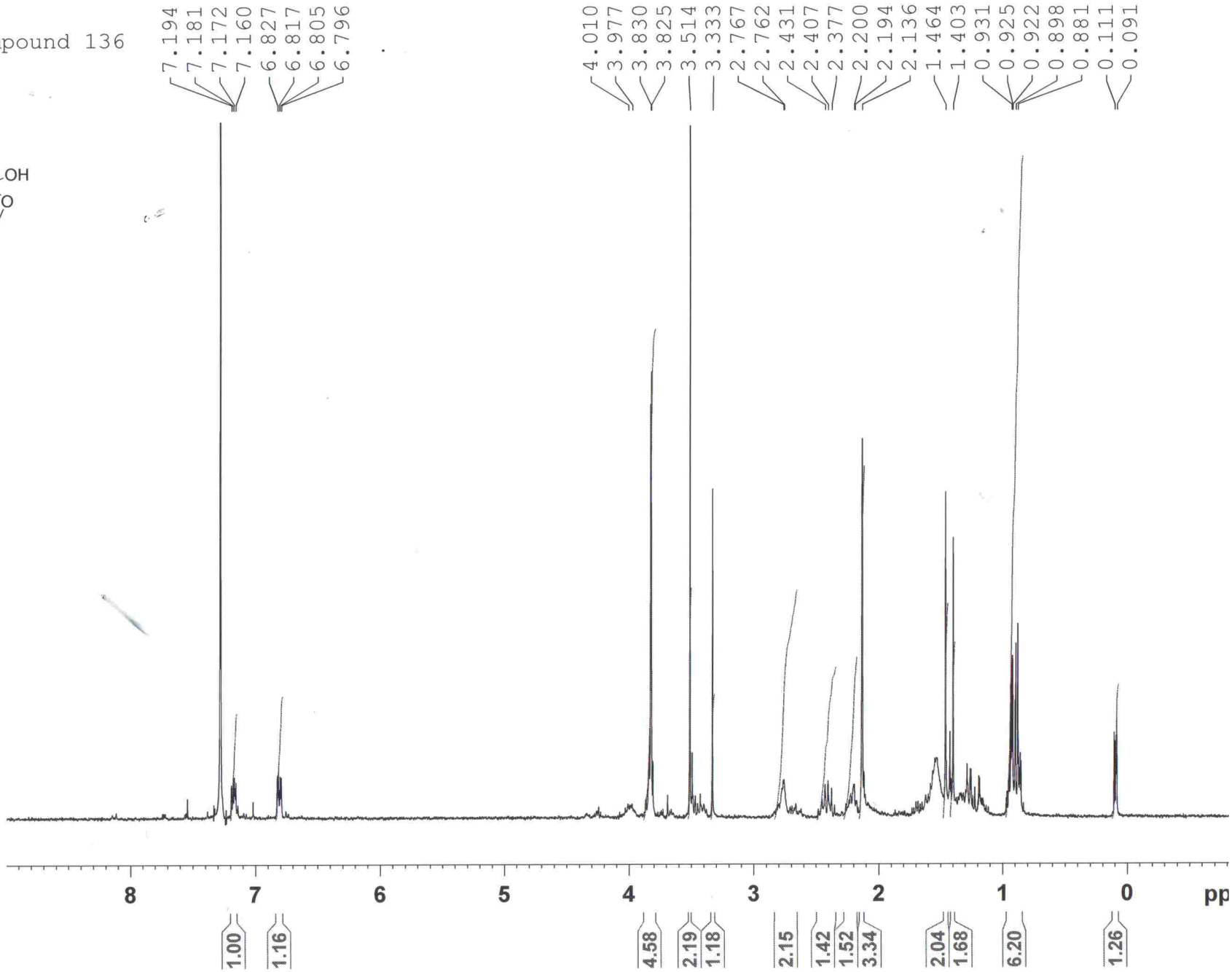
-0.056



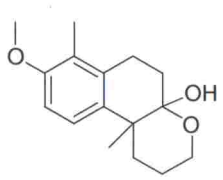
Data for Compound 136

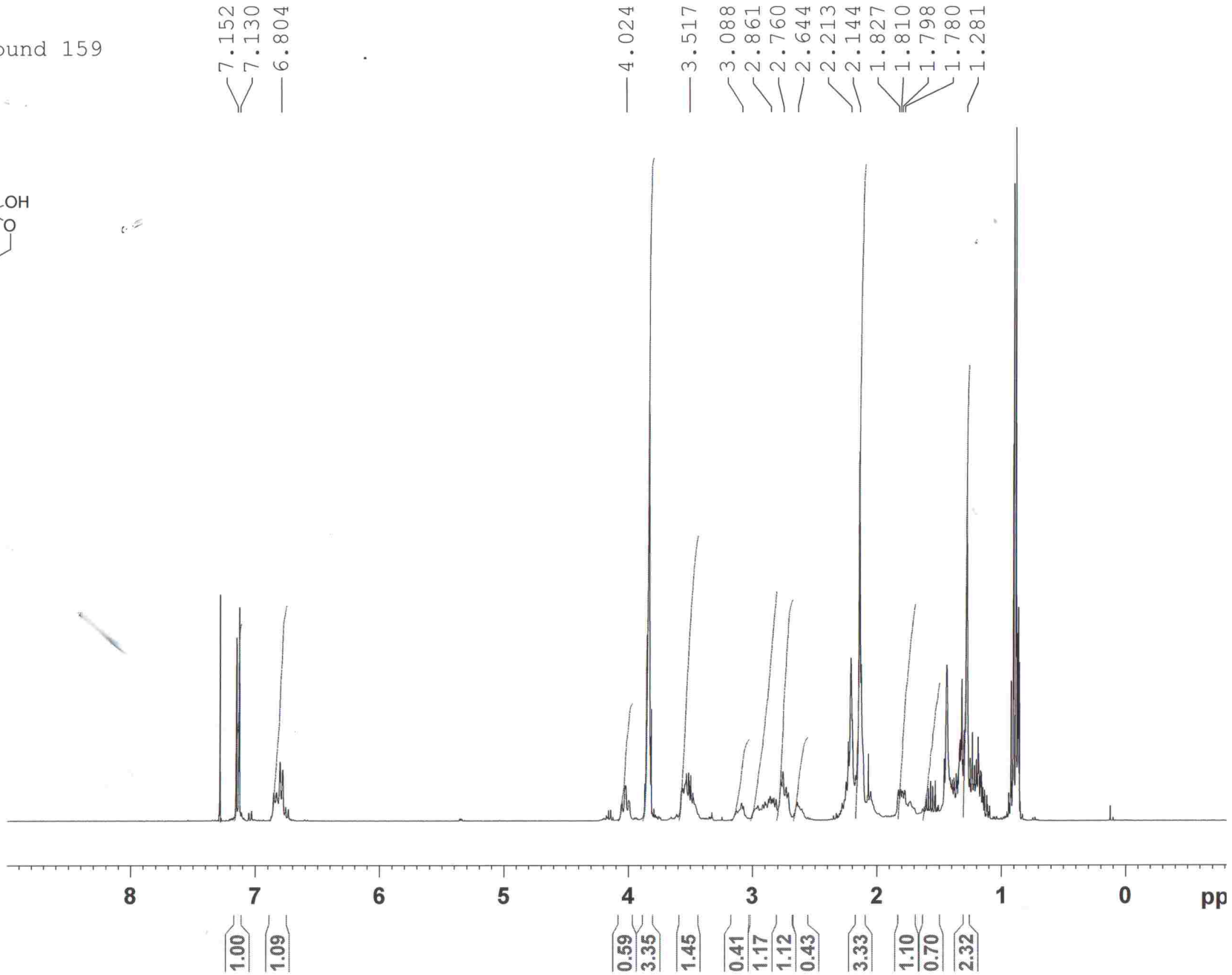




Data for Compound 140

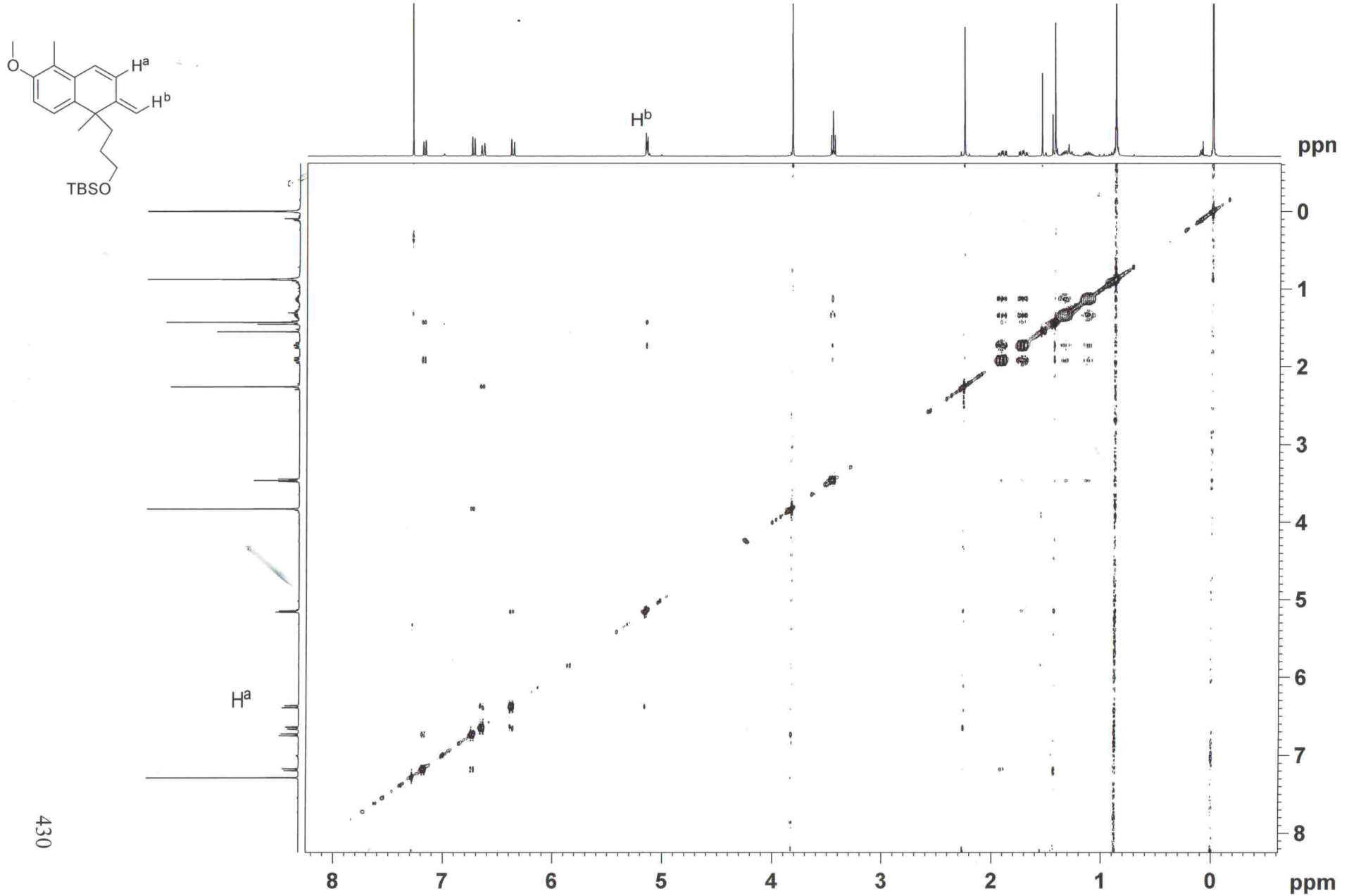
Data for Compound 159





Data for Compound 163

NOESY Analysis for Compound 170



NOESY Analysis for Compound 169