Novel routes to and reactions of cyclopropanes

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Abstract

An array of different cyclopropanes have been synthesised, including the structurally simple 1-phenylcyclopropanol. These were synthesised in yields upwards of 60%, using the well published Kulinkovich reaction. From 1-phenylcyclopropanol, variations of the cyclopropane core structure were synthesised, creating species ideal for palladium cross coupling reactions, such as 1-phenylcyclopropyl methanesulfonate and 1-phenylcyclopropyl 4-methylbenzenesulfonate. These were formed in 50 and 60% yield respectively. Once obtained these cyclopropanes were used to perform Suzuki cross coupling reactions towards the formation of 1,1-diphenyl cyclopropane. Unfortunately, despite various attempts, the palladium cross coupling reactions were unsuccessful. The work did facilitate the discovery of a novel methodology for the synthesis of tetra substituted alkenes.

Using similar methodology as that developed for the formation of 1-phenylcyclopropanol, a McMurry reaction was able to be performed on a number of different ketones. This reaction formed a wide array of different tetra-substituted alkenes with yields ranging from 20-99%, depending on the nature of the starting material. The method, involving the use of 9 equivalents of Grignard reagent and stoichiometric amounts of titanium isopropoxide, is a unique way of making low valent titanium in situ, as well as being homogeneous.

Methodology for the formation of vinyl cyclopropanes containing an amide moiety has been developed, allowing a variety of different amines to be coupled to two different cyclopropanes. Once these species were synthesised, a palladium catalysed cyclisation, Heck reaction, carbonylation cascade was developed. This allowed the core cyclic structure of the stemona alkaloids to be obtained in a single reaction vessel with good yields of up to 52% depending on the amine used.

The cascade was then applied to a fully substituted cyclic natural product core. However, the cascade reaction was unsuccessful. Efforts to alter the structure of the starting material, to remove the potentially hindering bromine, provided no improvement.

It was established that the tetrakis(triphenylphosphine) palladium (0) catalyst used was too encumbered for insertion in to the sterically hindered starting material, which is likely to be causing the failure of the reaction.
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Abbreviations

NMR - Nuclear Magnetic Resonance
Q – Quaternary carbon centre
d- Doublet splitting pattern
t- Triplet splitting pattern
q- Quartet splitting pattern
LCMS - Liquid Chromatography-Mass Spectrometry
MS - Mass Spectrometry
m.p. - melting point
b.p. - boiling point
TLC - Thin Layer Chromatography
DCM - Dichloromethane
DMF - Dimethylformamide
DMPU - 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO - Dimethylsulphoxide
EtOAc - Ethyl Acetate
EtOH - Ethanol
hex. - Hexane (mixture of isomers)
MeCN - Acetonitrile
MeOH - Methanol
NMP - 1-Methyl-2-pyrrolidinone
iPrOH - Isopropanol (Propan-2-ol)
THF – Tetrahydrofuran
DIPEA - Diisopropylethylamine (Hünigs base)
DMAP - 4-(Dimethylamino)pyridine
HATU - O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HBTU - O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate
T3P - Propylphosphonic anhydride solution
TBSCI - tert-Butyldimethylsilyl chloride
TBME - tert-Butyl methyl ether
TEA - Triethylamine
TFA - Trifluoroacetic acid
TFAA - Trifluoroacetic anhydride
TPE - Tetraphenylethene
DBU - 1,8-Diazabicycloundec-7-ene
TBAC - tert-butylammonium chloride
DPPE - 1,2-Bis(diphenylphosphino)ethane
BEMP - 2-tert-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
XPhos - 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
CM-Phos - 2-[2-(Dicyclohexylphosphino)phenyl]-1-methyl-1H-indole
RT – retention time
equiv. - equivalents
rt - room temperature
ppt. - precipitate
sat. - saturated
soln. - solution
temp. - temperature
General Introduction
The cyclopropane ring

The various aspects of cyclopropane chemistry and their derivatives continue to fascinate chemists from a broad range of disciplines. There are numerous challenges posed by the cyclic arrangement of three tetravalent carbons, ranging from the synthesis of highly strained molecules, to gaining an understanding of the mode of action of biologically active cyclopropyl derivatives.¹

Due to its unique electronic, conformational, and steric properties the cyclopropyl group is of great interest in medicinal chemistry, mainly due to its presence in a lot of natural products and biologically active synthetic compounds.² Arylcyclopropanes (also known as cyclopropylarenes) refer to compounds where an aryl group is directly bound to the cyclopropyl group. In these compounds the cyclopropyl ring acts as an electron donor group thus activating the phenyl ring. This behaviour is explained by the fact the molecular orbitals of a cyclopropyl group can enter into conjugation with adjacent p-orbitals or π systems.²

Figure 1: The Coulson-Moffitt model.³

The formation of a cyclopropane ring requires three CH₂ groups to form a 3-membered ring where all angles equal 60°, which is much lower than the usual 109.5° found in sp³ hybridised carbons, resulting in Bayer (angular) strain. Cyclopropane also has a high torsional strain due to the hydrogens being eclipsed within the structure. When this strain is relieved the energy released can be utilised as a potent thermodynamic driving force for various processes.³ The chemistry of the single carbon-carbon bond in a cyclopropane resembles that of a normal carbon-carbon double bond, and the cyclopropane ring forms electronic interactions with electron donor and acceptor substituents leading to asymmetry of the C-C bond lengths of the ring.⁴
Bonding in a cyclopropane is often described via the Coulson and Moffitt model, whereby the construction of the ring is thought of as three sp$^3$ hybridised CH$_2$ groups (Figure 1). This suggests the sp$^3$ hybrids point approximately 22° outward from the imaginary line connecting the nuclei, resulting in less overlap of the wave functions of pairs of electrons, and hence they are referred to as ‘bent’ bonds. The reduced overlap is considered to be the source of the angular strain. The greater p-character in the carbon-carbon σ-bonds of cyclopropane is often used to explain the similarity of the cyclopropane chemistry to that of alkenes.

Bonding can also be described using the Walsh model, which predicts that the ring is constructed from three sp$^2$ hybridised CH$_2$ groups. These groups are described in this model as pointing towards the centre of the cyclopropane ring (Figure 2) and angular strain is, as with the Coulson Moffitt model, attributed to poor overlap of orbitals.

Figure 2: The Walsh Model.

Classic approaches to organic chemistry consider σ bonds as localised entities, however this is often lacking as described by Dewar in 1989. Some of the chemical and physical properties of cyclopropanes can be explained by the concept of ‘σ-conjugation’; the three carbon-carbon σ-bonds form a cyclic array of 6 electrons, which following the 4n+2 rule, which means cyclopropane is aromatic. When invoked σ-aromaticity explains properties of cyclopropanes, which were previously thought anomalous, such as their reactivity towards electrophiles.
This high reactivity is often explained due to the relief of strain, but the conventional strain energy of cyclopropane is 27.5kcal mol\(^{-1}\), which is essentially the same as that of cyclobutane at 26.5kcal mol\(^{-1}\). According to a publication by Dewar \textit{et al.} in 1984, this small difference can be better understood on the basis of σ-aromaticity. As an example the group refer to the reaction of cyclopropane with an electrophile (Scheme 1).\(^7\) In this example aromaticity is maintained in the transition state (shown as a methyl cation/ethylene π-complex), thus meaning that the cyclopropyl group remains almost intact in the transition state, which accounts for its reactivity.\(^7\) If it were the ring strain which caused the reactivity the transition state would contain a substantially broken cyclopropane ring.\(^7\)

![Scheme 1: Reactivity of cyclopropane and electrophiles.\(^7\)](image)

However, a more recent publication by Wu \textit{et al.} detailed computational calculations regarding the σ-aromaticity found in a cyclopropane.\(^8\) The group found that the extra stabilisation energy is at most 3.5kcal mol\(^{-1}\), which they state is too small to explain the small difference in strain energies between cyclopropane and cyclobutane. Therefore there is no need to invoke σ aromaticity for cyclopropane energetically.\(^8\) This difference in opinion highlights the complex, and unique nature of the cyclopropane ring.\(^8\)

The introduction of aryl scaffolds to compounds of medicinal interest allows the exploration of lipophilic binding pockets, which can improve the metabolic stability of the scaffold when compared to that provided by linear alkyl groups. This results in a superior pharmacokinetic profile, as well as allowing the optimisation of hydrophobic interactions with a biological target.\(^9\) Cyclopropanes can also be used to ‘lock’ a molecule in its bioactive conformation, therefore creating a potential increase in potency.\(^2\)
Uses of cyclopropanes and their derivatives

Within the literature there are a vast number of reactions whereby the ring opening of a cyclopropane is utilised, as well as the rearrangement to other molecules such as cyclobutanes or cyclopentanes.

The cyclopropane group finds use in a wide number of areas in chemistry because of its unique properties, and because it can be used as a simple building block or scaffold for more complex molecules, such as those found in nature.

In medicinal chemistry the small cyclopropane group is often utilised in structure activity relationship (SAR) studies, because of the ability of the cyclopropane to lock a molecule in its bioactive conformation, thus enhancing potency.

An example of this is work published by Shiozaki who reported the formation of compound 1 as a potent ADAMTS-5 (A disintegrin and metalloprotease with thrombospondin motifs) inhibitor, which saw an important increase in potency once a cyclopropyl linker was introduced into the structure ([2] Scheme 2).\textsuperscript{10}

\begin{center}
\textbf{Scheme 2: Insertion of a cyclopropane into a medicinally active molecule.}\textsuperscript{10}
\end{center}

The increase in activity was attributed to the increased rigidity caused by the cyclopropane, which positions the pharmacophores in the optimal binding conformation.\textsuperscript{10}
The cyclopropane skeleton is also found in nature. For example, it has been found as part of a defence mechanism for certain pyrethrum flowers against insect attack. The molecule \((+)-\text{trans}-\text{chrysanthemic acid}\) (Figure 3) was isolated from the petals of these plants.\(^1\)

![Figure 3: \((+)-\text{trans}-\text{Chrysanthemic acid}\).\(^1\)](image)

The active ingredients in the plants are actually esters of \((+)-\text{trans}-\text{chrysanthemic acid}\), which can be easily modified and have been exploited commercially, giving rise to one of the most successful biomimetic insecticides, the pyrethroids with commercial products such as permethrin (Figure 4).\(^{11}\) This is a class of insecticides which has a market value of over 1.5 billion US dollars.\(^1\)

![Figure 4: Structure of Permethrin.\(^{11}\)](image)
Derivatives of chrysanthemic acid are not the only example of structures containing a cyclopropane in nature. It occurs in every green plant in the form of 1-aminocyclopropanecarboxylic acid (ACC) (Figure 5), which is a precursor to the plant hormone ethene. The cyclopropane group is also found in a number of other natural products including various cyclopropanated fatty acids and terpenes.\textsuperscript{1}

\begin{center}
\includegraphics[width=0.5\textwidth]{Figure5.png}
\end{center}
\textit{Figure 5: 1-Aminocyclopropanecarboxylic acid.}\textsuperscript{1}

Formation of amino acids containing the cyclopropane molecule are also of great interest, especially α-2,3-methanoamino acids because of their rigid conformation.\textsuperscript{12} Presence of a strained cyclopropane in an amino acid based drug molecule is thought to lead to new interactions with an enzyme active site (or receptor) therefore making it biologically active. The α-2,3-methanoamino acids are among the most common analogues of naturally occurring amino acids such as 2,3-methano-m-tyrosine (Figure 6).\textsuperscript{12}

\begin{center}
\includegraphics[width=0.5\textwidth]{Figure6.png}
\end{center}
\textit{Figure 6: (+)-(E)-2,3-Methano-m-tyrosine, (1R,2S)}\textsuperscript{12}

The above 1R 2S enantiomer is the most potent competitive inhibitor of DDC (L-aromatic amino acid decarboxylase) and thus finds a critical role in the biosynthesis of important neurotransmitters, such as serotonin.\textsuperscript{12}
Chapter 1

Novel approaches to 1,1-diaryl cyclopropanes from readily available carbonyl compounds
Introduction

There are a large number of reactions published in the literature regarding the formation of cyclopropanes and their derivatives as outlined in the general introduction of this thesis. The relevant method to the first part of this thesis, is the Kulinkovich reaction first published in 1989, which describes the use of a Grignard reagent and titanium isopropoxide to form phenyl cyclopropanol from simple esters such as methyl benzoate. Initial publications stated that 3 equivalents of Grignard reagent were needed to be reacted with stoichiometric amounts of titanium isopropoxide at -78°C to obtain the desired cyclopropane product (Scheme 3).

\[ \begin{align*}
R^1\text{CO}_2\text{R}^2 & \overset{\text{EtMgBr (3 equiv.)}}{\underset{\text{Ti(O'Pr)}_4 (1 equiv.)}{\xrightarrow{\text{Et}_2\text{O}, -78^\circ\text{C}, 1hr}}}
R^1\text{OH} \\
& \text{(7)}
\end{align*} \]

Scheme 3: The original Kulinkovich reaction conditions.

However later publications by Kulinkovich showed that it could also be achieved using just two equivalents at room temperature with a catalytic amount of titanium isopropoxide (Scheme 4).

\[ \begin{align*}
\text{PhCO}_2\text{OMe} & \overset{\text{EtMgBr (2 equiv.)}}{\underset{\text{Ti(O'Pr)}_4 (10\text{mol})}{\xrightarrow{\text{Et}_2\text{O}, \text{rt}}}}
\text{PhOH} \\
& \text{(8)}
\end{align*} \]

Scheme 4: Modified Kulinkovich reaction conditions

These reactions are thought to proceed through a catalytic cycle (Scheme 5) in which the titanium species dialkoxytitanacyclop propane and dialkoxy-(\(\eta^2\)-alkene)titanium complexes (10) Scheme 5) are considered to be the limiting species.
A number of variations on this reaction have been investigated, for example Cha studied the reaction using methyl cyclohexanecarboxylate and ethylmagnesium chloride in the presence of a number of titanium species, finding that this transformation is not particularly sensitive to the reagents used, with yields up to 93% when Ti[O(p-OMe)-C₆H₄]₄ is used.
The Kulinkovich reaction has been further investigated by Eisch \(^{18}\) who investigated the transfer-epititanation of the alkene whereby \(\pi\)-coordination of the ligand to titanium forms an octahedral transition state ((19) Scheme 7) and the importance of this on the formation of the key titanacyclopropane intermediate ((17) Scheme 6). They report that in the first ‘prototypical’ reaction performed by Kulinkovich (Scheme 3), it was thought that thermal decomposition of diethyltitanium(IV) diisopropoxide ((15) Scheme 6) generates the titanacyclopropane intermediate ((17) Scheme 6).

\[
\text{Ti(O'Pr)}_4 \xrightarrow{2 \text{EtMgBr}} \text{Et}_2\text{Ti(O'Pr)}_2 \xrightarrow{-2 \text{MgBr(O'Pr)}} \text{[Ti(O'Pr)_2]} + \text{H}_3\text{C}==\text{CH}_2 \xrightarrow{\text{H}_2\text{C}==\text{CH}_2} \text{Path a} \\
-\text{H}_3\text{C}==\text{CH}_3 \xrightarrow{\text{Path b}} \text{[(PrO)Ti]} \xrightarrow{\text{Ti(O'Pr)}}
\]

Scheme 6: Formation of the key titanacycle.\(^ {18}\)

However, if an ethereal solution of the titanium intermediate (15) is formed at -78°C, without the presence of any ester, and then brought to room temperature; the group found the solution turned black, which they report as the formation of (16). When they attempted to introduce an ester to this solution they found, after hydrolysis, that they could not detect any of the cyclopropanol (8). The group therefore concluded that the intermediate (17) is only stable for cyclopropanol synthesis at low temperatures.\(^ {18}\)
Eisch also examined the mode of ring formation within the Kulinkovich reaction.\textsuperscript{18} To do this they treated (\textit{i}Pr\textsubscript{2})\textsubscript{2}Ti(O\textit{i}Pr\textsubscript{2})\textsubscript{2} (18) with ethylene gas at -78°C, which after subsequent workup gave 1-phenylcyclopropanol (8). Then in a parallel experiment they treated Et\textsubscript{2}Ti(O\textit{i}Pr\textsubscript{2}) with propylene gas under the same conditions, however this resulted in 20% less yield of the desired cyclopropanol.\textsuperscript{18}

\[
\begin{align*}
\text{(18)} & \quad \text{H}_2\text{C}═\text{CH}_2 \\
\text{(19)} & \quad \text{methyl benzoate} \\
\text{(8)} & \quad \text{Ph} \quad \text{OH}
\end{align*}
\]

Scheme 7: Formation of cyclopropanol through ethylene transfer-epimettallation.\textsuperscript{18}

Therefore they concluded that ethylene is able to undergo transfer-epimettallation with (18) \textit{via} the transition state (19) shown in Scheme 7, and for steric reasons operative in the octahedral transition state propylene is unable to undergo a similar transfer-epimettallation. This supports their proposal that the Kulinkovich reaction is initiated by the presence of free ethylene necessary for initial transfer epimettallation. Thereafter, the ethylene by-product formed in Scheme 3 perpetuates the reaction.\textsuperscript{18}

The stereochemical outcome of cyclopropanation reactions has been investigated by Casey \textit{et al.} who hypothesised that the reaction occurs via a ‘w-shaped’ transition state.\textsuperscript{19} The group initially studied a cyclopropanation reaction originally reported by Gandon and Szymoniak, which occurs via hydrozirconation of allylic ethers followed by addition of a lewis acid (Figure 7).\textsuperscript{20}

\[
\begin{align*}
\text{\textit{R}_1\text{OR}_3} & \quad \text{1.}\text{C}_{\text{p}_2}\text{Zr(H)Cl} \\
\text{\textit{R}_1\text{R}_2\text{R}_3} & \quad \text{2.}\text{BF}_3\text{OEt}_2
\end{align*}
\]

Figure 7: Cyclopropanation reaction reported by Gandon and Szymoniak.\textsuperscript{20}
Casey et al reported that the backside of the carbon-zirconium bond attacks the backside of the carbon oxygen bond of the lewis acid co-ordinated ether (Figure 8), thus producing a cyclopropane with inverted configuration at the zirconium-carbon bond.\textsuperscript{19}

![Figure 8: Proposed transition state and mechanism for cyclopropane formation.\textsuperscript{19}](image)

This was proven through deuterium studies, whereby a number of hypothesised transition states were investigated. If, as predicted, the reaction proceeds via a ‘W-shaped’ transiton state, exclusive formation of \textit{cis} deuteriums in the product would be observed in the $^1$H NMR spectra. However, if another transition state were involved (Figure 9) \textit{trans} deuterium would be observed.\textsuperscript{19}

![Figure 9: Other possible transition states and their stereochemical outcomes.\textsuperscript{19}](image)

Upon investigating the $^1$H NMR spectra from the reaction the group found a mixture of 5:1 \textit{cis} deuterium products and only 3\% \textit{trans} (Figure 10), which they note is consistent with a W-shaped transiton state because the \textit{cis} formation requires inversion of configuration at the carbon bound to zirconium.\textsuperscript{19}

![Figure 10: Stereochemical outcome of deuterium studies.\textsuperscript{19}](image)
The group then went on to investigate the Kulinkovich hydroxycyclopropanation, to ascertain whether it proceeds with the same inversion at the carbon-titanium bond via a W-shaped transition state. The group proposed 3 pathways for ring closure; firstly by the backside of the carbon-titanium bond attacking the ketone carbonyl via a W-shaped transition structure, which involves inversion of configuration (pathway A Figure 11). Secondly via chelation of the ketone carbonyl to titanium, followed by front side attack of the carbon-titanium bond on the coordinated carbonyl to effect ring closure with retention of configuration (Pathway B Figure 11). Finally via the formation of an alkoxy bridged species, with one titanium acting as a Lewis acid to activate the carbonyl, and the other acting as a nucleophilic alkyl, again retaining configuration (Pathway C Figure 11).¹⁹

Figure 11: Potential pathways for Kulinkovich reaction ring closure.¹⁹
Upon investigating the $^1$H NMR spectra it was established only trans-3-deutero-1-methyl-cis-2-phenyl-1-cyclopropanol was being formed, indicating retention of configuration at the carbon bound to titanium, thus precluding a W-shaped transition state. For this to occur a ring closure involving front side attack by the carbon-titanium bond, facilitated by coordination to the same or second titanium must be observed (Figure 12).\(^{19}\)

![Figure 12: Transition states required for the Kulinkovich cyclopropanation.\(^{19}\)](image-url)
Current methods of cyclopropane preparation

There are various methods for the formation of cyclopropanes reported within the literature\textsuperscript{21,22} including the Simmons-Smith cyclopropanation reaction first reported in 1959.\textsuperscript{23} This reaction is still one of the most powerful methods for the stereospecific formation of cyclopropanes,\textsuperscript{24} and is often used for the cyclopropanation of alkenes via zinc carbene addition (Scheme 8).\textsuperscript{25} A variation modified by Furukawa involving the use of diethyl zinc and diiodo zinc is often employed because it works over a wider range of temperatures and in a larger variety of solvents, and producing improved yields.\textsuperscript{26}

\begin{equation}
\text{R}_1 \text{CH=CH}_2 + \text{Zn/Cu} + \text{CH}_2\text{I}_2 \rightarrow \text{R}_1\text{R}_2\text{C}_3 \quad \text{"I}_{\text{ZnCH}_2\text{I}"} \text{ carbene} \rightarrow \text{R}_1\text{R}_2\text{C}_3 + \text{ZnI}_2
\end{equation}

Scheme 8: Simmons-Smith cyclopropanation.\textsuperscript{25}

The latter modifications have proven to be more effective due to the use of readily reactive organometallic reagents such as diethyl zinc, instead of metallic zinc, therefore allowing the zinc carbene generation step with diiodomethane to occur more efficiently.\textsuperscript{25}

Another method involves the use of transition metals, such as ruthenium, as catalysts to perform a carbene transfer from aliphatic diazo compounds (Scheme 9).\textsuperscript{27} Stereocontrolled and highly selective syntheses of functionalised cyclopropanes are achieved with catalysts based on, in particular, copper and rhodium.\textsuperscript{28}
Ruthenium complexes are also finding use in this area, and are becoming more favourable due to a much lower cost of the catalyst, as well as a greater diversity of complexes created by a large number of oxidation states.\textsuperscript{27}

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme9.png}
\end{center}

\textit{Scheme 9: Catalytic cycle of carbenoid cyclopropane synthesis.}\textsuperscript{37}

A third method for cyclopropane synthesis is known as the Corey-Chaykovsky cyclopropanation (Scheme 10).\textsuperscript{29} This is a class of Michael-initiated ring closure reactions involving the reaction of a dimethylsulfoxonium methyliode (Corey’s reagent) with $\alpha,\beta$-unsaturated ketones to give cyclopropyl ketones\textsuperscript{30} or with $\alpha,\beta$-unsaturated nitriles to give the corresponding cyclopropynitriles\textsuperscript{31} in excellent yields. Dimethylsulfoxonium methyliode, or “the Corey ylide,” has proven to be very useful in the synthesis of a wide variety of functional groups since first being discovered in 1962.\textsuperscript{32} These include cyclopropanes, epoxides, and aziridines, and is one of the most straightforward and often cited cyclopropanation reactions.\textsuperscript{30}

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme10.png}
\end{center}

\textit{Scheme 10: General conditions for the Corey-Chaykovsky cyclopropanation.}\textsuperscript{29}

A fourth method known as the Kulinkovich reaction\textsuperscript{13} is also well reported in the literature and will be further discussed later in this chapter.
The synthesis of 1,1-diphenyl cyclopropane is published within the literature, but the reactions tend to be multi-step syntheses which can be tedious and overall yields can be low, and a number of which involve steps using non-standard conditions e.g. low temperatures.

This therefore highlights the importance of the research being outlined in this chapter; if a short, relatively simple synthesis can be optimised a number of reactions can be made much simpler and more efficient due to the reduced number of chemicals required and time for each of the steps involved.

A good example of a synthesis related to the formation of 1,1-diphenylcyclopropane is that of 1,1-diphenylcyclopropene, which was published in 2003 by Huang who reported the synthesis of the related compound 3,3-diphenylcyclopropene 23 (Scheme 11).³³

![Scheme 11: Huang's synthesis of 3,3-diphenylcyclopropene.³³](image-url)
The Huang synthesis involves synthesising 1,1-dibromo-2,2-diphenylcyclopropane (21) in a 3 step process starting from 1,1-diphenylethylene. This is then reduced to 1-bromo-2,2-diphenylcyclopropane (22) through the use of tri-n-butyltin hydride. Finally the product is synthesised by reaction with DMSO and potassium t-butoxide.

Further examples in the literature toward diaryl cyclopropane synthesis involve using α,β unsaturated ketones, such as those reported by Gandon et. al. whereby carbonyl compounds were converted to cyclopropanes using Cp₂Zr(ethylene) and TiCl₄ as a Lewis acid (Scheme 12).

This group also found that using their method, total chemoselectivity in favour of the more reactive functionality was possible (Scheme 13), allowing the formation of a wide array of cyclopropanes in the presence of several functional groups.

\[ \text{Scheme 12: Conditions for cyclopropanation of ketones.} \]

\[ \text{Scheme 13: Chemoselective cyclopropanation.} \]
Another related reaction published by Masalov shows the cyclopropanation of vinylogous esters, which again relies on the formation of the key intermediate dialkoxytitanacyclop propane \((10)\) Scheme 5) \textit{in situ}.\textsuperscript{35}

Masalov \textit{et al.} report that it is possible to use Kulinkovich conditions to successfully cyclopropane a number of vinylogous esters such as 3-methoxy-2-cyclohexen-1-one \((28)\) to give the corresponding cyclopropane products \((29)\) Scheme 14).\textsuperscript{35}

\[
\begin{array}{c}
\text{Scheme 14: Use of Kulinkovich conditions to form cyclopropane derivatives.}^{35}
\end{array}
\]

Masalov also reports that in some cases to induce ring closure a Lewis acid is required because it weakens the titanium-oxygen bond in the titanacyclic intermediate allowing it to cyclise (Scheme 15).

\[
\begin{array}{c}
\text{Scheme 15: Mechanism of Lewis acid facilitated ring closure.}^{35}
\end{array}
\]
The mechanism they propose involves the addition of the Lewis acid to the vinylogous ester of the postulated dialkoxytitanacyclopropane intermediate to give 30. Subsequent rearrangement of this species then involves delocalisation of the oxonium ion (31), formation of which is facilitated by an electrophilic titanate, then followed by ring closure.35

This work prompted the theory that Lewis acid facilitated ring closure could be utilised for the research outlined in chapter one of this thesis, by simply changing the starting material to that required to make the desired cyclopropanes from diaryl ketones.
**Cross coupling reactions**

Another method of formation of diaryl cyclopropanes involves the introduction of a second aromatic ring through the use of coupling reactions, utilising metals such as palladium. This form of coupling allows the introduction of a phenyl ring in to a number of systems including cyclopropanes.

The Suzuki-Miyaura reaction has a number of advantages in that it can tolerate a wide range of functional groups, and is largely unaffected by the presence of water within a reaction. The mild reaction conditions required, and the relative ease of removal of inorganic, non-toxic, by-products makes these reactions ideal for mass scale industrial processes, as well as research environments.\(^{36}\)

Charette reported in 1996\(^{37}\) a novel reaction involving the Suzuki cross-coupling of cyclopropyl iodides. Before their work no other literature had been published on the oxidative insertion of palladium (0) into a cyclopropyl iodide bond, however due to the cyclopropane having some sp\(^2\) character they theorised that the reaction should proceed.\(^{37}\) They examined the reaction between iodoncyclopropane (32) and vinylboronate ester (33).

![Scheme 16: Charrettes’ cyclopropyl iodide cross coupling reaction.\(^{37}\)](image)

Initial attempts only produced low yields (Table 1), around 25%. The solubility of the base in the organic phase was increased, which improved yields. A phase-transfer catalyst was then introduced as an additive to further increase the solubility of the base in the organic phase. The conversion increased up to 80% when 20% palladium (0) catalyst in benzene was employed (Table 1).\(^{37}\)
### Table 1: Effects of solvent and base on Charettes’ cross coupling.\(^{37}\)

<table>
<thead>
<tr>
<th>Entry(^{a})</th>
<th>Solvent</th>
<th>Additive</th>
<th>Conversion(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Benzene-H(_2)O (4:1)</td>
<td>Na(_2)CO(_3)</td>
<td>25%</td>
</tr>
<tr>
<td>2</td>
<td>Benzene-H(_2)O (4:1)</td>
<td>K(_2)CO(_3)</td>
<td>30%</td>
</tr>
<tr>
<td>3</td>
<td>Benzene-H(_2)O (4:1)</td>
<td>Cs(_2)CO(_3)</td>
<td>35%</td>
</tr>
<tr>
<td>4</td>
<td>Benzene-H(_2)O (4:1)</td>
<td>Cs(_2)CO(_3) + Bu(_4)NCl</td>
<td>50%</td>
</tr>
<tr>
<td>5(^c)</td>
<td>Benzene-H(_2)O (4:1)</td>
<td>Cs(_2)CO(_3) + Bu(_4)NCl</td>
<td>80%</td>
</tr>
<tr>
<td>6</td>
<td>DMF-H(_2)O (4:1)</td>
<td>Cs(_2)CO(_3) + Bu(_4)NCl</td>
<td>&gt;95%</td>
</tr>
</tbody>
</table>

\(^{a}\) Reactions were carried out at 90°C for 20 h using a mixture of iodocyclopropane 32 (0.10 mmol), boronate ester 33 (0.15 mmol), Pd(OAc)\(_2\) (0.01 mmol), PPh\(_3\) (0.05 mmol), and the additive (0.30 mmol). \(^{b}\) Conversions were determined by \(^1\)H NMR analysis and are based on the remaining iodocyclopropane 32. \(^{c}\) In this case, 0.02 mmol of Pd(OAc)\(_2\) used with 0.10 mmol of PPh\(_3\).

The group then applied these conditions to the coupling of a variety of aryl- and heterocyclic-derived boronic acids. They found phenyl boronic acid gave good coupling yields with both trans- and cis-iodocyclopropane, however o-substituted aryl boronic acids proved difficult. This was overcome through the introduction of fluoride ions, which are known to facilitate the cross-coupling process, by allowing the formation of a stable trifluoroborate intermediate.\(^{37}\)
Charette also reported the use of Suzuki cross-couplings to produce symmetrical and unsymmetrical contiguous cyclopropanes in 1997, via the coupling of a number of different iodocyclopropanes and cyclopropylboronate esters (Scheme 17).  

Scheme 17: Conditions and boronate esters used in suzuki coupling.

The initial conditions used were optimised from previous work i.e. a mixture of DMF-H$_2$O at 90°C with K$_2$CO$_3$ and Bu$_4$NCl as an additive to couple boronate ester (a) and iodocyclopropane (32), however only decomposed materials were recovered from the reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Y</th>
<th>Conditions$^a$</th>
<th>Time (h)</th>
<th>Yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>DMF, H$_2$O, K$_2$CO$_3$, Bu$_4$NCl</td>
<td>48</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>c</td>
<td>DMF, H$_2$O, K$_2$CO$_3$, Bu$_4$NCl</td>
<td>20</td>
<td>- c</td>
</tr>
<tr>
<td>3</td>
<td>b</td>
<td>DME, NaOEt$^d$, 80°C</td>
<td>90</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>b</td>
<td>DME, KO-t-Bu$^e$, 80°C</td>
<td>36</td>
<td>65 f</td>
</tr>
<tr>
<td>5</td>
<td>c</td>
<td>Toluene, K$_3$PO$_4$.3H$_2$O, 100°C</td>
<td>48</td>
<td>- c</td>
</tr>
<tr>
<td>6</td>
<td>c</td>
<td>DME, K$_3$PO$_4$.3H$_2$O, 80°C</td>
<td>48</td>
<td>- c</td>
</tr>
<tr>
<td>7</td>
<td>c</td>
<td>DME, KO-t-Bu$^e$, 80°C</td>
<td>36</td>
<td>69</td>
</tr>
<tr>
<td>8</td>
<td>d</td>
<td>DME, KO-t-Bu$^e$, 80°C</td>
<td>48</td>
<td>54</td>
</tr>
</tbody>
</table>

$^a$ All the reactions were carried out using a mixture of iodocyclopropane (1.0 equiv), the boronate ester or acid (1.1 equiv), Pd(OAc)$_2$ (0.1 equiv), PPh$_3$ (0.5 equiv) in the appropriate solvent (0.1M). The amount of base used was as follows: Entry 1-3: K$_2$CO$_3$ (3 equiv) and Bu$_4$NCl (2 equiv). Entry 4: K$_2$CO$_3$ (2 equiv). Entry 8-9: K$_3$PO$_4$.3H$_2$O (3 equiv). $^b$ Decomposition of the iodocyclopropane was observed. $^c$ Unreacted starting materials were obtained in these cases. $^d$ A 2.0M solution of NaOEt in EtOH (3 equiv) was used. $^e$ A 2.0M solution of KO-t-Bu in t-BuOH (2 equiv) was used. $^f$ Also obtained similar yields with PdCl$_2$(dpff) (59%), Pd[PPh$_3$]$_4$ (61%) and PdCl$_2$(PPh$_3$)$_2$ (55%).
After screening a number of different conditions DME was found to be the best solvent at 80°C with potassium t-butoxide as the base. A dramatic rate enhancement was noticed when potassium t-butoxide was present within the mixture, and conversely when a weaker base was used, e.g. sodium hydroxide, lower yields of the desired dicyclop propane were achieved.\textsuperscript{38}

\begin{center}
\includegraphics[width=0.2\textwidth]{bpb.png}
\end{center}

\textit{Figure 13: The boronate ester used to give the best yield in the Suzuki reaction.}\textsuperscript{38}

It was also noted that the nature of the group of the boronate ester affected both the rate and yields of the reactions, with boronate ester (b) producing the lowest yield in the longest time and ester (c) giving the best. The conditions were also applied to the formation of longer chains such as \textsuperscript{38}38.

\begin{center}
\includegraphics[width=0.2\textwidth]{bpc.png}
\end{center}

\textit{Figure 14: An example of the long chains of contiguous cyclopropanes which Charette produced.}\textsuperscript{38}
**Palladium catalysis**

The use of palladium in organic chemistry has increased dramatically in the last 20 years, with the discovery of the usefulness of organopalladium as a catalyst. Palladium enables a variety of very different reactions, including forming carbon-oxygen, carbon-carbon, carbon-sulfur and carbon-nitrogen bonds. Palladium is also useful due to its tolerance of a wide range of functional groups thus avoiding protecting group chemistry, and a number of palladium compounds can be used in catalytic amounts (below 10 mol%), making it economically beneficial. Further to this, palladium-based methodologies proceed stereo- and regioselectively, all of which have led to the significant growth in organopalladium chemistry over the last two decades.

Cross-coupling reactions are usually classified according to the nature of the organometallic reagent involved, for example organotin (Stille), organozinc (Negishi), organoboron (Suzuki-Miyaura), organosilane (Hiyama), organocopper (Sonagashira), and reaction of a Grignard reagent and an organic halide (Kumada). Not all cross coupling reactions involve the use of organometallics, further examples include reaction of an unsaturated halide (or triflate) with an alkene in the presence of base (Heck).

![Figure 15: A simplified cross coupling cycle.](image-url)
All of the types of cross coupling mentioned earlier follow a very similar catalytic cycle as shown in Figure 15; however some have advantages over others. For example the Stille coupling is a versatile C-C bond forming reaction between stannanes and halides or pseudohalides, with few limitations on R group. But, the high toxicity of tin compounds and their low solubility in water due to low polarity makes them unfavourable for wide use.\(^4\)

![Figure 16: General Stille cross coupling mechanism.\(^4\)](image)

Boronic acids and their derivatives are capable of undergoing much the same chemistry, and have almost the same versatility as stannanes, which is why the Suzuki cross coupling is very popular for C-C bond forming reactions. The required organoboron reagents are usually easily formed and their lack of toxic by-products and their general stability make them an attractive target for use in industrial settings.\(^4\)
Suzuki reactions have been extensively used for the coupling of two sp\textsuperscript{2} hybridised carbons as well as being capable of coupling carbons of other hybridisations.\textsuperscript{49} The mechanism for this coupling slightly differs from that of the Stille coupling due to the requirement to activate the boronic acid using base. Activation of the boron ligand facilitates transmetalation by enhancing the polarisation of the organic ligand (Figure 17).\textsuperscript{49}

![Figure 17: General Suzuki cross coupling mechanism.\textsuperscript{49}]

The uses of palladium outlined in this thesis mainly concentrate on the Suzuki-Miyaura and Heck cross coupling reactions.
Aims

The aim of the project, outlined in this chapter, was to find new novel routes to 1,1-diphenyl cyclopropane through the use of readily available carbonyl compounds, which may be achieved by the modification of the well-known Kulinkovich reaction (Scheme 4).

The intention is to exploit the Kulinkovich reaction, to ascertain whether a direct reaction of diaryl ketones under Kulinkovich type metal catalysis to yield the corresponding diaryl cyclopropanes, is possible (route a Scheme 18).

![Scheme 18: Proposed routes to 1,1-diarylcyclopropane.](images/scheme18.png)

If the formation proved problematic, the secondary route was to exploit versatile palladium cross coupling reactions (route b Scheme 18), to introduce an aromatic ring onto an intermediate which would be formed via the conventional Kulinkovich reaction (Scheme 19). Creating a simple stepwise approach to the desired 1,1-diphenyl cyclopropane product.

![Scheme 19: Cyclopropanols as precursors for 1,1-diarylcyclopropanes.](images/scheme19.png)
Results and Discussion

Optimisation of the formation of 1-phenylcyclopropanol

Research firstly aimed towards the optimisation of the formation of 1-phenylcyclopropanol via the Kulinkovich reaction, using conditions similar to those originally reported by Kulinkovich et al. (Scheme 4).\(^{14}\) Initially ethylmagnesium chloride was utilised as the Grignard reagent (Table 3 entries 1-5), however, after numerous changes to reaction conditions, including increasing the catalyst loading from 10 mol\% to a stoichiometric amount (Table 3 entries 4&5), there was no evidence that the cyclopropane was being formed (Scheme 20).

\[
\begin{align*}
\text{EtMgCl (2 equiv.)} & \quad \text{Ti(O\text{"Pr})}_4 (10 \text{ mol}\%) \\
\text{Et}_2\text{O, rt, 1hr} & \quad \text{(42)} \rightarrow \text{(43) OH} \\
\end{align*}
\]

Scheme 20: Initial route to 1-phenylcyclopropanol.

However, a side product was found, by \(^1\text{H}\) and \(^{13}\text{C}\) NMR spectroscopy and mass spectrometry a pinacol product was identified as the major product (Figure 18). It was concluded that, because only the pinacol product was being observed, the Grignard reagent was not sufficient for cyclopropanation to occur (Table 3).

\[
\begin{align*}
\text{HO} & \quad \text{OH} \\
\text{(46)} & \quad \text{(46)} \\
\end{align*}
\]

Figure 18: Proposed pinacol product
<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>43</th>
<th>46</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et₂O</td>
<td>-</td>
<td>30-50</td>
</tr>
<tr>
<td>2</td>
<td>Et₂O</td>
<td>-</td>
<td>35</td>
</tr>
<tr>
<td>3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Et₂O</td>
<td>-</td>
<td>37</td>
</tr>
<tr>
<td>4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Et₂O</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>Et₂O</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 3: Initial cyclopropanation results.

Isolated yield (%)

- Reaction carried out at -78°C, b: Stoichiometric amount of catalyst used.

Therefore the Grignard reagent ethylmagnesium chloride was replaced with ethylmagnesium bromide (Scheme 21), which is the reagent used for the original Kulinkovich reaction.<sup>13</sup>

![Scheme 21: Route towards 1-phenylcyclopropanol using an alternative Grignard.](image)

This initially yielded better results (Table 4), giving in most cases a higher isolated yield of the desired cyclopropanol product than pinacol side product. However, a large percentage of the pinacol product 46 was formed, and after attempting to change the solvent system from the standard diethyl ether (Table 4, entries 3 & 4) and increasing the catalyst loading to a stoichiometric amount (Table 4, entry 5) this could not be reduced.
Table 4: Results of changing solvent.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et₂O</td>
<td>35-55 23-40</td>
</tr>
<tr>
<td>2a</td>
<td>Et₂O</td>
<td>59 31</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>46 28</td>
</tr>
<tr>
<td>4</td>
<td>PhMe</td>
<td>28 12</td>
</tr>
<tr>
<td>5b</td>
<td>Et₂O</td>
<td>45 31</td>
</tr>
</tbody>
</table>

a: Reaction carried out at -78°C, b: Stoichiometric amount of catalyst used.

It was later discovered that the pinacol product was being formed due to inadequate techniques, which once addressed greatly increased the yield of cyclopropanol product with none of the pinacol observed. The isolated yield of cyclopropanol was not improved. A significant amount of starting material was recovered (Table 5, Scheme 21).

Table 5: Further optimised conditions (all reactions carried out at room temp.).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Methyl Benzoate</td>
</tr>
<tr>
<td>1</td>
<td>Et₂O</td>
<td>34-46 16-38</td>
</tr>
<tr>
<td>2</td>
<td>PhMe</td>
<td>48 34</td>
</tr>
<tr>
<td>3a</td>
<td>PhMe</td>
<td>60 -</td>
</tr>
<tr>
<td>4b</td>
<td>PhMe</td>
<td>42 20</td>
</tr>
<tr>
<td>5b</td>
<td>PhMe</td>
<td>60 17</td>
</tr>
<tr>
<td>6a,b</td>
<td>PhMe</td>
<td>50 -</td>
</tr>
</tbody>
</table>

a: Reaction carried out with 3 equivalents of ethyl magnesium bromide, b: 20% catalyst loading used.

It was found that toluene produces the higher ratio of cyclopropanol product (Table 5, entries 2-6), when compared to diethyl ether (Table 5, entry 1).
This is in agreement with the work published by Cha who noted that there is a significant solvent effect when less polar solvents are used. The most notable results are entries 3 and 6, whereby 3 equivalents of the EtMgBr Grignard reagent were used, which produced a fairly good yield of phenyl cyclopropanol, but most importantly, there was no methyl benzoate starting material observed.

The effect of increasing the catalyst loading from 10% (Table 5, entries 1-3), to 20% (Table 5, entries 4-6) was also investigated, however no obvious advantage was observed.

In all reactions detailed in Table 5, a side product was also observed in the $^1$H NMR spectra of the purified product. It is most likely that this is 3-phenylpentan-3-ol (Figure 19), which, due to its polarity being almost exactly the same as the expected 1-phenylcyclopropanol, is not easily removed through the use of column chromatography meaning the isolated yield of this side product could not be obtained; however the $^1$H NMR suggested yields up to 10%. The most likely reason for the presence of this side product is the reduction of the ester by ethyl magnesium bromide (Scheme 22).

![Figure 19: Side product of Kulinkovich reaction.](image)

![Scheme 22: Proposed mechanism for side product formation.](image)
The Kulinkovich catalytic cycle for the formation of 1-phenyl cyclopropanol is outlined in Scheme 23. The cycle is initiated by the formation of dialkyloxytitanacyclopropane via a sequence of simple steps (Scheme 24).

Scheme 23: Kulinkovich catalytic cycle for phenyl cyclopropanol formation.\textsuperscript{16}

Initially 2 equivalents of Grignard reagent react with Ti(O\textsubscript{Pr})\textsubscript{4} to form the thermally unstable diethyl titanium intermediate 9, which rapidly undergoes β-hydride elimination yielding the dialkoxytitanacyclopropane intermediate 10 and ethane (Scheme 24).
Scheme 24: Formation of dialkyloxytitanacyclopropane to initiate the cycle.  

A complex between organotitanium species (10) and methyl benzoate forms, followed by 1,2-insertion of the ester carbonyl to form an oxatitanacyclopentane intermediate ((12) Scheme 23). This is a fast, exothermic, irreversible process which occurs at the less hindered carbon-titanium bond. Wolan et al. suggest that this is due to unfavourable repulsion between the ester and the methyl group in the transition state.  

A β-metallated ketone is then formed by elimination of the alkoxy group. The rate determining step of this cycle is the formation of the cyclopropane ring from the β-metallated ketone intermediate, via a 1,2-insertion process, which can be seen as an intramolecular Lewis acid-assisted nucleophilic addition onto the ketone.  

Finally the formed titanium cyclopropane complex can replace the starting Ti(O'Pr)₄ precatalyst, reacting with 1 equivalent of Grignard reagent to regenerate the dialkyloxytitanacyclopropane, thus completing the cycle.
Kulinkovich et al. then state the titanacyclopropane 10 then acts as a 1,2-dicarbanionic equivalent, in that it performs an overall 2-fold alkylation of the alkoxy carbonyl group, most likely happening by insertion of the ester carbonyl in to one of the titanium-carbon bonds. Subsequent ring contraction yields the titanium cyclopropanolate 14. This then reacts with another equivalent of Grignard reagent to reform intermediate 9 and give the magnesium cyclopropanolate, which is hydrolysed upon workup to the expected product.  

From the catalytic cycle, it can be seen that there is a clear need for the extra equivalent of Grignard reagent to allow a high amount of the dialkyloxytitanacyclopropane to be maintained throughout the cycle. Hence when only two equivalents are used not all of the methyl benzoate is able to react. The need for extra oxytitanacyclopropane was also addressed in this research. The introduction of a higher percentage of titanium isopropoxide, with only two equivalents of Grignard reagent, seemed to improve the yield of the desired product, although there was still a small percentage of methyl benzoate obtained in the final product. Following these results it was concluded that the optimum conditions for phenyl cyclopropanol formation were 3 equivalents of ethylmagnesium bromide, 10 mol % of titanium isopropoxide, with toluene being used as the solvent (Scheme 25).
Formation of 1,1-diphenyl cyclopropane

Following the work published by Masalov et al. discussed earlier in this chapter (see page 19-20) involving the cyclopropanation of vinylogous esters (Scheme 26), it was envisaged that the same transformation could be applied towards the synthesis of diaryl cyclopropanes due to the similarities in the products obtained.

![Scheme 26: Masalov et al. synthesis of fused cyclopropanes.](image)

The initial intention for the formation of 1,1-diphenyl cyclopropane was to carry forward the optimised conditions from the cyclopropanol formation, because it was thought that a diphenyl ketone (i.e. benzophenone), would undergo cyclisation via the same Kulinkovich reaction mechanism (Scheme 23).

![Scheme 27: Proposed formation of diphenyl cyclopropane using Kulinkovich conditions](image)

However, after attempts (Table 6) using the initial optimum conditions (Scheme 27), there were no indications from the $^1$H NMR spectra that 52 was being formed, instead 53 was observed as the major product.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Isolated yield of 53 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^a$</td>
<td>42</td>
</tr>
<tr>
<td>2$^b$</td>
<td>68</td>
</tr>
</tbody>
</table>

a: diethyl ether used as solvent, b: toluene used as solvent.
After further investigation of the $^1$H NMR spectra, it was noticed that two peaks at around 1ppm (t) and 2ppm (q) corresponding to an ethyl group were present. This lead to the theory that either direct addition of the Grignard reagent to the benzophenone, or protonation of the oxatitanacyclopentane intermediate were occurring (Scheme 28). The structure of the product was confirmed by mass spectrometry.

![Scheme 28: Possible method of formation of 51.](image)

To further confirm the product a control reaction was performed without the use of the titanium isopropoxide catalyst. This produced the same $^1$H NMR and mass spectra, confirming this was in fact 1,1-diphenylpropan-1-ol (Figure 20) being formed, however the exact mechanism for its formation under typical reaction conditions is still not clear.

![Figure 20: 1,1-diphenylpropan-1-ol product of the control reaction.](image)

Because the cyclopropane was not formed, reference was again made to the work published by Masalov et al. (see page 19-20), who showed the addition of a Lewis acid tended to induce cyclisation by weakening the carbon oxygen bond, therefore promoting the cyclopropane product to form (Scheme 29).**35**
Following the Maslov groups’ success two different Lewis acids were introduced in to the reaction – boron trifluoride diethyl etherate and zinc chloride, each producing different results. However, neither of these Lewis acids appeared to produce the expected spectra for diphenyl cyclopropane. Initial experiments introduced the Lewis acids into the reaction mixture before the Grignard reagent was added, potentially allowing the titanacycle to form with the Lewis acid bonded to the oxygen, which should allow the cyclopropane to form.

![Scheme 29: Proposed mechanism when introducing a Lewis acid.](image)

In spite of the success shown by Masalov et al.\textsuperscript{35} after addition of a Lewis acid to the reaction, under the modified Kulinkovich conditions, the product spectra still did not show the presence of diphenyl cyclopropane.
Table 7: Yields produced from introducing the Lewis acid later in the synthesis.

<table>
<thead>
<tr>
<th></th>
<th>Yield of 53 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BF&lt;sub&gt;3&lt;/sub&gt;·OEt&lt;sub&gt;2&lt;/sub&gt;</td>
<td>7</td>
</tr>
<tr>
<td>ZnCl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>62</td>
</tr>
</tbody>
</table>

When the two Lewis acids were introduced into the reaction, a large difference in isolated yields was observed (Table 7). ZnCl<sub>2</sub> gave the higher isolated yield of 1,1-diphenylpropan-1-ol, and also produced a much cleaner crude <sup>1</sup>H NMR spectrum making purification simpler. Boron trifluoride produced only a small yield of isolated 1,1-diphenylpropan-1-ol, probably due to the presence of additional unidentified material in the product, which made purification very difficult.

Due to this lack of success only these two Lewis acids were sampled, and the decision was made to change the approach towards cross coupling reactions.
**Palladium cross coupling reactions**

*Suzuki Couplings*

A new approach, other than direct Kulinkovich reaction, towards the synthesis of diphenyl cyclopropane utilising Suzuki cross couplings was investigated next. A publication by Stolle *et al.* outlined Pd(0) catalysed nucleophilic substitutions on vinyl cyclopropanes containing a tosylate group (Scheme 30),\(^{51}\) which allowed the group to substitute a tosylate for a phenyl.

\[
\begin{align*}
\text{OTs} + \text{PhZnCl} & \xrightarrow{\text{dppe (2mol\%)}, \text{Pd(db)2 (2mol\%)}} \text{Ph} \\
\text{(58)} & \text{THF, 40\(^0\)C, 4 hours} \\
\text{(59)}
\end{align*}
\]

Scheme 30: Pd(0) catalysed substitution of tosylate for a phenyl group.\(^{51}\)

The reaction produced a product related to that of the other products formed in this chapter, due to the similarities of vinyl groups electronic properties, and reactivity, to the phenyl group.

The intention was to repeat the work initially reported by Stolle *et al.*\(^ {51}\) A cyclopropanone ethyl hemiacetal is converted into a 1-alkenyl cyclopropanol derivative containing a tosylate functional group. From this compound the target 1-phenyl-1-ethenylcyclopropane molecule is formed through the use of two different routes, one catalysed with Pd(0), and one by Ni(0).

Once achieved the chemistry could be applied to the 1-phenylcyclopropyl-4-methylbenzenesulfonate (Figure 21), the formation of which is discussed later in this chapter, to potentially allow a second phenyl group to be introduced to the cyclopropane ring.
To initially form the cyclopropanone ethyl hemiacetal starting material, a method whereby sodium sand is reacted with chlorotrimethylsilane and ethyl 3-chloropropanoate originally published by Salaün et al. was found to be the most cited within the literature (Scheme 31).\(^{52}\)

\[\text{Cl-} \text{C(O)OEt} \xrightarrow{2 \text{ Na, Me}_3\text{SiCl, PhMe, reflux}} \text{Si-OEt} \xrightarrow{\text{MeOH, rt, 12 h}} \text{HO-OEt}\]

Scheme 31: Most cited procedure for formation of cyclopropanone ethyl hemiacetal.\(^{53}\)

However, because of the high risk involved with the use of sodium sand this was disregarded, and a secondary method of formation was adopted. The second synthesis involved treating a conjugated ester (ethyl acrylate) with a Grignard reagent in the presence of Ti(O'Pr)\(_4\) to form the intended 1-vinyl cyclopropanol, work published by Racouchot et al. (Scheme 32).\(^{54}\)

\[\text{CH}_2=\text{C(O)OEt} \xrightarrow{\text{EtMgBr (2.5 equiv), Ti(O'Pr)\(_4\) (20 mol\%)}} \text{HO-C(O)=CH}_2\]

Scheme 32: Racouchot synthesis of 1-vinyl cyclopropanol.\(^{54}\)

However after numerous attempts at repeating this work, the isolated product was not the intended vinyl cyclopropanol 62. The crude \(^1\)H NMR spectrum appeared to show the expected peaks, two peaks at approximately 1ppm corresponding to the cyclopropane protons, and multiplets at 5-6 ppm corresponding to the vinyl group; however the peaks which correspond to the cyclopropane are very large broad multiplets.

Therefore (1-ethoxycyclopropoxy) trimethylsilane 63 was purchased and subjected to methanolyysis to form the 1-ethoxycyclopropanol product. This product was treated with vinylmagnesium bromide to form 1-vinylcyclopropanol, which was the intended product from the earlier Salaün method (Scheme 31).\(^{52}\)
A substitution with $p$-toluenesulfonyl chloride, thus forming the tosylate product (65), was performed using the same conditions as reported earlier. This product was easily obtained and rarely required purification.

Nickel catalysed substitutions could then be attempted, using phenylmagnesium bromide as the source of the aromatic ring to be attached to the target molecule (66). Each of these steps were performed with moderate to good yields (Scheme 33).

The target molecule (66) was obtained, however purification proved to be difficult due to the non-polar nature of the product. A silica gel column using 100% light petroleum ether as the eluent was used, but co-elution was still unavoidable. Nonetheless, the evidence strongly supports that the correct product is being produced, due to the $^1$H NMR data i.e. integrations and J couplings (see experimental section for full spectrum assignment), mass spec data and $^{13}$C NMR data match that of the literature, where the pure product is claimed to have been isolated.55
Once the literature had been repeated the same nickel reaction could be attempted with 1-phenylcyclopropyl 4-methylbenzenesulfonate (67) (formed from the reaction of 1-phenylcyclopropanol with tosyl chloride), thus allowing 1,1 diphenyl cyclopropane to be formed (Scheme 34).

However, after a number of attempts the same result as that produced by the literature could not be achieved. This may be due to a large amount of steric hindrance on the cyclopropane, caused by two phenyl rings attempting to bond to the same carbon. Both $^1$H NMR spectroscopy and mass spectrometry were used in an attempt to identify the product being formed, but the $^1$H NMR spectrum was complex even after purification attempts, making it difficult to ascertain exactly what had been formed. The mass spectrum was also difficult to interpret, though this did confirm the absence of any starting materials.

As the reaction was not forming the expected product following the literature method, the reaction was instead performed under reflux after allowing the reaction to proceed for 1 hour as usual. After isolating the product the crude spectra appeared even more complex, suggesting some of the reactants and/or products may be degrading due to the heat being applied.

The same reaction was also attempted using the palladium conditions originally outlined by Stolle et al.\textsuperscript{51}, however the same result as that obtained when using a nickel catalyst occurred. None of the desired diphenyl cyclopropane was observed.

\begin{center}
\textbf{Scheme 34: Nickel catalysed reaction using tosylated phenylcyclopropane.}
\end{center}
Because the reactions following literature procedures were not producing the expected product, it was decided to follow a known synthesis of similar chemistry from the literature in order to ensure the conditions required to perform palladium cross coupling reactions were able to be obtained within the laboratory.

The reaction involving copper free Sonogashira coupling of a terminal alkyne with a cyclopropyl iodide, a reaction reported by Benoît de Carné-Carnavalet \(^5^6\) in 2011, was chosen as it was thought to represent the range of techniques and conditions required. The results shown in Scheme 35 are those obtained when the literature reaction was repeated in our laboratory (values shown in red correspond to literature yields, blue correspond to laboratory yields).

**Scheme 35: Copper free Sonogashira coupling. (red corresponds to literature yields, blue corresponds to the yields achieved in the laboratory).**

Firstly (Z)-β-iodoethylacrylate (68) was formed from ethyl propiolate, which was then reduced with diisobutylaluminium hydride to (Z)-1-iodoprop-1-en-3-ol (69). This product was cyclised through the use of chloriodomethane and diethyl zinc to cis-2-iodocyclopropane methanol (70).
The coupling of the terminal acetylene was achieved with the use of bis(acetonitrile)dichloropalladium(II) and 2-dicyclohexylphosphino-2’,4’,6’-triisopropylbiphenyl (XPhos) to yield the desired ((1R*,2S*)-2-phenylethynylcyclopropyl)methanol (71) in 76% yield (Scheme 35). The fact the literature has successfully been repeated with satisfactory yield suggests the palladium cross coupling experiments are feasible when the correct conditions are found.

A new method of Suzuki cross coupling reactions was utilised next. The initial intention of the reaction was to form a number of phenyl cyclopropanes, where the alcohol group was substituted for a better leaving group. This would allow the cross coupling to proceed more effectively (Scheme 36).

![Scheme 36: Retrosynthetic analysis towards 1,1 diaryl cyclopropane using palladium.](image)

The planned compounds were the mesylate, tosylate, and triflate forms of 1-phenylcyclopropane (Figure 21). The proposed order of reactivity i.e. effectiveness as a leaving group is triflate > tosylate > mesylate.
Initially the formations of these species were attempted through the use of triethylamine, and a catalytic amount of 4-dimethylaminopyridine, with the reactants suspended in dichloromethane (Scheme 37). Using this method it was possible to easily form the mesylate which, following the use of column chromatography, gave a pure sample. However the yield for the reaction was very low averaging approximately 25% of isolated product (Table 8).

The formation of the tosylate (73) initially provided some positive results, producing the desired compound in 20% yield. However, despite very precise column chromatography it proved difficult to obtain a pure product. It was discovered that a secondary product was forming, caused by the reaction of triethylamine with p-toluenesulfonyl chloride, producing N,N-diethyl-4-methylbenzenesulfonamide 75 (Figure 22).
The presence of this side reaction explained the disappointing isolated yields of 73 being observed. The proposed mechanism for the formation of this by-product is outlined in Scheme 38.

Scheme 38: Proposed mechanism for the triethylamine salt (58) formation.

Table 8: Yields from the initial substitution reactions.

<table>
<thead>
<tr>
<th>Expected Product</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Structure of (72)" /></td>
<td>26</td>
</tr>
<tr>
<td><img src="image" alt="Structure of (73)" /></td>
<td>22-33</td>
</tr>
<tr>
<td><img src="image" alt="Structure of (74)" /></td>
<td>-</td>
</tr>
</tbody>
</table>

Due to the lack of success and low yields from the initial method, an alternative was found. For this pyridine was employed as both the base and solvent, with the use of 1.5 equivalents of each of the corresponding sulfonyl chloride staring materials (Scheme 39).
Scheme 39: Improved synthesis of sulfonate cyclopropanes.\textsuperscript{51}

The original publication by Stolle \textit{et al.}\textsuperscript{51} stated the reaction should be performed at 0°C; however this proved ineffective for the desired products, only recovering the 1-phenylcyclopropanol starting material. A range of reactions were carried out at room temperature, 50°C, and reflux, to determine the optimum temperature for this reaction to proceed. It was determined that at 50°C the reaction proceeded with the most satisfactory yield. Reaction time was also investigated, with overnight (17 hours) found to be the optimum reaction time to allow a good yield (approximately 50%) to be isolated.

Through the use of pyridine as a base the production of 75 was eliminated thus providing a pure crystalline product.

When first attempting the formation of the triflate (74), the optimum conditions were used i.e. pyridine as the base, and trifluoromethanesulfonic anhydride as the triflating agent (Scheme 40). However, after characterising the product through $^1$H NMR and IR spectroscopy the desired product was not present. No identifiable material was isolated, which is most likely because the triflating agent is so reactive it caused the cyclopropane to decompose.

Therefore an alternative milder triflating agent, N-phenyl-bis(trifluoromethanesulfonimide) was used under the same conditions, in the hope that this would be mild enough to allow the 1-phenylcyclopropyl trifluoromethanesulfonate target to form (Scheme 40).
Yet after purification through column chromatography the major product from the reaction was found to be the starting material 1-phenylcyclopropanol. It was clear the synthesis of the triflated cyclopropane was going to be complicated, therefore the decision was made to proceed with the cross coupling reactions using only the mesylate and tosylate forms of cyclopropane. These were available in relatively good yields (Table 9), and were competent starting materials for the Suzuki coupling reaction.

Table 9: Yields obtained from using pyridine as the base.

<table>
<thead>
<tr>
<th>Expected Product</th>
<th>Isolated Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Structure" /></td>
<td>50%</td>
</tr>
<tr>
<td><img src="image" alt="Structure" /></td>
<td>40-60%</td>
</tr>
<tr>
<td><img src="image" alt="Structure" /></td>
<td>-</td>
</tr>
</tbody>
</table>
The two sulfonates were introduced into a palladium catalysed Suzuki coupling reaction starting with the least reactive mesylate compound (Scheme 41).

The proposed reaction mechanism proceeds firstly through the oxidative addition of the palladium catalyst into to 1-phenylcyclopropyl methanesulfonate thus forming the organopalladium species ((methylsulfonyl)oxy)(1-phenylcyclopropyl)palladium (78). This reacts with the base to produce the substituted product tert-butoxy(1-phenylcyclopropyl)palladium (79), which undergoes transmetallation with the boronate complex tert-butoxydihydroxy(phenyl)borate (80) to form the organopalladium species phenyl(1-phenylcyclopropyl)palladium (81). 

Reductive elimination of the desired 1,1-diphenylcyclopropane then reforms the Pd(0) species, thus restarting the cycle. Hence, the better the leaving group on the cyclopropane, the more likely the base is to substitute into the complex, and therefore the cycle proceeds.
As reported earlier, the triflate had not been successfully synthesised, so only reactions with tosylate and mesylate compounds were attempted. After a number of reactions using THF and DME as the solvent system and employing different conditions (Scheme 42) only boronic acid starting material, (confirmed through TLC and $^1$H NMR spectroscopy), and degraded materials were isolated. None of the starting 1-phenylcyclopropyl-4-methylbenzenesulfonate was observed, confirmed through TLC.

![Scheme 42: Attempted Suzuki coupling.](image)

To determine whether the failure of the reaction was due to the presence of oxygen within the system, the reaction was prepared via a Schlenk line. Firstly using standard vacuum and back fill techniques, and secondly using a freeze thaw evacuation technique. There was no noticeable difference in the final product from each reaction.

Due to the non-polar nature of the products it proved difficult to purify any products obtained from the cross coupling reactions. Also the anticipated products were symmetrical, which caused difficulty when trying to use $^1$H NMR to identify any products, because of the overlap of the phenyl rings in the aromatic region from the starting material and product. Therefore some polarity was added to the system through the introduction of methoxy groups. It was envisaged that this would not only allow for better separation during column chromatography, but also allow the introduction of a second phenyl ring to be easily identified, as the aromatic regions would differ.
The initial investigation, firstly, involved the synthesis of the starting cyclopropanol using methyl 4-methoxybenzoate (82) as the starting ester.

![Scheme 43: Conditions for the formation of a p-methoxyphenyl cyclopropanol.]

Once formed it would then be possible to attempt the palladium cross couplings and Grignard reactions, (as shown previously) in order to introduce the second phenyl ring to the cyclopropane.

Yet, when using the same optimised conditions as those reported earlier in this chapter, only direct addition of the Grignard reagent was observed. After attempting a number of different reaction conditions, it was found that increasing the titanium isopropoxide to a stoichiometric amount allowed the correct cyclopropane to form in a moderate yield of 65% (Scheme 43).

With this cyclopropane in hand, work could begin on the synthesis of molecules suitable for Suzuki couplings. This started with the attempted synthesis of 1-(4-methoxyphenyl)cyclopropyl methanesulfonate (84), through the use of the same conditions optimised earlier in this chapter (Scheme 44).

![Scheme 44: Synthesis of 1-(4-methoxyphenyl)cyclopropyl methanesulfonate]
The $^1$H NMR spectrum of the isolated product appeared to show cyclopropane was present. This did not correspond to the starting material as there was a shift observed in the aromatic region of the spectrum. This led to the conclusion that an electron withdrawing group was now attached to the cyclopropane, probably substituted for the hydroxyl group. The most likely explanation for this is that a chloride from the methanesulfonyl chloride starting material was now bonded to the cyclopropane (Scheme 44). The proposed mechanism for this formation is outlined in Scheme 45.

![Scheme 45: Proposed mechanism for chlorocyclopropane formation.](image)

To ascertain whether this was the case the reaction was repeated with the addition of a large excess of lithium chloride (5 equiv), which would ensure there were a large number of chloride ions present in the solution, and hence the product formed should be that of the cyclopropane containing a chloride group. The $^1$H NMR spectrum appeared the same as that obtained for the product in Scheme 44 (i.e. the suspected 1-(1-chlorocyclopropyl)-4-methoxybenzene). This was supported by the presence of an ion at an m/z=147.0804 in the mass spectrum corresponding to the cyclopropane minus the chloride ion, probably from in source fragmentation.

Work involving further reaction of 1-(1-chlorocyclopropyl)-4-methoxybenzene (85) in Friedel Crafts reactions was carried out by MChem students, who produced promising results towards 1,1-diaryl cyclopropane, proving this route of synthesis might be useful in the future.

Due to the failure of the mesylate formation, attention was then turned towards the formation of the tosylate (Figure 23). This initially started with the use of the earlier optimised conditions.
The optimal conditions did not form the expected product, only starting material was isolated from the reaction. A catalytic amount of DMAP was added under the same reaction conditions as previously, in the hope that this would help improve the yield by activating the pyridine (Scheme 46). Unfortunately this was not the case, only starting material was isolated from the reaction.

Next the reaction temperature was increased to 80°C, in an attempt to favor the reaction. Again none of the target tosylate was observed, but there was also none of the starting material present by $^1$H NMR spectroscopy or TLC. Upon closer inspection of the $^1$H NMR spectrum, it could be seen that there were no cyclopropane peaks present, but there were peaks corresponding to the presence of an alkyl chain. It was later discovered that the ring opened product was being formed in 70% yield (Figure 24).
It was suggested that the presence of some tosic acid in the tosyl chloride, which when combined with the mesomeric effect from the methoxy group, caused the cyclopropane ring to open.

As it was proving difficult to synthesise the cyclopropane with a good leaving group it was not possible to attempt any Suzuki cross coupling reactions in order to introduce a second phenyl ring. Therefore the reactions involving the use of a diphenyl ketone were revisited, employing 4,4'-dimethoxybenzophenone as the starting ketone (Scheme 48). This would, again, allow more polarity to be introduced into the product, making purification simpler, and remove the need for any palladium cross coupling reactions.
However, when initial reactions were performed, 9 equivalents of Grignard reagent were mistakenly added to the reaction, and as a result none of the expected cyclopropane was observed. Only peaks for what was initially thought to be starting material were present in the $^1$H NMR spectrum.

Upon further inspection, it was noted that the peaks in the aromatic region of the $^1$H NMR spectrum were shifted from those expected for the starting ketone. Further investigation through IR spectroscopy, and $^{13}$C NMR spectroscopy, showed there were more carbon signals than would be expected for the starting material, and the IR showed there was no longer a carbonyl present in the product.

This led to the deduction that a tetra substituted alkene i.e. a stilbene type product was being formed (Figure 25) in good yields of 75%.

![Proposed structure of the stilbene product.](image)

As this looked to be an interesting route towards these tetra-substituted alkenes further investigation was undertaken, which is discussed in chapter 2 of this thesis.

Due to the reactions utilising the $p$-methoxy reagents proving to be unsuccessful, the use of palladium reactions was revisited. Instead of trying the standard Suzuki coupling i.e. using tetrakis(triphenylphosphine)palladium (0), other sources of palladium were utilised; one being Pd(dba)$_2$ and the other Pd(OAc)$_2$. In order to use these palladium sources a ligand also had to be employed in the reaction.
Work then continued to focus on the introduction of a second phenyl ring with and without a \( p \)-methoxy group, via a cross coupling reaction using \( \text{Pd(OAc)}_2 \), which is a better palladium source for couplings involving tosylates, along with phenylboronic acid, and two different ligands; CM-Phos\(^\text{57} \) and XPhos\(^\text{58} \) (Figure 26).

![Figure 26: The 2 ligands to be used for Pd cross coupling reactions.](image)

Firstly the reaction was attempted with 2 mol\% of \( \text{Pd(OAc)}_2 \) and 5 mol\% of the XPhos ligand. However, this did not produce any positive signs of product forming, so this was increased to 3 mol\% and 7 mol\% respectively, but this still did not produce any of the expected diphenylcyclopropane product.

![Scheme 49: Attempted couplings using \( \text{Pd(OAc)}_2 \).](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Pd load (mol%)</th>
<th>Ligand</th>
<th>Ligand load (mol%)</th>
<th>Isolated product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>2</td>
<td>XPhos</td>
<td>5</td>
<td>SM</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>3</td>
<td>XPhos</td>
<td>7</td>
<td>SM</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>2</td>
<td>CM-Phos</td>
<td>8</td>
<td>SM</td>
</tr>
<tr>
<td>4</td>
<td>OMe</td>
<td>2</td>
<td>XPhos</td>
<td>5</td>
<td>SM</td>
</tr>
<tr>
<td>5</td>
<td>OMe</td>
<td>3</td>
<td>XPhos</td>
<td>7</td>
<td>SM</td>
</tr>
<tr>
<td>6</td>
<td>OMe</td>
<td>2</td>
<td>CM-Phos</td>
<td>8</td>
<td>SM</td>
</tr>
</tbody>
</table>
When the ligand was changed to CM-Phos there was still no positive result observed from the reaction.

The exact same reactions were then attempted using Pd(dba)$_2$ instead of Pd(OAc)$_2$, however the same outcome from each reaction was observed; only starting material was isolated from the reactions.

Since the new reaction conditions were showing poor results, it was decided to attempt to introduce an acetate onto the cyclopropane (Scheme 50). This would help determine whether the failure of the reactions was due to the palladium conditions being incorrect, or whether two aromatic rings are difficult to attach to the same carbon due to steric restraints. This reaction proved unsuccessful, with only starting material being observed from the reaction, suggesting that the main reason for the failure of the palladium reactions is caused by the conditions.

Scheme 50: Attempted cross coupling using Pd(dba)$_2$.
Conclusions

It has been demonstrated that, contrary to previous reports in the literature, the optimum conditions for the formation of 1-phenylcyclopropanol via the Kulinkovich reaction involves the use of 3 equivalents of magnesium bromide, 10 mol% of titanium isopropoxide, and toluene as the reaction solvent, allowing 60-65% of the product to be isolated.

Secondly it has been demonstrated that the Kulinkovich conditions are not able to form a 1,1-diphenylcyclopropane from its starting ketone, whether a Lewis acid is employed within the reaction mixture or not. A number of different reaction conditions and methodologies have been screened, none of which have proved successful. This is an unexpected outcome given that there are reports of similar chemistry using vinylogous esters within the literature, whereby cyclopropanation has been successful, especially when a Lewis acid is introduced.

Although it has been clearly demonstrated that palladium chemistry, through the copper free Sonogashira reaction, is capable of coupling a cyclopropane to the desired molecule, it is not able to couple a second phenyl ring. Even when various sources of Pd are utilised, onto a number of substituted phenyl cyclopropanes, namely the mesylate and tosylate forms, the coupling of the second phenyl ring did not proceed. Ideally the triflate protected cyclopropane would be employed in the reaction; however it has been shown that this product is difficult to produce.
Chapter 2

Novel conditions for McMurry type carbonyl coupling reactions towards tetrasubstituted alkenes
**Introduction**

**The McMurry reaction**

It has been known for many years that the McMurry reaction is capable of coupling aldehydes and ketones in order to produce alkenes (Scheme 51), and a wide variety of publications have been produced outlining the numerous applications of this reaction.\(^{59-62}\)

\[
\text{R}^+\text{R}^- \xrightarrow{\text{Low valent Titanium}} \text{R}^+\text{R}^-
\]

\(\text{R=}\text{R}'=\text{H, aryl, alkyl}\)

*Scheme 51: General McMurry reaction.*

However, all of the publications to date use relatively harsh reagents in order to obtain the low valent titanium needed to catalyse the coupling reaction, such as those reported by McMurry.\(^{59}\) John McMurry initially proposed a TiCl\(_3\)-LiAlH\(_4\) system, which was adapted from a well-known combination of LiAlH\(_4\) and AlCl\(_3\) capable of reducing \(\alpha,\beta\)-unsaturated ketones to alkenes.\(^{63}\) Using this new combination McMurry *et al.* produced a small selection of tetrasubstituted alkenes from ketones and aldehydes to investigate the scope of the reaction (Table 11).\(^{63}\)

All of their examples produced the desired product in excellent yields, via a mechanism that McMurry *et al.* assume proceeds through the involvement of a Ti(II) species, a strong reducing agent, which should be capable of causing a pinacol reduction to an intermediate diol. Further reduction, either by step-wise loss of oxygen, or through formation of a Ti(II) complex followed by concerted loss of TiO\(_2\) then gives the alkene product (Scheme 52).\(^{63}\)

\[
2\text{Ti(II)} + \text{O}_2 \xrightarrow{\text{e}^-} \text{Ti}^{3+} \text{Ti}^{3+} \xrightarrow{\text{TiO}_2} \text{C=C}
\]

*Scheme 52: Hypothesised mechanism of the McMurry coupling.*\(^{63}\)
The initial conditions were then later improved by McMurry et al. in 1976 through the introduction of other metals to produce TiCl$_3$–Zn(Cu). The group reports that by preparing their reactive species via an active Ti(0) powder, they were able to further the scope of their McMurry coupling of carbonyls to alkenes, and through the theory that pinacol di anions are formed during the coupling reaction, were able to further the reaction to include the reduction of diols to alkenes in very good yields (Table 12).
Table 12: Diol reductions using McMurry optimised conditions.\textsuperscript{64}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting diol</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>![diol1]</td>
<td>![product1]</td>
<td>55</td>
</tr>
<tr>
<td>2</td>
<td>![diol2]</td>
<td>![product2]</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>![diol3]</td>
<td>![product3]</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>![diol4]</td>
<td>![product4]</td>
<td>0</td>
</tr>
</tbody>
</table>

The group postulate that it is not necessary to pre-form the dianions because the free diols reduce directly, which they presume is because the dianions are formed \textit{in situ} by reaction with Ti(0). The group's rational for why entry 4 produces none of the expected alkene is that it is unable to form the required intermediate via a boat conformer, unlike the \textit{trans} diaxial diol (entry 3) which can, therefore rendering it unreactive.\textsuperscript{64}

A few years later McMurry \textit{et al.} attempted to further optimise the reaction conditions for carbonyl coupling reactions by introducing potassium and lithium to the TiCl\textsubscript{3}, however they found neither of these metals were as effective, in terms of reaction yields, as the copper-zinc couple previously reported.\textsuperscript{65} The group then went on to further study the mechanism for this reaction and reported the four most likely possibilities (Scheme 53).
Mechanistic studies

Path A assumes that the pinacol forms a five membered intermediate with both oxygens bound to the same titanium atom. The intermediate can then either further react via a concerted mechanism (path A1), giving the alkene and TiO2, or can react via a non-concerted mechanism (path A2), whereby the two C-O bonds are broken at different times. Path B differs from path A in that there is no five membered ring present and the oxygens are bound to different titanium atoms, which would further react by a non-concerted mechanism to give the target alkene. Path C considers the possibility that the deoxygenation reaction happens on the surface of an active titanium particle in a heterogeneous process.

McMurry et al. propose that path C is the actual pathway the reaction takes after conducting some experiments with cis and trans diols. The group firstly show that path B is unlikely through reaction of cis and trans-9,10-decalindiol under identical conditions (Figure 27).
The group found that the *cis*-diol reacted smoothly to give the expected alkene in 80% yield; however the *trans*-diol did not give any expected product. They deduce the only obvious difference between the two is the *cis* isomer is capable of bonding to a single titanium atom through both oxygens whereas the *trans* is not.

They note that a *cis*-diol would reduce at a much faster rate than a *trans*-diol if going via a five membered transition state, which is due to the *trans* form having its hydroxyl groups held rigidly too far apart to accommodate a five membered ring whereas the *cis* diol can easily form the five membered transition state. Therefore after reacting a mixture of *cis*- and *trans*-diols in side by side reactions they found that both were reduced at almost the same rate, strongly suggesting that a five membered transition state is not required and hence path C is most likely.

All of these variations require the use of TiCl$_3$, which can be difficult to handle due to its corrosive nature, as well as needing elemental metals in order to achieve the desired results. It is the use of these difficult reagents throughout the literature for these types of couplings that prompted us to find milder conditions.
Uses of tetra-substituted alkenes
The target tetrasubstituted alkenes, especially those containing aromatic rings, are of interest due to their redox and photophysical properties owing to the presence of both an aromatic centre as well as an alkene. These products can also be used as electron transfer catalysts and rich electrochemical properties provide excellent energy transfer research modes. A large number of publications outlining this kind of reaction involve the formation of symmetrical alkenes, and the synthesis of unsymmetrical analogues often requires the use of nickel or palladium catalysed coupling reactions.

In 2010 Wang et al. reported that tetra-substituted alkenes, namely tetraphenylethene (TPE), provide perfect models for research with the extended π-systems being important candidates for incorporation into various organic optomechanical and optoelectronic storage and switching devices. The group formed TPE from benzophenone and BuLi followed by acid catalysed dehydration (Scheme 54).

Scheme 54: Conditions for formation of PTE.
The group then formed a number of oligomers based on TPE derivatives (Figure 28) using low valent titanium McMurry coupling techniques, and went on to conduct a number of physical measurements in order to observe a change from aggregation-induced emission to aggregation-induced emission enhancement.\(^{61}\)

These materials also find use as transfer catalysts in a variety of polymerisations and coupling reactions.\(^{62}\) In 2007 Wang \textit{et al.} studied the effect tetraphenylethylene on rates of propagation of polymerisation of styrene finding that the π-complexing nature caused a large decrease in rate of propagation.\(^{67}\)

In 2014 Wang \textit{et al.} developed graphene-like macrocycles, which are based on tetraphenylethene as a starting material. The group initially formed 1,1-bis(4-phenylcarbonyl)-2,2-diphenylethene in 57% yield (Scheme 55), from TPE.\(^{68}\)
Once formed they synthesised a tetraphenylethene macrocycle (TM) via another McMurry coupling, which the group then oxidised to form a less twisted compound (TMC) (Scheme 56), thus allowing the group to test for comparisons in abilities to carry charge.

Scheme 56: Synthesis of TM and TMC.

Once formed the group found the more rigid of the two macrocycles (TMC) is more conjugated than (TM) due to its less twisted structure, and hence has a higher charge mobility. Wang et al. found that the results from their electrical properties tests make these macrocycles viable for use in applications such as light-emitting diodes.

With all these possible applications of this chemistry in mind it is clear there is a need for a milder synthetic route to these compounds in order to allow them to be more readily accessed for use in these areas of research.
Aims

The aim of the research outlined in this chapter was to develop a new methodology towards tetrasubstituted alkenes, via a modification of the well-known McMurry reaction.

![Scheme 57: A typical McMurry reaction towards a tetrasubstituted alkene.](image)

The current methods use of harsh reagents to produce low valent titanium is undesirable, so the development of a new method removing the need for these reagents will improve future synthesis of these types of compounds.

Once an optimal synthesis has been developed, the scope of the reaction will be investigated. A variety of ketones will be tested, including ketones containing electron withdrawing, and electron donating groups, which will highlight any limitations with the new methodology.
Results and discussion

As mentioned earlier in chapter 1, an interesting reaction product was observed when attempting the Kulinkovich reaction with a large excess of Grignard reagent (see page 54-55). This was of particular interest because it is the first example within the literature of this transformation being performed homogeneously. After the initial success forming tetrasubstituted alkenes (described in chapter 1 pages 54-55), from starting materials such as benzophenone and 4,4' dimethoxybenzophenone (Scheme 58), attempts at optimisation of the reaction were undertaken.

![Scheme 58: Initial conditions for the McMurry coupling reaction.](image)

Firstly the equivalents of Grignard were changed in order to discover whether such a large excess was necessary. When 3 equivalents were used, i.e. reproducing the Kulinkovich cyclopropanation conditions, the expected tetrasubstituted alkene was only observed in 9% yield, with the remainder being starting material. When the equivalents of Grignard were increased to 6 the yield of the expected product increased to 35%, which was still much lower than the 75% obtained when using 9 equivalents. When a further excess of 12 equivalents were used no additional increase in yield was observed, suggesting 9 is the optimal for this reaction.
This leads to a possible mechanism being hypothesised (Scheme 59). It was thought that the key titanacyclopropane intermediate (110) from the Kulinkovich reaction, also plays an important role in this mechanism.

The formation of the titanacyclopropane intermediate 111 is outlined in Scheme 24 (chapter 1, page 34 of this thesis). It was hypothesised that the titanacyclopropane would co-ordinate to the carbonyl of the starting ketone, through the loss of ethene, producing a radical. This would then undergo a radical reaction with another of the same species in the reaction, to form an oxatitanacyclopentane species (113). Deoxygenation then produces the expected alkene, and diisopropyl titanate (114). This then reacts with further equivalents of Grignard to reform the titanacyclopropane intermediate.

Once the equivalents of Grignard reagent required for this transformation had been optimised, the amount of titanium isopropoxide was changed to see the effect on the reaction. As shown in Scheme 58 when 10 mol% is used the yield is 75%, however when this was increased to a stoichiometric amount the yield increased to 90%. When this was increased further again to 2 equivalents, no further increase in yield was observed.
Finally a lewis acid was added to the reaction to determine whether this would further increase the yield. When 1 equivalent of boron trifluoride diethyl etherate was added to the reaction, no change was observed in terms of exclusive formation of the product or yield, therefore it was determined that lewis acid was not necessary for this reaction. This lead to the conclusion that the optimal conditions for this reaction are the use of 9 equivalents of Grignard with 1 equivalent of titanium isopropoxide (Scheme 60).

With the optimal conditions obtained, the scope of the reaction could be investigated involving the use of a range of ketones including electron rich, electron poor, and unsymmetrical materials (Table 13).
Table 13: Examples of the McMurry coupling reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>Product</th>
<th>Yield(^a) (%)</th>
<th>Ratio(^b) (E:Z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Starting material 1" /></td>
<td><img src="image2" alt="Product 1" /></td>
<td>71</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Starting material 2" /></td>
<td><img src="image4" alt="Product 2" /></td>
<td>36</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Starting material 3" /></td>
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<td>52(^a)</td>
<td>1:1</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Starting material 4" /></td>
<td><img src="image8" alt="Product 4" /></td>
<td>74</td>
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<td>6</td>
<td><img src="image11" alt="Starting material 6" /></td>
<td><img src="image12" alt="Product 6" /></td>
<td>75</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td><img src="image13" alt="Starting material 7" /></td>
<td><img src="image14" alt="Product 7" /></td>
<td>99</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^a\): Product isolated as a mixture of isomers, \(^b\): ratio determined by \(^1\)H NMR.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Ratio&lt;sup&gt;b&lt;/sup&gt; (E:Z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
<td>90</td>
<td>b</td>
</tr>
<tr>
<td>9</td>
<td><img src="image3" alt="Image" /></td>
<td><img src="image4" alt="Image" /></td>
<td>80&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1:1</td>
</tr>
<tr>
<td>10</td>
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<td><img src="image6" alt="Image" /></td>
<td>41&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1:1</td>
</tr>
<tr>
<td>11</td>
<td><img src="image7" alt="Image" /></td>
<td><img src="image8" alt="Image" /></td>
<td>65&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1:1</td>
</tr>
<tr>
<td>12</td>
<td><img src="image9" alt="Image" /></td>
<td><img src="image10" alt="Image" /></td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>: Product isolated as a mixture of isomers, <sup>b</sup>: ratio determined by <sup>1</sup>H NMR.

From Table 13 it can be seen that this new method is applicable to a wide array of products ranging from electron rich such as entries 4, 5, 6, 8, and 9, which show good yield of around 75%, to electron poor such as entries 1, 2, 3, and 10, which show moderate yields. When unsymmetrical ketones were used as starting materials, such as that in entry 3, the product is isolated as a 1:1 mixture of isomers.
The differences observed between electron rich and electron deficient alkenes are what were expected prior to the reactions. This is because the mechanism is thought to involve radicals, which when an electron withdrawing or donating group is present, causes the free radical to become either destabilised or stabilised respectively, thus affecting their reactivity.

In the particular case of Table 13 entry 3 the ratio of cis and trans isomers across the double bond was determined through the use of $^{19}$F NMR, which showed the mixture was 1:1. The other products which were produced as mixtures (Table 13, entries 9, 10, and 11), were also isolated as a 1:1 mixture, determined by $^1$H NMR.

Table 13 entry 12 shows it is also possible to do an internal McMurry coupling between 2 ketones in the same molecule producing a cyclic product, however this was only achieved in poor yields.

It was then decided to further this methodology by applying the chemistry to a pharmaceutically interesting drug such as Tamoxifen (Figure 29).\(^\text{69}\)

![Figure 29: The structure of Tamoxifen.\(^\text{69}\)](image-url)
This is a drug that is used as a treatment for breast cancer, which is usually formed using more standard McMurry coupling conditions i.e. using low valent titanium. A synthesis towards Tamoxifen, using the McMurry coupling, has been published by Coe et al. The group reported the use of either TiCl₃-Li, or TiCl₄-Zn to perform the key McMurry step of the synthesis to form the tetrasubstituted alkene. These are notoriously difficult to handle chemicals, hence if the method outlined in this chapter could be proved effective towards the formation of these kinds of compounds, it would simplify their synthesis. The retrosynthetic analysis of Tamoxifen is outlined in Scheme 61.

The important step in the synthesis was the reaction of two different ketone starting materials, propiophenone and 4-methoxybenzophenone, because this would form the tetrasubstituted alkene and prove the concept towards the drug target.

Scheme 61: Retrosynthetic analysis of Tamoxifen to simple ketones

Following the same procedure as outline in Scheme 60, the expected product (126) was obtained in a moderate yield of 46%, as a 1:1, E:Z mixture, however it was isolated along with 2 other products formed through the ketone starting materials reacting with themselves, thus providing an explanation for the low yield of the desired product (Scheme 62).
Coe et al. reported a yield of 75% of the desired compound, as a 8:3, Z:E ratio, which is quite a lot higher than the yield detailed in Scheme 62. But, with some further optimisation, such as temperature control, it should be possible to achieve the same yield using the method outlined in this chapter.

The reaction in Scheme 62 highlights the versatility of this methodology, and shows it has applications towards simplifying the synthesis of important medicinal targets such as Tamoxifen.
Conclusions

The work outlined in this chapter has shown the development of new methodology, towards tetrasubstituted alkenes, using a McMurry type reaction. This method proved to be unique; because usual McMurry reactions require harsh conditions to produce the low valent titanium, such as TiCl$_4$/Zn, whereas the research detailed in this chapter has illustrated that this is not always the case.

A number of examples were subjected to the reaction conditions, ranging from electron withdrawing substrates such as bromine, to electron donating such as an alcohol. All of the examples tested, showed positive results towards the synthesis of the expected products, with electron donating substituents producing the better yields on average.

The effect of symmetrical versus unsymmetrical alkene products was also investigated highlighting the versatility of this reaction. It was found that neither showed a particular preference towards producing a better yield, however the unsymmetrical products were only isolated as mixtures of isomers.

The usefulness of this new methodology towards current medicinal drug compounds has also been demonstrated. The core tetrasubstituted alkene core of Tamoxifen was able to be formed in 46% yield, which is lower than current reported methods. But, without the need for low valent titanium the reaction is safer and more user friendly than other published methods, and therefore improves the synthesis of drugs such as Tamoxifen.
Chapter 3

A novel palladium catalysed rearrangement route to heterocyclic compounds
Introduction

Previous work

Previous work by members of the Pritchard group has shown that activated vinyl cyclopropanes can undergo a previously unreported, novel rearrangement, to yield 5-vinylpyrrolidinones (Scheme 63). The treatment of such a cyclopropane, in which one of the activating groups is an amide, with a catalytic amount of palladium in methanol, gives the hydroindole core in a stereocontrolled manner with essentially quantitative yields (Scheme 63).

Vincent Neary worked in this area with his main focus being on extending the scope of the cyclopropanations and amide couplings, followed by the subsequent Pd cascade reactions.
Vincent found it was possible to easily form fused cyclopropanes using a Rh(II) acetate catalysed cyclopropanation of various dienes (Figure 30).\(^7\)

![Figure 30: Fused cyclopropanes formed in Vincent Neareys' work.\(^7\)](image)

Peptide couplings on ring sizes up to 8 carbons were undertaken and the palladium cyclisation was possible up to ring sizes of 7 carbons. The 8 carbon ring proved difficult to cyclise under the standard conditions (Scheme 64).\(^7\)

![Scheme 64: Peptide couplings and Pd cyclisations undertaken by Vincent.\(^7\)](image)

Vincent then went on to optimise the cascade/Heck rearrangement reaction in a one-pot process (Scheme 65). This allowed easy access to the tricyclic core of the Lycorine alkaloids, and hence led to the formation of natural products such as lycorane.\(^7\)

![Scheme 65: An example cascade rearrangement/Heck reaction illustrating the effectiveness and versatility of the work.\(^7\)](image)
**Cascade reactions**

Cascade, or domino reactions, can be an extremely powerful way of constructing complex molecules through a 'one-pot' synthesis of multiple bonds. A domino reaction is technically defined as a process where two or more bond forming transformations take place under the same reaction conditions, without the addition of any other reagents and catalysts. There are numerous different types of domino reaction within the literature, including radical domino reactions. An example of this was published by Takahashi et al. whereby they form a bicyclic system through the use of tributyltin hydride and AIBN (Scheme 66).

![Scheme 66: An example radical domino reaction.](image)

Another example of a cascade reaction is transition metal-catalysed domino reactions including novel reactions involving rhodium-catalysed transformations, such as that published by Dauben et al, where a diazo-1,3-dicarbonyl compound is converted into an oxidobridged cycloheptanone through a 1,3-dipolar cycloaddition (Scheme 67).
Palladium catalysed domino reactions are of great value in synthetic methodology as they are usually performed catalytically. With Pd catalysed reactions becoming more popular an increasing number of examples outlining different Pd catalysed cascade reactions are being published. One excellent example published by Trost et al. in 1993, outlines the polycyclisation of polyenes like 150 to give a polyspirane 151. This clearly demonstrates how powerful this type of chemistry can be for the formation of products with numerous cycles at their core, as through the use of just 2.5 mol% Pd a structure containing 3 spiranes can be readily achieved.

More recent examples of palladium cascades include that published by Lu et al. in 2010, who reported a rapid synthesis of diverse carbo- and heterocyclic skeletons, but also showed that they could control the regioselectivity of the reaction simply by including or excluding water.
Lu et al. reported a novel process whereby the five-membered palladacycle, could be regioselectively trapped by Heck, as well as Suzuki cross-coupling or cyanation, to give migration ‘off’ product (path a) or migration ‘on’ product (path b) (Scheme 69). They reported that it is possible to form the bicyclic product shown in Scheme 70 as the sole product of what they refer to as the migration ‘on’ process.

Scheme 69: Migration ‘on’ and ‘off’ products proposed in Lu's synthesis.

Scheme 70: Optimised conditions for the Lu domino reaction.
If the reaction solvent is changed to DMF/H$_2$O (95:5), the sole product is then that shown in Figure 31 and referred to as the migration ‘off’ product.

![Figure 31: The product of using 5% water in the reaction.](image)

Lu et al. went on to explore the scope of the cascade reaction including trapping of the aryl palladium intermediates, with a previously unreported Suzuki coupling, via both the migration ‘on’ and ‘off’ processes, as well as forming fused polycycles via a Pd-catalysed Heck/ C-H activation/ intramolecular arylation domino reaction (Table 14).

**Table 14: Fused polycycles synthesised via Pd domino process.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Substrate" /></td>
<td><img src="image" alt="Product" /></td>
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</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Substrate" /></td>
<td><img src="image" alt="Product" /></td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Substrate" /></td>
<td><img src="image" alt="Product" /></td>
<td>88</td>
</tr>
</tbody>
</table>
The Lu groups proposed mechanism for these transformations is outlined in Scheme 71.76

Scheme 71: Proposed mechanism for the "on" and "off" palladium cascade.76
Stemona alkaloids

*Stemona* is a genus of flowering plants comprising about 25 species, and is the largest genus of the small monocotyledonous family Stemonaceae. The extracts of plants from the Stemonaceae family (*Stemona*, *Croomia*, and *Stichoneuron* genera) have been used in traditional medicine in Japan, China, and South Asia as treatment for respiratory diseases such as bronchitis and tuberculosis, and have also found use as anti-parasitics on humans and animals.

The *Stemona* alkaloids are a class of polycyclic compounds with relatively complex structures, which are characterised by the presence of a pyrrolo[1,2-a]azepine core (Figure 32). Over 100 structurally diverse compounds have been identified so far from the *Stemona* genus, by contrast only four alkaloids from the other genera of the family (*Croomia*, and *Stichoneuron*) are known. Innovation in powerful synthetic methods is driving improvements of the synthesis towards these alkaloids.

![Figure 32: The pyrrolo[1,2-a]azepine core of stemon.]({})

Some pure alkaloids derived from the extracts of leaves and roots of *Stemona* have been shown to have significant antitussive activity in guinea pigs after cough induction.

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The alkaloids can be classified into five groups according to their structural core; stemoamide (168), stenine (169), tuberostemospironine (170), stemoamine (171), and tuberostemoamide (172) (Figure 33) all of which contain the key azepine core.\textsuperscript{81}

\textbf{Figure 33: The structures of the five alkaloid groups.}\textsuperscript{81}
**Stemoamide group**

The stemoamide group currently consists of nine alkaloids all displaying the tricyclic 2H-furo[3,2-c]pyrrolo[1,2-a]azepine (A, B, C) core: stemoamide (173), stemonine (174), neostemonine (175), bisdehydroneostemonine (176), protostemonine (177), didehydroprotostemonine (178), isoprotostemonine (179), tuberostemoamide (180), and stemoninine (181) (Figure 34).

![Stemona alkaloids of the stemoamide group](image)

The tricyclic alkaloid stemoamide (173), a classic representative of this group, was first isolated in 1992 from the roots of *Stemona tuberosa* and has since attracted considerable synthetic attention within the literature. The first total synthesis of (-) stemoamide was reported by Williams *et al.* in 1994 (Scheme 72).
Reagents and conditions: a) 1M KMnO₄, 0.5M NaH₂PO₄, t-BuOH, 15 min; b) t-BuC(O)Cl, Et₃N, THF, 0°C to rt, 30 min; then cool to -78°C, (s)-benzyl)-2-oxazolidinone, n-BuLi, THF, 94%; c) n-Bu₂BOTf, CH₂Cl₂, -78°C, 1h; then Et₃N, -78°C to 0°C, 1h; then 4-benzyloxybutanal, 88%; d) 48% aq HF, CH₃CN, then sat aq NaHCO₃, K₂CO₃, 82%; e) t-BuMe₂SiOTf, collidine, CH₂Cl₂, -78°C to rt, 97%; f) 4-iodo-1-butene, t-BuLi, Et₂O, -100°C, 45 min; then add (185), then collidine, t-BuMe₂SiOTf, 78%; g) LiEt₂BH, THF, -78°C to rt, 91%; h) MsCl, pyridine, rt, 96%; i) NaN₃, HMPA, rt, 9h; j) O₃, CH₂Cl₂/CH₃OH (3:1), -78°C; then Me₂S, -78°C to rt, 49% from mesylate; k) NaClO₂, NaH₂PO₄·H₂O, CH₃CN, t-BuOH, H₂O, 2-methyl-2-butenone, 0°C; l) CH₂N₂, Et₂O, 0°C, 96%; m) PPh₃, THF/H₂O, reflux, 48h, 87%; n) H₂, 10% Pd-C, EtOH, 24h; o) MsCl, pyridine, rt, 15 min; p) NaH, THF, rt, 71%; q) HF·NEt₃, CH₃CN, rt, 7h, 63%; r) Dess-Martin periodinane, pyridine, CH₂Cl₂, rt, 30 min; s) n-Bu₂NF, THF, rt, 15 min, 94% (2 steps); t) PDC, CH₂Cl₂, reflux, 1.5h, 80%.

Scheme 72: Williams total synthesis of (-)-stemoamide.¹⁴
In the Williams total synthesis firstly aldehyde (182) was oxidised through the use of permanganate, to give the corresponding carboxylic acid, which was then converted to the imide (183) via the mixed pivalic anhydride. An asymmetric Evans aldol reaction exclusively formed the syn-aldol derivative (184). Subsequent deprotection of the silyl ether with HF, followed by addition of base to release the chiral auxiliary, and hydride reduction, afforded the t-butylimethylsilyl ether (185). Condensation of the lactone and protection of the intermediate alcohol gave (186) in a one pot procedure. Reduction of the ketone to the corresponding alcohol followed by mesylation gave (187), which was treated with sodium azide. Immediate ozonolysis afforded aldehyde (188). This was now ready for the crucial sequential ring cyclisations to afford the final stemoamide product (173).

First oxidation through the use of sodium chlorite and esterification of the resulting carboxylic acid to the methyl ester, followed by mild reduction of the azide, and hydrolysis of the resulting iminophosphorane led to in situ cyclisation to lactam (189). Hydrogenation and mesylation of the primary alcohol, followed by treatment with sodium hydride afforded the aza-bicyclic structure (190) with the A and B rings in place. Selective deprotection of the primary silyl ether, and oxidation of the resulting alcohol using Dess-Martin periodinane gave an intermediate aldehyde, which was immediately treated with n-butylammonium fluoride to remove the remaining silyl ether and give (191) as a 1:1 mixture of lactols. Finally pyridinium dichromate oxidation of the lactols gave the target (-) stemoamide (173).84

This first synthesis outlined by Williams et al. was achieved over 20 steps, which is not very efficient in terms of cost, time, and overall yield making this synthesis excessively complicated as a routine synthetic route to the stemoamide natural product.
Since publication of this first synthesis, numerous others have appeared within the literature, each using different methodologies, and improving the efficiency of the synthesis.

One of the most efficient syntheses was published by Wang et al. in 2011 who reported the synthesis of (±) stemoamide in 8 steps with an overall yield of 37% (Scheme 73).\textsuperscript{80}

\[ \text{Scheme 73: Wang total synthesis of (±) Stemoamide.}\textsuperscript{80} \]

Reagents and conditions: a) \( n\)-BuLi (1.0 equiv), THF, -78°C, 93%; b) TBSCI (1.4 equiv), DBU (1.4 equiv), CH\(_2\)Cl\(_2\), RT, 1 h, 87%; c) succinimide (2.0 equiv), K\(_2\)CO\(_3\) (2.0 equiv), DMF, RT; d) NaBH\(_4\) (5.0 equiv), EtOH, 0°C, 93% (two steps); e) FeCl\(_3\) (1.0 equiv), toluene, 0°C, 2 h, 86%; f) TBAF (3.0 equiv), THF, RT, 96%; g) [Ru\(_3\)(CO)\(_{12}\)] (3 mol%), CO (10 atm), TEA, 100°C, 6 h, 81%; h) NaBH\(_4\) (4.0 equiv), NiCl\(_2\) (0.3 equiv), MeOH, RT, 2 h, 74%.
Wangs' synthesis begins with a modified procedure for the alkynylation of aldehyde \( \textbf{192} \) with propargyl trimethylsilane (\textbf{193}) to form the propargylic alcohol, which was protected with TBS to give (\textbf{194}). The bromide was then reacted with succinimide and subsequent reduction with sodium borohydride yielded the hemiacetal (\textbf{195}). The use of anhydrous iron trichloride then successfully promoted the cyclisation to give \textbf{197} in a 3:1 d.r. Subsequent removal of the TBS and careful purification allowed the major isomer to be identified as \textit{cis} \textbf{198}. The mixture of distereoisomers of \textbf{198} was then subjected to ruthenium-catalysed CO-insertion to exclusively form the \textit{trans}-\textbf{199} due to an unprecedented epimerisation of the allenic alcohol. Further investigation into the mechanism indicated that an equilibrium between \textit{cis} and \textit{trans}-\textbf{198} allows both isomers to be converted into one diastereomer of \textbf{199}.

The synthesis was then completed through the use of nickel-catalysed reduction to give (±) stemoamide (\textbf{173}).
Aims

The aim of the research outlined in this chapter was to develop a new palladium catalysed cyclisation, Heck coupling cascade reaction, which will allow access to the complex cyclic natural product cores of the stemona alkaloids, with focus on the stemoamide group (Figure 35), via a relatively easy synthetic route using a single reaction vessel.

![Figure 35: The tricyclic core of the stemoamide group of stemona alkaloids.](image)

This should allow for an improvement on current methods, in terms of overall yield, due to fewer intermediates needing to be isolated. The new method will need less solvent, and other starting materials, due to the reaction being achieved in a single vessel.

![Scheme 74: Synthesis of the bicyclic core structure of stemoamide.](image)

Once the core bicyclic structure synthesis has been optimised (Scheme 74), investigation into performing a third palladium catalysed carbonylation reaction in the same reaction vessel will be undertaken. This will allow the third ring of the natural product, the lactone, to be inserted in to the molecule as part of the one pot process (Scheme 75).

![Scheme 75: Carbonylation reaction from bicyclic structure towards tricyclic core of stemoamide.](image)
Results and discussion

Synthesis of stemoamide

The formation of Stemoamide (Figure 36) was targeted, which would utilise a palladium cyclisation cascade allowing for a continuation of the previous work carried out within the Pritchard group by Vincent Neary as discussed in the introduction of this chapter.

Figure 36: The natural product stemoamide

It was envisaged that the core of the molecule could be easily formed by coupling a vinyl cyclopropane with a simple aliphatic amine chain (Scheme 76).

Scheme 76: Retrosynthesis of stemoamide to the starting amine and cyclopropane.
A route to the synthesis of amine 208 had already been achieved by Craig Early, but some optimisation was required. The resulting yields from this optimisation are detailed in red in Scheme 77.

Starting from commercially available 3-butyne-1-ol (209), bromination of the terminal triple bond, through the use of elemental bromine in a solution of potassium hydroxide in water, was achieved in almost quantitative yields.

The following reduction of the alkyne was performed using tosyl hydrazide resulting in the isolation of the cis alkene 211 in good yields of up to 90%. Initially this step was performed on smaller scale due to the explosive nature of the material, but after further careful investigation it was discovered, contrary to what had been previously reported, that it is possible to perform this step on a scale using upwards of 15g of the tosyl hydrazide without any safety issues, or adverse effects on the product yield.
The subsequent mesylation, and conversion to the iodide using the Finkelstein reaction, were carried out in 87% and 94% yield respectively. The displacement of the iodine for a phthalimide was also performed in a good yield of 69%. However, when it came to cleaving the phthalimide (Scheme 78) to complete the synthesis and produce the primary amine 208, problems with the yield began to arise. The product amine could only initially be isolated in an inconsistent yield of 15-35%.

Scheme 78: The phthalimide cleavage mechanism.

After increasing the equivalents of hydrazine monohydrate from 1 to 5, the yield showed a vast improvement producing amine 208 in a consistently good yield of 75%.
The vinyl cyclopropane could be easily synthesised, as previously shown by Vincent Neary.\textsuperscript{70} Firstly sodium methoxide is made \textit{in situ} from sodium pieces dissolved in methanol. To this dimethyl malonate and 1,4 dibromobut-2-ene were added forming dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (218) in a good yield of 85%. Hydrolysis of one of the esters was then accomplished using lithium hydroxide producing 1-(methoxycarbonyl)-2-vinylcyclopropanecarboxylic acid (200) in a yield of 90% (Scheme 79).

![Scheme 79](image)

The target cyclopropane was isolated in good overall yield of 77\% over the two steps. It was expected that the hydrolysis step between 218 and 200 would occur on the least hindered face of the cyclopropane, thus producing the \textit{cis} product as shown in Scheme 79. This stereochemistry was confirmed using selective-nOe (Figure 37).

![Figure 37](image)

Once the two units of the core were synthesised they were coupled together, initially using the peptide coupling reagent HBTU (Scheme 80).\textsuperscript{70}
This produced the desired product (207) in 63% yield (Scheme 80); however HBTU is a very expensive reagent. T3P was a viable cheaper alternative.86

Due to the limited quantity of amine 208, benzylamine was used as a substitute in a trial reaction with T3P (Figure 38). Once it was discovered that T3P was a viable substitute for HBTU (Scheme 81) the reaction was optimised (Table 15).

Figure 38: The structure of the coupling agent T3P.

The trial reaction formed the expected product in 36% yield. This showed it was a viable coupling reagent for this reaction, and it was hoped that after some optimisation it would be as effective as HBTU.
Table 15: Optimisation of T3P coupling conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>T3P equivalents</th>
<th>Time (hours)</th>
<th>Isolated yield (%)</th>
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<td>3</td>
<td>36</td>
</tr>
<tr>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.1</td>
<td>3</td>
<td>55</td>
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<tr>
<td>3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.1</td>
<td>17</td>
<td>57</td>
</tr>
<tr>
<td>4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.1</td>
<td>17</td>
<td>59</td>
</tr>
<tr>
<td>5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.5</td>
<td>17</td>
<td>88</td>
</tr>
</tbody>
</table>

a: DMF used as the solvent, b: EtOAc used as the solvent

Initially the reaction was performed in DMF, (the solvent previously used by Vincent when using HBTU), with the T3P in EtOAc (Table 15, entry 1). However, the yield was much lower than that obtained with HBTU at 36%. Therefore the solvent was changed to EtOAc to match the solvent the T3P was in, which increased the yield to 55% (Table 15, entry 2), suggesting that there may be a solubility issue when the two solvents in the system are different.

This was still below the yield achieved through the use of HBTU. The reaction time was increased using both DMF and EtOAc as the solvent for direct comparison. These yielded similar results, both showing an increase in yield, but both still below the target of 63% (Table 15, entries 3&4). Although the yields were similar it was decided that EtOAc would be the best choice to proceed with during optimisation, due to the difficulties encountered when attempting to remove DMF on workup.

The T3P was then increased to 1.5 equivalents, because the leaflet supplied with the chemical claimed this was the optimal amount. The solvent was maintained as EtOAc and the reaction performed overnight. This gave a much greater yield of 88% (Table 15, entry 5), which was deemed to be optimised. As this is a much higher yield obtained compared to HBTU, (Scheme 80) it is a viable replacement in the synthesis.

With these optimal conditions in hand, the peptide coupling, on the previously synthesised amine 208 and vinyl cyclopropane 200 could be performed, producing the target amide in a 76% yield (Scheme 82).
Now the key molecule (207) was synthesised, the palladium cyclisation, and hence cascade reaction, could be attempted. Initially the cascade was performed step-wise, firstly performing the palladium cyclisation, followed by the Heck reaction, thus ensuring each step would produce the expected product. The palladium cyclisation of vinyl cyclopropane 200 produced the expected 5-membered ring as a mixture of inseparable diastereoisomers in a moderate yield of 40%, with a ratio of 3 : 2 major : minor products (Scheme 83).

Using selective-nOe it was determined that the anti-product with respect to the vinyl and ester groups is the major product of the cyclisation (Figure 39).
Once the success of the first step had been determined, the product could be subjected to Heck conditions. This could be achieved either via addition of triethylamine \textit{in situ}, after the initial cyclisation had been performed, followed by heating the reaction to reflux. Performing the reaction this way meant no intermediate work up was required (Scheme 84). This allowed the expected product (203) to be obtained in 18\% yield over the two steps.

![Scheme 84: In situ addition of triethylamine.](image)

Alternatively the 5-membered ring could be isolated and then further reacted with fresh Pd(0) and the addition of triethylamine (Scheme 85).

![Scheme 85: Heck reaction carried out after isolating the 5-membered ring.](image)

The Heck reaction was carried out successfully in 45\% yield, thus giving an overall yield of 18\% for the two steps. This yield was equal to that obtained when carrying out the transformation step-wise. The \textit{in situ} method was favored, due to the purification of the intermediate not being required.

Once the two steps of the synthesis had been successfully performed separately the one pot method could then be attempted.
This was done using the same reagents as the step wise method, however they were all put in the reaction together, and the reaction only refluxed for 24 hours (Scheme 86).

![Scheme 86: One pot palladium cascade](image)

Doing the cyclisation as a one-pot reaction allowed the reaction yield to be increased to 38%, which was a vast improvement on the 18% yield achieved via the step wise method. In an attempt to further improve this yield the reaction was attempted in the microwave, which after some optimisation increased the yield to 52% (Table 16).

**Table 16: Optimisation of microwave cascade conditions.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction time</th>
<th>Catalyst load (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1h</td>
<td>10</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>2h</td>
<td>10</td>
<td>42</td>
</tr>
<tr>
<td>3</td>
<td>2x1h</td>
<td>10</td>
<td>52</td>
</tr>
</tbody>
</table>
Carbonylation

Once the cascade reaction had been optimised, focus moved towards performing the reaction under a carbon monoxide atmosphere. It is known within the literature,\(^\text{87}\) that carbonylation can occur when a reaction is performed under a carbon monoxide atmosphere, and palladium catalysis conditions. Therefore it was hoped that after the Heck coupling, the ester required to form the lactone functionality of the final molecule, could be introduced via the same one-pot reaction (Scheme 87).

![Scheme 87: Target carbonylation reaction.](image)

This was initially attempted using the same standard setup as that for the Heck coupling. Once all reagents were prepared the system was evacuated using a standard pump and backfilled with CO. However, this method proved ineffective forming the target molecule 205 in a low, irreproducible yield, of 29\%. The major product from the reaction was found to be the Heck product 203 (Figure 40).

![Figure 40: Major product from initial carbonylation reactions.](image)
This led to a theory that if a methyl group was added on to the vinyl group (Figure 41) it would block the formation of the Heck product 203 (Figure 40), and therefore promoting the exclusive formation of the target carbonylated product 228 (Scheme 88).

One method towards the synthesis 1-(methoxycarbonyl)-2-(prop-1-en-2-yl)cyclopropanecarboxylic acid 222 is reported in the literature by Georgakopoulou et al.\textsuperscript{88} (Scheme 89). The group claim that through the use of isoprene as the starting diene, and rhodium acetate as a catalyst, it is possible to form the target cyclopropane 222 in good yields. The group also report that it is possible to control the outcome of the reaction simply by reducing the reaction time, making it a potentially easy way to form the target cyclopropane.
However, after attempting to repeat the literature reaction, it was found exclusive formation of the target compound (Scheme 90) was not possible. A number of different reaction conditions were used (Table 17). Lowering the catalyst loading was the primary focus, as it was thought maybe the high reactivity of the rhodium catalyst was the problem.

Scheme 90: Attempted cyclopropane formation.

Table 17: Attempted optimisation of the cyclopropane reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst loading (%)</th>
<th>Time (mins)</th>
<th>Temperature</th>
<th>Ratio (222:229)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>5</td>
<td>reflux</td>
<td>1:1</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>5</td>
<td>reflux</td>
<td>1:1</td>
</tr>
<tr>
<td>3</td>
<td>0.1</td>
<td>5</td>
<td>reflux</td>
<td>1:1</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>30</td>
<td>reflux</td>
<td>1:2</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>5</td>
<td>rt</td>
<td>1:1</td>
</tr>
</tbody>
</table>

Despite these attempts at optimisation, only a 1:1 inseparable mixture of stereoisomers could be obtained.

Attempts were also made to separate the compounds, firstly by hydrolysing one of the esters on both compounds in the mixture (Scheme 91), however the two stereoisomers still proved impossible to separate by column chromatography.

Scheme 91: Ester hydrolysis on mixture of regioisomers.
As the isoprene approach was proving unsuccessful, a different route previously reported in a thesis by Jamie Cummins\textsuperscript{89}, involving the use of methyl vinyl ketone and dimethyl bromomalonate to produce a ketocyclopropane (Scheme 92).

\[
\text{CH}_2=\text{CHCO}_2\text{Me} + \text{MeOCOBr}\text{Me} \xrightarrow{\text{K}_2\text{CO}_3, \text{DMF, rt, 2h}} \text{CO}_2\text{Me} \text{CO}_2\text{Me}
\]

\textbf{Scheme 92:} Formation of a ketocyclopropane from methyl vinyl ketone.

This produced a ketocyclopropane in a good 70\% yield. A Wittig reaction could then be performed to produce the target cyclopropane, whereby the methyl would be in the correct position on the double bond (Scheme 93).

\[
\text{CO}_2\text{Me} \text{CO}_2\text{Me} + \text{Br}^-\text{Me} \xrightarrow{\text{n-BuLi, Et}_2\text{O}} \text{CO}_2\text{Me} \text{CO}_2\text{Me}
\]

\textbf{Scheme 93:} Wittig reaction to give the target cyclopropane.

This produced the diester in a moderate 44\% yield. Some attempt was made to optimise this yield (Table 18), however no further improvement could be achieved.

\begin{table}[h]
\centering
\begin{tabular}{cccc}
\textbf{Addition} & \textbf{Temperature (°C)} & \\
\hline
\textbf{Entry} & \textbf{Solvent} & \textbf{n-BuLi} & \textbf{Ketone} & \textbf{Yield (\%)} \\
1 & Et\textsubscript{2}O & -78 & -78 & sm \\
2 & Et\textsubscript{2}O & -78 & rt & 6 \\
3 & DCM & -78 & rt & sm \\
4 & THF & -78 & rt & 15 \\
5 & THF & rt & rt & 22 \\
6 & Et\textsubscript{2}O & rt & rt & 44 \\
\end{tabular}
\caption{Optimisation of Wittig reaction.}
\end{table}
As can be seen in Table 18 the optimal conditions appear to be addition of the n-BuLi at room temperature. This might be due to the deprotonation of methyltriphenylphosphonium bromide being too slow at -78°C, causing only a small amount of methyltriphenylphosphine ylide to be available under the reaction times used, thus resulting in lower yields.

Hydrolysis of one of the esters was then performed using the same conditions as outlined earlier (Scheme 79), allowing the target mono acid cyclopropane (Scheme 94) to be formed in 75% yield.

The stereochemistry was again determined through the use of selective-nOe, which showed that, as expected, the ester and methyl alkene are on the same face (Figure 42).

Once the target cyclopropane containing the desired methyl blocking group was synthesised it could be coupled to amine 208 in good yields of 77% (Scheme 95).
The cyclisation cascade procedure could then be performed on this substrate, which would determine whether the blocking methyl group had the desired effect. Initially the cyclisation Heck cascade was performed under a nitrogen atmosphere (Scheme 96). Although it was expected this would only form the 5-membered ring, due to the methyl blocking group being positioned to prevent the Heck product forming, this reaction would allow for the identification of any occurring side reactions, as well as proving the concept of the blocking groups effectiveness against the Heck reaction.

![Scheme 96: Cyclisation, Heck cascade.](image)

As predicted the cascade only formed the 5-membered ring in a good yield of 54%. This is a slight improvement compared to the substrate without the blocking methyl in place. No other side products were observed, giving a good indication that this method would improve the yield of the carbonylation reaction.

![Figure 43: Expected product after carbonylation.](image)

However, when the cascade reaction was attempted under a carbon monoxide atmosphere the expected product (Figure 43) was not observed in the $^1$H NMR. After further investigation of the $^{13}$C and HMQC it was determined that a cyclopropane had formed in place of the methyl ester (Scheme 97).
The product 236 (Scheme 97) was identified by $^1$H & $^{13}$C NMR. The peaks corresponding to the cyclopropane in the $^1$H NMR spectrum were observed at 0.42 and 0.84ppm, both integrating to 1. The HMQC confirmed the two protons were on the same CH$_2$ carbon. The formation of this type of product under palladium catalysis conditions is known, and although it is not the desired product, it proves that the required intermediate (Figure 44) must be forming in the reaction.

Once this intermediate (237) is formed in the reaction the expectation is that CO will then insert in to the carbon palladium bond thus forming the expected ester (Scheme 98, path A). However, in this case a 3-exo-trig cyclisation occurs instead, forming the observed cyclopropane product (Scheme 98, path B).
With this in mind, the reason for the failure of the carbonylation reaction must be attributed to a poor CO atmosphere in the system. This could have been caused due to an inferior pump not fully degassing the solution, or the system was not sealed sufficiently to allow a sufficient CO atmosphere to be obtained.

This lead to the use of a freeze, evacuate, thaw technique with the use of a strong vacuum and a schlenk tube. The reaction was prepared in the Schlenk tube, following the standard procedure under nitrogen. Once all the reactants were added the flask was sealed. Using a two way tap the flask was firstly evacuated, then CO introduced via balloon in to the system by switching the tap, finally the tube was frozen in liquid nitrogen for 10 minutes. While still under CO pressure from the balloons, the flask was allowed to thaw. This cycle was repeated 4 times to ensure a strict CO atmosphere was achieved. Once this new technique was employed the expected product began to form in a reproducible yield (Scheme 99).
This then lead to a number of different amines being incorporated with the two
cyclopropanes (Figure 45), giving a variety of examples of this cascade (Table 19).
The amines were chosen to allow different ring sizes to be obtained after the
cyclisation.

![Figure 45: Amines and cyclopropane examples to be subjected to cascade conditions.](image)

In the reactions involving amines 2 & 3 (Figure 45), iodine was positioned in place of bromine, because when the cyclisation was attempted on substrates containing a bromine only 5-membered ring products could be obtained (Scheme 100) i.e. no Heck reaction was being observed.

![Scheme 100: Product from CO reaction when bromide used.](image)

Therefore it was hoped that by having the iodine instead it would facilitate the Heck reaction, which Table 19 entries 2, 3, and 6 show to be true. However, one example Table 19 entry 5, shows the Heck coupling was still proving elusive, which might be able to be corrected through the use of longer reaction times.

![Scheme 101: Formation of 2-iodobenzylamine.](image)
2-Iodobenzylamine (amine 2, Figure 45) was not commercially available, and was therefore synthesised using a method devised by Dr Andrew Culshaw involving using 7M ammonia in methanol, forming the desired amine in 76% yield (Scheme 101).

Table 19: Summary of results from CO cascade reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cyclopropane</th>
<th>Amine</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>1</td>
<td><img src="https://example.com/structure1.png" alt="" /></td>
<td>28</td>
</tr>
<tr>
<td>2</td>
<td>a</td>
<td>2</td>
<td><img src="https://example.com/structure2.png" alt="" /></td>
<td>52</td>
</tr>
<tr>
<td>3</td>
<td>a</td>
<td>3</td>
<td><img src="https://example.com/structure3.png" alt="" /></td>
<td>51</td>
</tr>
<tr>
<td>4</td>
<td>b</td>
<td>1</td>
<td><img src="https://example.com/structure4.png" alt="" /></td>
<td>52</td>
</tr>
<tr>
<td>5</td>
<td>b</td>
<td>2</td>
<td><img src="https://example.com/structure5.png" alt="" /></td>
<td>46</td>
</tr>
<tr>
<td>6</td>
<td>b</td>
<td>3</td>
<td><img src="https://example.com/structure6.png" alt="" /></td>
<td>36</td>
</tr>
</tbody>
</table>

Table 19 summarises the results from the various CO cascade reactions attempted, showing that it is applicable to a variety of ring systems.
The introduction of the blocking methyl group produced mixed results, despite the theory that it would improve yields by blocking the Heck product. Table 19 entries 1 & 4 actually showed a reduction in overall yield going from 52% without the blocking methyl down to 28% when the methyl group was present, completely contradicting the expected effect.

Whereas, Table 19 entries 3 & 6 highlight the expected effect of the change, with the yield increasing from 36% without the blocking group up to 52% when it is. This result is probably caused by the reduction of side products being formed when the blocking methyl group is in position.

The reaction outlined by Table 19 entry 6 also produced two other products, which most likely explains the lower than expected yield (Scheme 102).

\[
\text{Scheme 102: Products from reaction shown in Table 19 entry 6}
\]

In this particular reaction although the major product was still the expected carbonylated compound, the second highest yield was observed as a product which only contained the 5-membered ring. Once further investigation was carried out in to why the Heck reaction had not occurred, it was discovered carbonylation had occurred on the iodine position of the phenyl ring. This was determined through $^1$H NMR which showed two clear methyl esters were present in the molecule, however an aromatic proton was shown to be at 8 ppm suggesting an electron withdrawing group was still present on the ring. This was further confirmed using mass spectrometry showing iodine was no longer present in the product.
This suggested that the carbonylation at the iodine position was now occurring faster than the Heck reaction, which after discovering that the bromine in the same position was not reactive enough to allow the Heck reaction to occur as discussed earlier, was not good news for a one pot cascade.

In order to improve the yield of the desired product outlined in Scheme 102, further work would firstly need to involve performing the Heck reaction without the presence of a CO atmosphere then carry out the carbonylation afterwards, which should still make the product obtainable in a single one pot reaction.

The stereochemistry of the products in Table 19 was determined using nOe. The example shown in Figure 46 is the analysis of Table 19 entry 6.
Conclusion

The work outlined in this chapter has shown the development of a one-pot palladium cascade reaction, allowing the synthesis of complex tricyclic cores of natural products, such as stemoamide, to be simplified. Firstly the synthesis of the amine chain 208 and vinyl cyclopropane 200 were optimised, which were then successfully coupled together, using HBTU in relatively good yields. The peptide coupling was then optimised through the use of T3P, which is a cheaper alternative to the previously used HBTU, as well as providing the product in an improved yield compared to previous methods.

The key palladium cyclisation cascade step was performed step-wise producing the expected products at each step in relatively good yields, however producing a low overall yield of only 18% for the two steps. When performed in a single vessel reaction, the yield was improved to 38%. Further optimisation of the cascade was achieved, improving the yield to 52%.

Once the cascade was optimised, attention turned to introducing the third ring (lactone) to the core, as part of the same one pot cascade. This was achieved by performing the reaction under a CO atmosphere; prepared using freeze, evacuate, thaw techniques to produce the expected carbonylated product in 28% yield. In an attempt to further improve this yield a blocking methyl group was intended to be placed on the vinyl group of the cyclopropane to block the Heck coupling product being formed.

This synthesis was eventually achieved, producing the target cyclopropane in 44% yield. This cyclopropane was then subjected to the same coupling and palladium cyclisation conditions producing the cyclic product in 52% yield, a large increase from the previous 28%.

A number of different examples, involving a variety of different amines coupled to the two cyclopropanes, were undertaken. This provided evidence of the scope of success of the reaction towards the formation of a variety of ring sizes.
Chapter 4

Synthesis of a fully substituted natural product core
Introduction

Highly substituted natural products are difficult to synthesise, due to the number of different functionalities present within the structure. The amaryllidaceae alkaloids are an important class of natural products, which constitute a number of highly substituted alkaloids. The lycorine-type alkaloids are a significant subclass of this family, and have attracted attention due to the interesting biological activities of some of its members, such as antibacterial, antifungal, and antineoplastic activities.  

![Figure 47: Galanthan ring structure of the lycorine type alkaloids.](image)

The lycorine-type alkaloids are characterised by the presence of a galanthan ring A, B, C, D core structure (Figure 47), and consist of a large number of examples. These include lycorine (250), α-lycorane (251), γ-lycorane (252), fortucine (253), siculinine (254), lycoricidine (255), narciclasine (256), 7-deoxypancratistatin (257), pancratistatin (258) (Figure 48).

The tetracyclic pyrrolo[d,e]-phenanthridine (galanthan) structure has been of great interest to synthetic chemists ever since the structure of lycorine was determined in 1955 by Uyeo and Wildman, primarily because its heterocyclic framework provides a basis to demonstrate the utility of new strategies.
Many lycorine-type alkaloids contain a trans-B-C ring juncture (such as lycorine 250, and α-lycorane 251), but compounds with a cis-B-C ring juncture are also known (such as γ-lycorane 252 and siculine 254).\textsuperscript{92}
A recent publication by Liu et al. outlined a total synthesis of some of these lycorine-type alkaloids. Through the utilisation of a cyclopropyl ring-opening rearrangement the group formed 2 alkaloids; anhydrocatanine (another example of lycorine type alkaloids), and γ-lycorine (Scheme 103).\textsuperscript{91}

\begin{equation}
\begin{aligned}
\text{MeO} & \quad + \quad (259) \\
\text{O} & \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \}
The group proposed that the equilibrium at the important cyclopropane ring opening rearrangement step occurred via a non-classical carbocation intermediate (Figure 49).  

![Figure 49: Proposed equilibrium via a non-classical carbocation intermediate.](image)

The core of γ-lycorine shows a similar ring structure as that of the stemona alkaloid natural products. This therefore suggests that lycorine type alkaloids should be able to be formed by the same novel palladium cascade outlined in chapter 3 (Figure 50), thus making these classes of natural products viable for use as a model to further display the effectiveness of the afore mentioned novel cascade.

![Figure 50: a,b,c core of lycorine.](image)
Aims

The aim of the research outlined in this chapter was to synthesise a bicyclic core which was fully substituted, with a view to extending the scope of the palladium cyclisation/Heck cascade reaction detailed in chapter 3 to highly substituted systems. This will provide an easy route to the synthesis of complex natural products.

The work was undertaken with no specific natural product in mind (Scheme 104); however the target core was chosen to include a number of different functionalities, so that an array of different products could be easily obtained once the core synthesis was optimised.

Scheme 104: Retrosynthesis of the target fully substituted core.
Results and discussion

The target fully substituted core was initially chosen without a specific natural product target in mind. This was because once the core structure, with the stereocenters and rings, was in place it would be relatively straightforward to introduce any extra functionality to the molecule. With this in mind it was decided to include a diol and double bond in the core structure, thus allowing a large number of possibilities for future development of the molecule (Scheme 105). This synthesis would also follow on from the research outlined in chapter 3, with the eventual goal being a one-pot cascade to produce the target structure.

![Scheme 105: Retrosynthesis of target core molecule.](image)

In order to achieve the goal, firstly the palladium cascade (developed in chapter 3) needed to be tested and potentially optimised, and for this to be possible a fused cyclopropane needed to be synthesised using methodology previously optimised by Vincent Neary.\textsuperscript{70}
The synthesis was started with (1S, 2S)-3-bromocyclohexa-3,5-diene-1,2-diol, which was commercially available as a single isomer. Initially this needed to be protected, thus allowing the diol to be preserved during the subsequent steps of the synthesis (Scheme 106). With the bromine present in the molecule it would allow a Heck reaction to be possible, hopefully as part of a cascade reaction, later in the synthesis.

![Scheme 106: Protection of the diol.](image)

The protection was achieved in good yields of up to 90% in a short reaction time of one hour, at room temperature without the need for further purification. The cyclopropanation of the protected compound (1S, 2S)-4-bromo-2,2-dimethyl-3,7-dihydrobenzo[1,3]dioxole could then be attempted (Scheme 107).

![Scheme 107: Cyclopropanation of the protected diol.](image)

Previous work found that the optimal temperature for this reaction is the reflux temperature of DCE. However, because diazomalonate is known to be explosive at high temperatures, ideally a lower temperature would be used for the reaction. Therefore, initially, optimisation of the conditions for the cyclopropanation was the focus.
Table 20: Results from the cyclopropanation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Time (hours)</th>
<th>Isolated yield of cyclopropane (282) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DCE</td>
<td>20</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>DCE</td>
<td>20</td>
<td>72</td>
<td>12-21</td>
</tr>
<tr>
<td>3</td>
<td>DCM</td>
<td>reflux</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>DCE</td>
<td>55</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>DCE</td>
<td>reflux</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>DCE</td>
<td>reflux</td>
<td>3</td>
<td>15-30</td>
</tr>
</tbody>
</table>

Previous work found that when forming the fused cyclopropane on 1,3-cyclohexadiene, the optimal solvent was dichloroethene, therefore initially the reaction was attempted at room temperature in DCE (Table 20, entry 1).

However, after a reaction time of 3 hours, none of the expected product was observed by $^1$H NMR spectroscopy or TLC. Therefore the reaction time was increased, and monitored by TLC. After 3 days a low yield of 15% was observed. Due to the low yield observed the reaction was repeated numerous times, but the only outcome of this was an inconsistent yield between 12-21% of the fused cyclopropane being observed (Table 20, entry 2).

Since this was a much lower yield than expected, the solvent was changed to DCM, and the temperature increased to reflux, which is still much lower than the temperature required when refluxing DCE (Table 20, entries 3&4). However, in agreement with previous work, this yielded none of the expected fused cyclopropane product. The solvent was therefore reverted back to DCE and the temperature maintained at 55°C overnight in an attempt to drive the reaction forward without the need for reflux.
This again did not yield any of the expected product (Table 20, entry 4). The temperature was then increased to reflux, hence reproducing the conditions outlined by Vincent Neary.\textsuperscript{70} This produced only starting material from the reaction, which was an unexpected result, because these were the conditions expected to give at least a moderate yield. It was therefore deduced that, even though the \textsuperscript{1}H NMR spectrum for diazomalonate appeared to be correct, the material must have decomposed a sufficient amount to cause issues with the synthesis.

When a fresh sample of diazomalonate was used in the reaction the expected fused cyclopropane was observed, however only in poor yields of 15-30\% (Table 20, entry 6).

Because the diazomalonate was not producing acceptable yields for the cyclopropanation reaction, an alternative was found in a phenyliodonium ylide (Scheme 108).\textsuperscript{94}

\[
\begin{array}{c}
\text{O} \quad \text{O} \\
\text{MeO} \quad \text{CO} \\
\text{MeO} \quad \text{OMe} \\
\text{Ph}(\text{OAc})_2 \quad \text{KOH} \\
\text{CH}_2\text{Cl}_2, \text{rt}, 2\text{h} \\
\end{array}
\begin{array}{c}
\text{O} \quad \text{O} \\
\text{MeO} \quad \text{CO} \\
\text{MeO} \quad \text{OMe} \\
\text{Ph} \\
\end{array}
\]

\textit{Scheme 108: Formation of the phenyliodonium ylide.}

This was reported in the literature to be a superior reagent for the formation of cyclopropanes, and it would also be beneficial for the synthesis due to no reports of explosive decomposition. Nonetheless, when this ylide was directly substituted in to the synthesis none of the expected product was observed, and it was quickly realised that this was because it rapidly decomposes at high temperatures. Therefore the temperature was reduced to room temperature, but this again did not produce any of the expected fused cyclopropane.
Therefore the synthesis was continued using the low yielding method involving the use of rhodium acetate dimer (Scheme 107). Once the fused cyclopropane was obtained, the next step was to simply hydrolyse one of the ester groups to the carboxylic acid. This was achieved in good yields of 85% in 2 hours (Scheme 109).

![Scheme 109: Hydrolysis of one of the cyclopropane esters.]

The peptide coupling of (284) to a simple amine, benzylamine, could then be performed. At this stage there was no need for a more complex amine, because the initial palladium cyclisation needed to be tested before further development of the molecule could commence. The peptide coupling was performed using the optimised conditions of T3P described in chapter 3 (Table 15). This was achieved in good yields of 86% without the need for any further purification.

![Scheme 110: Peptide coupling to benzylamine.]

Now that the intermediate had been synthesised the key palladium cyclisation could be attempted, using the same conditions as used previously (Scheme 111).
After leaving the solution stirring overnight there was no evidence of any cyclisation taking place, which was confirmed with LC-MS and $^1$H NMR spectroscopy, with both showing only starting material was isolated from the reaction. More forcing reactions were then attempted. Firstly heating the reaction gently overnight, but this had no effect on the outcome of the reaction. Therefore the temperature of the reaction was increased further, utilising the microwave oven so that the pressure could also be increased (Table 21).

### Table 21: Microwave conditions used for cyclisation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Time (minutes)</th>
<th>Isolated product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^a$</td>
<td>120</td>
<td>15</td>
<td>SM</td>
</tr>
<tr>
<td>2$^b$</td>
<td>120</td>
<td>15</td>
<td>SM</td>
</tr>
<tr>
<td>3$^a$</td>
<td>120</td>
<td>30</td>
<td>SM</td>
</tr>
<tr>
<td>4$^a$</td>
<td>120</td>
<td>60</td>
<td>Degraded</td>
</tr>
<tr>
<td>5$^a$</td>
<td>130</td>
<td>30</td>
<td>SM</td>
</tr>
<tr>
<td>6$^a$</td>
<td>130</td>
<td>2x30</td>
<td>Degraded</td>
</tr>
</tbody>
</table>

- a: Methanol used as the solvent, b: Propan-2-ol was used as the solvent.

Initially the reaction was attempted in the usual methanol as well as propan-2-ol to ascertain whether it would affect the reaction. After 15 minutes reaction time in the microwave at 120°C (5 bar) neither set of conditions produced any evidence of cyclised product.
Previously Vincent hypothesised a mechanism for the cyclisation, which outlines the involvement of the solvent during the cyclisation.\textsuperscript{70}

\begin{scheme}
\begin{center}
\includegraphics[width=\textwidth]{scheme112.png}
\end{center}
\end{scheme}

\textit{Scheme 112: Hypothesised mechanism for the Pd rearrangement.}

Therefore, the rest of the attempted cyclisations were performed in methanol, because this was deemed the solvent most likely to allow a rearrangement to occur. The microwave reaction was performed again this time increasing the time to firstly 30 minutes, then 1 hour again at 120°C, but neither produced the expected product, only starting material and degraded material were isolated from the respective reactions (Table 21, entries 3&4).

The reaction was then performed at 130°C for 30 minutes, which again only produced starting material, then it was repeated using 2 x 30 minute reactions while monitoring the reaction by LC-MS, however after the second 30 minute reaction the product was found to only be degraded material with multiple peaks in the LC-MS none of which corresponded to the rearranged product (Table 21, entry 6).
This led to the conclusion that either; the bromine being in position on the double bond was withdrawing enough electron density from the double bond to deactivate it, and therefore hindering the Pd inserting into the alkene, or the active palladium species, Pd(PPh\(_3\))\(_2\), was too large to attack either face of the molecule, due to both faces being fairly hindered (Figure 51).

![Space filling model of Pd(PPh\(_3\))\(_2\) and fused cyclopropane structure 285 highlighting the steric issues with the insertion of the active palladium species in to the double bond.](image)

The space filling model shown in Figure 51 highlights the difficulty of fitting Pd(PPh\(_3\))\(_2\) into the small space, highlighted by a circle, in compound 285. This further suggests that steric hindrance is likely to be to blame for the failure of the palladium cyclisation.

This led to work being firstly aimed towards the formation of the starting diol without the bromine in position on the alkene. It was hoped that by removing the bromine it would definitively show whether the sterics were the problem with the cyclisation, or whether it was the bromine deactivating the double bond to such an extent that the palladium was unable to insert in to the bond. Ideally the bromine would be substituted for a methyl group or replaced for just a proton. Then, if the palladium rearrangement still did not work with tetrakis(triphenylphosphine)palladium(0), this would strongly suggest that the sterics of the system are to blame, and other palladium sources could then be investigated.
It was initially envisaged that it would be fairly easy to remove the bromine and replace it with a proton using a simple BuLi reaction.

\[
\begin{align*}
\text{Br} & \quad 1. \text{n-BuLi} \\
(281) & \quad \text{Et}_2\text{O}, -78^\circ\text{C}, 1\text{h} \\
\text{O} & \quad 2. \text{H}_2\text{O} \\
\text{H} & \quad (292)
\end{align*}
\]

Scheme 113: Removal of the bromine using BuLi

But, when this reaction was attempted in diethyl ether, after 1 hour only starting material could be observed from the reaction, there was no evidence that the symmetrical acetal was being formed. The reaction was then repeated in a number of different solvents, but none of the reactions indicated any evidence that the target acetal was being formed (Table 22).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Isolated product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Diethyl ether</td>
<td>Starting material</td>
</tr>
<tr>
<td>2</td>
<td>DME</td>
<td>Starting material</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>Starting material</td>
</tr>
</tbody>
</table>

Table 22: Alternative solvents for the BuLi reaction.

Ideally the reaction would have then been attempted in either sec or tert-BuLi, but because of safety restrictions at Horsham this was not possible. Therefore attention was turned towards substituting a methyl group into the bromine position. Three different reactions were attempted in order to achieve this.

\[
\begin{align*}
\text{MeMgBr} & \quad \text{Pd(PPh}_3\text{)}_4 (10\%) \\
(285) & \quad \text{PhMe, rt, 17h} \\
\text{CO}_2\text{Me} & \quad (293)
\end{align*}
\]

Scheme 114: Grignard reagent substitution reaction.
Initially a reaction utilising a Grignard reagent – methylmagnesium bromide and tetrakis palladium was attempted (Scheme 114).\textsuperscript{95} The intention was, if this reaction worked, to substitute the methyl in to the bromine position as part of the palladium cascade reaction, because it is the same source of palladium used for the cascade reaction (Scheme 112). However, only starting material was observed from the reaction, which was confirmed by LC-MS and \textsuperscript{1}H NMR spectroscopy. This again could be due to the sterics of the system not allowing the palladium to interact with the molecule.

Subsequent reactions were performed on the uncyclised diol 281 starting material, which is less sterically hindered, thus ensuring the failure of the reaction isn’t due to these factors (Scheme 115).

Scheme 115: Conditions for addition of a methyl group.\textsuperscript{95}

Two different reactions were attempted both using the same methylboronic acid and utilising two different palladium sources. Firstly [1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) was used with potassium carbonate and reacting this in the microwave for 1 hour (Scheme 115).\textsuperscript{95} This only produced decomposed starting material, so was deemed too harsh for the substrate. The second, milder conditions, utilised tetrakis(triphenylphosphine)palladium(0) and potassium carbonate at room temperature (Scheme 116),\textsuperscript{95} but this only produced starting material from the reaction.

Scheme 116: Milder conditions for the introduction of a methyl group.\textsuperscript{95}
As it was proving difficult to obtain the starting diol without a bromine, a completely different route to the starting substrate was sought. The target of the synthesis was now (1R,2S)-cyclohexa-3,5-diene-1,2-diol (Figure 52), which is not commercially available.

![Figure 52: Target (1R,2S)-cyclohexa-3,5-diene-1,2-diol.](image)

One option towards the synthesis of this diol published in the literature involves the dioxygenase-catalysed oxidation of aromatic rings, using the bacterium *Pseudomonas putida* UV4 to form the cis-dihydrodiol. It was decided this was not a realistic option, because, not only do you need some experience at handling these cultures, the yield from the reaction is very poor.

A second option from the literature involved starting from 1,4-cyclohexadiene, and forming a mixture of the mono and diacetate through the use of iodine, and potassium acetate, then carrying the crude mixture forward to form the diol via use of an anion exchange resin – Amberlite IRA-400 (Scheme 117). This two-step synthesis produced the cis diol in 56% overall yield without the need for purification at either stage.
The diol could then be protected. Initially it was decided, that because the molecular weight was so low without the bromine attached, protection with DMP was not ideal. So a higher molecular weight protecting group in TBS was employed. This was able to be performed on large scales with excellent yields of 95%. Once protected the next step was to brominate the double bond to yield the trans bromo diol in good yields of 60% (Scheme 118).

Scheme 118: Bromination of the double bond.

All that was left to do was eliminate the bromine to form the diene and hence the target starting material. This was attempted using DBU as the base in toluene. However, after allowing this to react for 6 hours none of the expected diene was observed, only starting material was isolated from the reaction.

Table 23: Attempted conditions for elimination of bromine.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Time</th>
<th>Isolated product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1^a</td>
<td>Toluene</td>
<td>85</td>
<td>6</td>
<td>SM</td>
</tr>
<tr>
<td>2</td>
<td>Toluene</td>
<td>85</td>
<td>24</td>
<td>SM</td>
</tr>
<tr>
<td>3</td>
<td>Toluene</td>
<td>100</td>
<td>6</td>
<td>SM</td>
</tr>
<tr>
<td>4</td>
<td>DME</td>
<td>85</td>
<td>6</td>
<td>SM</td>
</tr>
<tr>
<td>5</td>
<td>NMP</td>
<td>85</td>
<td>6</td>
<td>SM</td>
</tr>
</tbody>
</table>

a: BEMP used as the base.

Therefore a number of different conditions including different solvents and temperatures were attempted, despite this only starting material was ever isolated from the reaction (Table 23). It was hypothesised that due to the large size of the TBS groups the bromines were not able to sit in their required axial position due to the steric hindrance caused by the TBS group.
The most favourable conformation would be where both bromines are equatorial, with the TBS groups sitting axial and equatorial, due to the size of the substituents, and the required stereochemistry of the oxygens (Figure 53).

![Figure 53: The most favoured conformation of the TBS protected diol.](image)

However, in order for the elimination of the bromine to occur, the bromine and the proton to be eliminated need to be *trans* to each other, thus allowing *trans* diaxial elimination to occur. This would therefore mean the bromines would need to be axial. However, due to the large steric hindrance caused in this conformation it is unfavourable (Figure 54).

![Figure 54: The ideal conformation for bromine elimination to occur.](image)

There are some cases where syn elimination is possible, when the correct solvent and reaction conditions are achieved, but despite this after the attempts shown in Table 23, it appeared in this case this would not be possible.

Therefore different protecting groups were trialled, mainly aiming at those which protect both oxygens through the same atom, thus holding the molecule in a more rigid flat conformation. So the use of DMP as a protecting group was revisited (Scheme 119).
Scheme 119: DMP protection and subsequent attempted bromination.

This was a successful way to protect the diol, with this step being achieved in moderate yields of 47%. But when it came to attempting to brominate the double bond, it was noticed that the reaction began to fume, indicating something undesirable was occurring. Upon closer inspection of the product $^1$H NMR spectrum, it appeared that the diol was now deprotected and the starting material had degraded, which could have been due to some HBr forming in solution, thus deprotecting the diol then the bromine decomposing the molecule. This theory was confirmed with IR spectroscopy which showed the presence of a very large broad OH peak. The reaction was repeated numerous times always producing the same outcome.

An alternative, similar protecting reagent, in di-tert-butylsilyl bis(trifluoromethanesulfonate) was found and utilised in the protection of the diol. This protecting group is acid stable; therefore no issues with future steps should arise. The diol protection was achieved in a moderate yield of 45%. Although this is only a low yield, when the bromination was attempted it was performed successfully in 78% yield, and the bromine was able to be successfully eliminated in a low yield of 15%. This is realistically too low to be synthetically viable, but it did allow the target starting material to be obtained so the rest of the synthesis could be performed (Scheme 120).
From the starting material all further steps in the synthesis were performed without any issues. Firstly the cyclopropanation was achieved in 23\% yield, followed by hydrolysis of one of the esters in a yield of 80\% and finally the coupling to benzylamine using T3P was achieved in 72\% yield, producing the intermediate required for the key Pd cyclisation step to be reattempted without the bromine in position, highlighting the reason for the previous failure of the rearrangement (Scheme 121).

Scheme 120: Formation of the rearrangement intermediate without a bromine in position on the double bond.

Scheme 121: Attempted palladium cyclisation of 307.
Table 24: Conditions for the Pd cyclisation of 307.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time (hours)</th>
<th>Temperature (°C)</th>
<th>Isolated product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17</td>
<td>20</td>
<td>SM</td>
</tr>
<tr>
<td>2</td>
<td>72</td>
<td>20</td>
<td>SM</td>
</tr>
<tr>
<td>3</td>
<td>17</td>
<td>reflux</td>
<td>Degraded material</td>
</tr>
</tbody>
</table>

After attempting the Pd cyclisation under the standard conditions of room temperature, overnight, only starting material was again observed from the reaction (Table 24, entry 1). The reaction was repeated leaving it stirring at room temperature for 3 days, but this still only produced starting material. In an attempt to promote formation of the expected product the reaction was performed at reflux overnight, but after running a crude $^1$H NMR spectrum it was found the starting material had fully decomposed (Table 24, entry 3).

This suggests that the reason for the failure of the cyclisation is not due to the deactivating nature of the bromine on the double bond, but more likely to be due to the sterics of the system preventing the palladium from being able to insert into the double bond. Further work now needs to be undertaken on this area, using different forms of palladium, which have smaller ligands than those in tetrakis(triphenylphosphine) palladium, in order to ascertain whether this rearrangement will be possible at all.
Conclusions

The research outline in this chapter discusses attempts to further the scope of the novel palladium cascade, detailed and optimised in chapter 3, through the formation of a fully substituted cyclohexene. The formation of key starting material 285 proved to be quite straightforward, with exception to the cyclopropanation step. A number of attempts were made to optimise the yield of the cyclopropanation using rhodium (II) acetate dimer, however only a moderate yield of up to 30% could be achieved.

When the palladium cyclisation reaction was attempted, only starting material could be obtained. Investigations were undertaken to determine whether the reason for the failure of the cyclisation was due to the bromine in the structure. To achieve this, focus moved to forming the starting diol without a bromine. After failures to achieve this through using butyl lithium, and Grignard reactions, eventually the starting diol was formed in a 5 step synthesis in relatively good yields. During the synthesis, problems caused by the protecting group on the diol had to be overcome. This may have been because the initial TBS protecting group caused the structure to adopt the wrong conformation needed for bromine elimination. This was overcome through the use of di-tert-butylsilyl bis(trifluoromethanesulfonate) as the protecting group.

The diol was then successfully cyclopropanated and coupled to benzylamine using the standard conditions, which allowed the key palladium cyclisation to be reattempted. However, the cyclisation was still unsuccessful producing only starting material from the reaction. When the conditions were attempted to be optimised, again only starting material could be obtained at room temperature, and when the reaction was heated to reflux the starting material completely decomposed.

The reasons for the failure of the cyclisation are still not certain, however current experimental data strongly suggests it is related to the steric of the molecule preventing the tetrakis triphenylphospine palladium inserting in to the double bond, therefore stopping the possibility of cyclisation occurring. A space filling model has also been produced, which further suggests the failure is linked to the size of the palladium ligands.
Chapter 5

Future work
Following on from the various aspects of the formation, and uses, of cyclopropanes detailed in this thesis, a number of different avenues of research could be continued in the future.

One such avenue could be the further development of the work carried out by MChem students involving Friedel Crafts reactions on 1-(1-chlorocyclopropyl)-4-methoxybenzene (85), which has shown promising initial results towards the formation of diaryl cyclopropane. Work towards diphenyl cyclopropane could also be furthered by future screening of a large number of palladium sources, along with a variety of different ligands and additives, (such as further investigation in to the use of CM-Phos and XPhos).

Another avenue of future research could be directed towards furthering the scope of the novel conditions detailed in chapter two of this thesis, towards tetrasubstituted alkenes. A large number of examples, mainly of unsymmetrical alkenes, could be investigated, as well as further optimisation of the current conditions. Studying a large number of further examples would also highlight what type of substrate, if any, produces a preference for E or Z products. The mechanism for this coupling also needs further investigation. This could be achieved by using NMR studies to monitor the reaction with the aim of discovering the intermediates being formed during the reaction. If the intermediates can be identified, then this would give a much greater insight into the mechanistic pathways this reaction takes under these novel conditions.
A third area of future research could be focussed on the palladium cascade work detailed in chapter 3 and 4 of this thesis. This would involve producing more examples of the palladium, Heck, carbonylation cascade, to allow any limitations of the cascade to be identified. The palladium catalyst used for the cascade could also be screened, with the aim of finding a catalyst which is still capable of performing the palladium cascade in good yields. But, more importantly the aim would be to find a catalyst which is capable of catalysing both, the cascade reaction when performed using a fully substituted core, as well as the usual cascade towards stemoamide, because the current tetrakis(triphenylphosphine) palladium (0) catalyst is not able to do this.

Once the fully substituted natural product core is successfully synthesised, a number of different natural products could be obtained via manipulation of the variety of functional groups present in the fully substituted tricyclic core structure.

The use of flow could also be utilised for this area of research, especially for the synthesis of amine 208. This would allow for improvement in not only the overall yield of the reaction, but also a reduction in the overall reaction time required for the multi-step synthesis, and the cost of the synthesis due to the small amount of reagents required for a flow reaction.

![Figure 56: Multi-step amine synthesis that could be subjected to flow studies.](image)

A further avenue for future research on the palladium cascade reaction would be to perform the carbonylation at a higher pressure than the current 1 atmosphere. This would require the use of specialised equipment that would allow the system to be evacuated and back filled with CO, as well as being able to withstand the high pressures the reaction vessel would be put under while undergoing the reaction. If this could be achieved, the yield for the carbonylation cascade would be expected to be significantly improved.
Chapter 6

Overall conclusions
This thesis has demonstrated the versatility of the cyclopropane ring and the effectiveness of utilising the unique properties it possesses. A number of different phenyl cyclopropanes have been produced containing the good leaving groups needed for Suzuki cross coupling reactions. However these reactions proved unsuccessful in the formation of 1,1-diphenylcyclopropane. Following the failure a second set of $p$-methoxyphenyl cyclopropanes were synthesised in an attempt to promote the cross coupling reactions. Despite these attempts the coupling still failed. Following this a different approach was attempted, involving starting with benzophenone, and trying to convert this into 1,1-diphenylcyclopropane. This was again unsuccessful. Despite the failures, the methodology developed for this has prompted new avenues of research, allowing for future development in this area.

The strain of cyclopropanes has also been utilised, through the use of a vinyl cyclopropane containing an amide, in the development of a palladium catalysed cyclisation, Heck coupling, carbonylation cascade. After optimisation of the methodology, the cascade was achieved in good yields up to 52%, varying with the length of amine chain, and hence the size of rings produced from the reaction. The scope of the reaction was investigated, with 5, 6 and 7 membered rings being successfully synthesised. This new methodology allows for the easy creation of complex multi-cyclic cores of natural products in a single reaction vessel.

The cyclisation of fused cyclopropanes has also been shown to be possible, when used towards the synthesis of highly substituted natural product cores. After some optimisation a cyclopropane was able to be fused to a cyclohexadiene. When bromine was present within the structure, cyclisation was unsuccessful, which was suspected to be because the electron withdrawing effect of the bromine was stopping the tetrakis(triphenylphosphine) palladium (0) catalyst being able to insert into the molecule. Therefore, efforts were driven towards forming the cyclohexadiene without the bromine. This was eventually achieved in 5 steps. But, once the required cyclopropanation and peptide coupling were achieved, and the cyclisation reattempted, still none of the cyclised product could be obtained.
Chapter 7

Experimental Section
**General experimental**

All the reagents used were obtained commercially and were not purified further. Tetrakis(triphenylphosphine)palladium(0) was obtained from two sources, Strem® and Sigma Aldrich®. THF was freshly distilled from sodium benzophenone prior to use, dichloromethane distilled from calcium hydride. All other solvents were used straight from the bottle. All reactions were run under a nitrogen atmosphere in oven-dried glassware (or flame-dried under nitrogen) unless otherwise stated.

All columns were monitored using TLC, on pre-coated aluminium backed silica plates. TLC plates visualised by Ultra Violet light, or phosphomolybdic acid dip. Flash column chromatography was performed under pressure, using silica gel 60 from Davisil Fluorochem. Some column chromatography was performed at Novartis using an ISCO combiflash® rf autocolumn. This is clearly stated when used.

$^1$H and $^{13}$C-NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer. Samples were dissolved in CDCl$_3$ (unless otherwise stated) using TMS (tetramethylsilane) as the internal reference. Coupling constants are measured in Hertz and are quoted to the nearest 0.1 Hz and chemical shifts are quoted in ppm.

Mass spectra were recorded using a Thermo Fisher Exactive with an ion max source and ESI probe fitted with an Advion Triversa Nanomate. IR spectra were recorded using Perkin Elmer FTIR Spectrometer (Paragon 100) as solutions using CH$_2$Cl$_2$ as solvent. Melting points were recorded on a Stuart Scientific apparatus and are uncorrected.

When reporting the $^1$H NMR assignments for cyclopropanes, due to the position of the plane of symmetry, each carbon has its two protons in different environments. Therefore the protons are reported as CHH’, whereby the proton on the ‘top’ face is denoted by no apostrophe, and the proton on the ‘bottom’ face is denoted by an apostrophe.
Chapter 1 experimental
1-Phenyl cyclopropanol (43)\textsuperscript{14}

\[
\begin{align*}
\text{EtMgBr (2 equiv.)} & \quad \text{Ti(O-i-Pr)}_4 (10\text{mol\%}) \\
\text{Et}_2\text{O, rt, 1h} & \quad \text{(43)} \quad + \\
\quad & \quad \text{(46)}
\end{align*}
\]

To a solution of methyl benzoate (0.68 g, 5.02 mmol) in anhydrous diethyl ether (20 mL) was added titanium (IV) isopropoxide (0.15 mL, 0.51 mmol) followed by slow addition over 1 hour via syringe pump of EtMgBr (3.60 mL, 10.80 mmol, 3M in diethyl ether). The reaction mixture was stirred for 10 minutes, then poured into 10\% aq. sulphuric acid at 0°C. The organic layer was removed and the aqueous layer extracted with diethyl ether (3x50 mL), the organic layers were combined and washed with water (50 mL), dried (MgSO\textsubscript{4}), filtered, and the solvent removed in vacuo to yield a yellow oil. Purification by silica gel column chromatography (5\% EtOAc in light petroleum) gave the target product (43) as a yellow oil (0.18 g, 52\%).

\[\text{\textsuperscript{1}H NMR (400MHz, CDCl}_3 \delta 0.89 (t, 2H, J=3.6, CH}_3\text{CH}_2, CH}_3\text{H}, CH}_3\text{H}, 1.07 (t, 2H, J= 3.6, CH}_3\text{H}, CH}_3\text{H}, 3.69 (s, 1H, OH), 7.03-7.19 (m, 5H, ArH). \text{\textsuperscript{13}C NMR (100MHz, CDCl}_3 \text{16.7 (2xCH}_2, 55.4 (Q), 123.4 (2xCH), 125.6 (2xCH), 127.4 (CH), 143.2 (Q). MS (ESI): [M-H]} \text{ requires 133.0659, found 133.0658. IR (thin film)/cm}^{-1}3584 (br s), 3054 (m), 2972 (w), 2937 (w), 2880 (w).

Also isolated was 3,4-diphenylhexane-3,4-diol (46) as a mixture of isomers as an orange oil (0.24 g, 35\%). \text{\textsuperscript{1}H NMR (400MHz, CDCl}_3 \delta 0.68 (t, 6H, J=7.2, 2xCH}_3\text{CH}_2, 1.65-1.81 (m, 4H, 2xCH}_3\text{CH}_2), 3.72 (s, 2H, 2xOH), 7.11-7.30 (m, 10H, ArH). \text{\textsuperscript{13}C NMR (100MHz, CDCl}_3 \text{7.8 (2xCH}_3, 34.9 (2xCH}_2, 80.8 (2xQ), 123.4 (4xCH), 125.6 (4xCH), 127.3 (2xCH), 144.7 (2xQ). MS (ESI): [M-H]} \text{ requires 269.1547, found 269.1547. IR (thin film)/cm}^{-1}3608 (br s), 3585 (s), 3154 (m), 2972 (w), 2937 (m), 2880 (w), 2253 (m).
**Control reaction – formation of 1,1-diphenylpropan-1-ol (53)**

![Control reaction diagram]

To a solution of benzophenone (0.91 g, 5.00 mmol) in anhydrous diethyl ether (20 mL) was added EtMgBr (3.40 mL, 10.20 mmol, 3M in diethyl ether) over a period of 1 hour. The solution was allowed to stir for a further hour then quenched with 10% aq. H₂SO₄, the organic layer removed, and the aqueous layer extracted with diethyl ether (3x10 mL), dried (MgSO₄), filtered, and the solvent removed in vacuo to yield a colourless oil. (0.49 g, 46%). \(^1\)H NMR (400MHz, CDCl₃) \(\delta\) 0.86 (q, 2H, J=7.4, CH₃CH₂), 2.08 (s, 1H, OH), 2.30 (t, 3H, J=7.4, CH₃CH₂), 7.14-7.41 (m, 10H, ArH). \(^1^3\)C NMR (100MHz, CDCl₃) 9.2 (CH₃), 35.6 (CH₂), 79.9 (Q), 127.4 (4xCH), 128.1 (4xCH), 129.5 (2xCH), 148.2 (2xQ). MS (ESI) [M+H]^+ requires 213.1274, found 213.1275. IR (thin film)/cm⁻¹ 3583 (br s), 3054 (m), 2986 (w), 1265 (s).
1-Phenylcyclopropyl 4-methylbenzenesulfonate (73)

To a solution of 1-phenyl cyclopropanol (0.07 g, 0.56 mmol) in pyridine (10 mL) was added p-toluene sulfonyl chloride (0.11 g, 0.56 mmol) and the solution stirred at 50°C for 20 hours. The colour of the solution changed from pale yellow to dark orange. The solution was poured into a mixture of crushed ice and distilled water (30 mL), the organic layer removed, and the aqueous layer extracted with diethyl ether (3x40 mL). The combined ethereal extracts were washed with 1M aq. HCl (3x40 mL) and brine (40 mL). The solution was dried (MgSO₄), filtered, and the solvent removed in vacuo to yield a yellow oil. Purification by silica gel column chromatography (20% diethyl ether in light petroleum) gave product as an orange solid (0.39 g, 62%). m.p : 68-69°C. ¹H NMR (400MHz, CDCl₃) δ 1.21 (m, 2H, J=1.2, CH'H', CH'H), 1.65 (m, 2H, J=1.2, CH'H', CH'H'), 3.65 (s, 3H, CH₃), 7.25-7.38 (m, 5H, ArH), 7.46-7.47 (d, 2H, J= 6.8, ArH), 7.91-7.93 (d, 2H, J= 6.8, ArH). ¹³C NMR (100MHz, CDCl₃) 13.5 (2xCH₂), 21.53 (CH₃), 67.1 (Q), 127.7 (2xCH), 128.0 (2xCH), 128.1 (3xCH), 129.3 (2xCH), 135.1 (Q), 137.7 (Q), 144.1 (Q). MS (ESI) [M+Na]⁺ requires 311.0718, found 311.0712. IR (thin film)/cm⁻¹ 3424 (m), 3056 (m), 2985 (m), 1376 (s), 1179 (s).
1-Phenylcyclopropyl methanesulfonate (72)

Following the general method outlined for the tosylate 73, methane sulfonyl chloride (0.18 mL, 2.33 mmol) was added to a solution of 1-phenylcyclopropanol (0.21 g, 1.53 mmol) in pyridine (10 mL). Purification by silica gel column chromatography (20% ethyl acetate in light petroleum) gave the target product (72) as an orange oil (0.18 g, 55%). 1H NMR (400MHz, CDCl3) δ 1.21 (t, 2H, J=1.2, CHH’, CHH’), 1.66 (t, 2H, J=1.2, CHH’, CHH’), 2.54 (s, 3H, CH3), 7.26-7.59 (m, 5H, ArH). 13C NMR (100MHz, CDCl3) 13.4 (2xCH2), 39.7 (CH3), 67.4 (Q), 128.7 (2xCH), 128.9 (2xCH), 129.1 (CH), 137.2 (Q). MS (ESI) [M+Na]+ requires 235.0405, found 235.0412. IR (thin film)/cm⁻¹ 3059 (m), 2974 (w), 1377 (s), 1174 (s).
(Z)-β-Iodoethylacrylate (68)²⁸

\[
\text{AcO\vspace{-1.5cm}} + \text{\text{NaI}} \xrightarrow{\text{AcOH}} \text{\text{O}} \vspace{-1.5cm} \text{(68)}
\]

A solution of sodium iodide (5.63 g, 37.50 mmol) and glacial acetic acid (25 mL) was stirred for 5 minutes and ethyl propiolate (2.5 mL, 24.67 mmol) added in one portion. The reaction mixture was heated at 70°C for 12 hours, and then cooled to room temperature, and water (25 mL) added followed by diethyl ether (25 mL). The organic layer was removed and the aqueous layer extracted with diethyl ether (2x10 mL). The combined organic layers then washed with 3M KOH (3x15 mL) until the aqueous phase was neutral, washed with brine (25 mL), dried (MgSO₄), filtered, and solvent removed in vacuo to yield a pale yellow liquid. Purification via vacuum distillation at 80°C yielded (68) as an orange liquid (4.55 g, 82%). ¹H NMR (400MHz, CDCl₃)  δ 1.33 (t, 3H, J=7.2, CH₃), 4.25 (q, 2H, J=7.2, CH₂), 6.90 (d, 1H, J=12, CHCO), 7.46 (d, 1H, J=12, ICH=CH). ¹³C NMR (100MHz, CDCl₃) 13.2 (CH₃), 59.5 (CH₂), 93.7 (CH), 129.1 (CH), 163.8 (Q).

All Spectroscopic data is consistent with that previously reported.²⁸
A solution of (Z)-β-iodoethylacrylate (1.13 g, 5.02 mmol) in anhydrous DCM (20 mL) was cooled to -80°C using a liquid nitrogen bath and EtOAc. Diisobutylaluminium hydride (10.00 mL, 10.00 mmol, 1M in hexane) was added dropwise at such a rate that the internal temperature never exceeded -70°C. After addition the cloudy white solution was allowed to warm to room temperature. Hydrolysis was carried out at -5°C via dropwise addition of 1M aq. HCl (10 mL). The organic layer was removed and the aqueous layer extracted with diethyl ether (2x10 mL), the combined extracts dried (MgSO₄), filtered, and the solvent removed in vacuo to yield a pale yellow oil. Purification by silica gel column chromatography (10% ethyl acetate in light petroleum) gave the product as a pale yellow oil (0.53 g, 58%). ¹H NMR (400MHz, CDCl₃) δ 2.08 (s, 1H, OH), 4.31-4.36 (m, 2H, CH₂), 6.36 (dt, 1H, J=7.2, 5.4, CH=CH₂), 6.49 (d, 1H, J=7.2, CH=CH). ¹³C NMR (100MHz, CDCl₃) 64.9 (CH₂), 81.4 (CH), 139.5 (CH).

All Spectroscopic data is consistent with that previously reported.⁹⁸
cis-2-Iodocyclopropane methanol (70)  

\[
\begin{array}{c}
\text{Et}_2\text{Zn} \\
\text{DCM, 0°C, 1.5 hrs} \\
\begin{array}{c}
\text{ClCH}_2\text{I} \\
(69) \\
\end{array} \\
\begin{array}{c}
\text{OH} \\
(70) \\
\end{array}
\end{array}
\]

To a solution of diethyl zinc (2.70 mL, 2.70 mmol, 1M in hexane) in DCM (20 mL) at 0°C was added chloroiodomethane (0.93 g, 5.25 mmol). The resulting solution was stirred for 10 minutes while maintaining the temperature at 0°C, and a solution of 69 (0.25 g, 1.38 mmol) in DCM (3 mL) was added via cannula. This was stirred at 0°C for a further 1.5 hours and quenched with saturated ammonium chloride (5 mL) then allowed to warm to room temperature. A solution of saturated ammonium chloride (30 mL) and DCM (30 mL) was added, the layers separated, and the aqueous layer extracted with DCM (3x20 mL). The combined extracts were washed with brine (20 mL), dried (MgSO₄), filtered, and the solvent removed in vacuo to yield pale yellow oil. Purification by silica gel column chromatography (30% ethyl acetate in light petroleum) gave the product as a clear oil (0.11 g, 42%). ¹H NMR (400MHz, CDCl₃) δ 0.68 (m, 1H, CHH'), 0.95 (m, 1H, CHCH₂OH), 1.32 (m, 1H, CHH'), 1.97 (s, 1H, OH), 2.62 (m, 1H, CHCH₂), 3.51 (dd, 1H, J=12, J=8.6, CH₂OH), 4.12 (dd, 1H, J=12, J=5.2, CH₂OH). ¹³C NMR (100MHz, CDCl₃) 12.3 (CH₂), 19.8 (CH), 21.2 (CH), 69.6 (CH₂).

All Spectroscopic data is consistent with that previously reported. ⁵⁶
(2-Phenylethynylcyclopropyl) methanol (71) \(^{56}\)

![](image)

To a solution of bis(acetonitrile)dichloropalladium(II) (0.0050 g, 0.018 mmol) in dry THF (2 mL), were added XPhos\(^\circledR\) (0.020 g, 0.050 mmol), cesium carbonate (0.27 g, 0.83 mmol) and 70 (0.11 g, 0.53 mmol). The resulting mixture was degassed for 10 minutes then phenyl acetylene (0.09 mL, 0.82 mmol) added. The reaction mixture was heated at 60°C for 1.5 hours. The solution was cooled to room temperature then filtered through a pad of celite (EtOAc), and the solvent removed in vacuo to give an oil. Purification by silica gel column chromatography (5% diethyl ether in DCM) gave the product as a brown oil (0.071 g, 76%). \(^1\)H NMR (400MHz, CDCl\(_3\)) \(\delta\) 0.75-0.78 (m, 1H, CH\(^-\)), 1.11-1.18 (m, 1H, CH\(_2\)), 1.51-1.53 (m, 1H, C≡CCH), 1.69-1.72 (m,1H, CHCH\(_2\)OH), 1.76 (s, 1H, OH), 3.69 (dd, 1H, J=11.8, 8.6, CH\(_2\)), 3.97 (dd, 1H, J= 11.8, 5.4, CH\(_2\)), 7.29-7.34 (m, 3H, ArH), 7.38-7.41 (m, 2H, ArH). \(^{13}\)C NMR (100MHz, CDCl\(_3\)) 4.2 (CH), 12.2 (CH\(_2\)), 29.8 (CH), 63.0 (CH\(_2\)), 77.6 (Q), 88.5 (Q), 122.9 (Q), 126.7 (CH), 127.1 (CH), 127.2 (CH), 130.5 (CH), 130.8 (CH).

All Spectroscopic data is consistent with that previously reported.\(^{56}\)
1-Ethoxycyclopropanol (64)\textsuperscript{52}

A solution of (1-ethoxycyclopropanoxy) trimethylsilane (1.00 mL, 4.97 mmol) in methanol (10 mL) was stirred at room temperature for 16 hours. A sample of the solution was then concentrated in vacuo in a cold water bath and monitored by $^1$H NMR to determine the completion of the reaction. Once complete the methanol was removed in vacuo to yield a colourless oil (0.44 g, 87%). No further purification was required. $^1$H NMR (400MHz, CDCl$_3$) $\delta$ 0.61-0.64 (m, 2H, CHH', CHH'), 0.68-0.72 (m, 2H, CHH', CHH'), 0.98 (t, 3H, J=7.2, CH$_3$), 3.48 (q, 2H, J=7.2, CH$_2$), 3.95 (s, 1H, OH). IR (thin film)/cm$^{-1}$ 3450 (br s), 3096 (m), 3011 (m), 1071 (m).

All Spectroscopic data is consistent with that previously reported.\textsuperscript{52}
**1-Vinyl cyclopropanol (62)**

![Chemical Reaction]

To a refluxing solution of dry THF (20 mL) and vinyl magnesium bromide (9.30 mL, 9.30 mmol, 1M in THF) was added 64 (0.32 g, 3.13 mmol), dropwise to the refluxing solution, and the reaction mixture allowed to reflux for a further 40 minutes. The solution was cooled and rapidly poured into saturated aqueous ammonium chloride (30 mL). The organic layer was removed and the aqueous layer extracted with diethyl ether (3x50 mL), the combined extracts dried (MgSO₄), filtered, and the solvent removed in vacuo to yield a yellow oil (0.18 g, 51%). No further purification was required. ¹H NMR (400MHz, CDCl₃) δ 0.75 (m, 2H, CCH, CCH), 1.05 (m, 2H, CHH, CHH), 1.85 (s, 1H, OH), 5.07 (dd, 1H, J=16.8, 1.2, CH=CH₂), 5.27 (dd, 1H, J=10.8, 1.2, CH=CH₂), 5.60 (dd, 1H, J=10.8, 16.8, CH=CH₂).

IR (thin film)/cm⁻¹ 3450 (br s), 3105 (m), 3015 (m), 1435 (m), 1147 (m).

All Spectroscopic data is consistent with that previously reported. ⁵²
1-Vinylcyclopropyl 4-methylbenzenesulfonate (65)$^{51}$

To a solution of 62 (0.18 g, 2.18 mmol) in pyridine (10 mL) was added $p$-toluene sulfonyl chloride (0.63 g, 3.29 mmol). The solution was heated to 50°C and stirred for 17 hours. The resulting red solution was poured in to a mixture of crushed ice and distilled water (30 mL) and extracted with diethyl ether (3x40 mL). The combined ether extracts then washed with 1M aq. HCl (3x40 mL) and brine (40 mL), dried (MgSO$_4$), filtered, and the solvent removed in vacuo to yield an orange oil (0.20 g, 39%). No further purification was required. $^1$H NMR (400MHz, CDCl$_3$) $\delta$ 0.91-0.94 (m, 2H, $CH\text{H}^\text{'}$, $CH\text{H}^\text{''}$), 1.33-1.39 (m, 2H, $CHHH$, $CHHH$), 2.44 (s, 3H, $CH_3$), 5.01 (dd, 1H, J=16.8, 1.2, $CH=CH_2$), 5.11 (dd, 1H, J=10.8, 1.2, $CH=CH_2$), 5.91 (dd, 1H, J=10.8, 16.8, $CH=CH_2$), 7.27-7.33 (m, 2H, ArH), 7.76-7.78 (m, 2H, ArH). IR (thin film)/cm$^{-1}$ 3028 (m), 2988 (m), 2895 (m), 1603 (m), 1499 (s), 1375 (s), 1035 (s).

All Spectroscopic data is consistent with that previously reported.$^{51}$
(1-Vinylcyclopropyl)benzene (66)  

**Using Nickel catalyst**

\[
\text{Me} \quad \text{O} \quad \text{S} \quad \text{SO}\]

(65) \quad \xrightarrow{\text{NiCl}_2(\text{PPh}_3)_2 (5 \text{ mol\%}), \text{PhMgBr (3 equiv)}} \quad \text{Et}_2\text{O, rt, 1hr} \quad \text{(66)}

To a solution of 65 (0.040 g, 0.17 mmol) in anhydrous diethyl ether (1 mL) was added bis (triphenylphosphine) nickel(II) dichloride (0.0060 g, 0.0092 mmol). The reaction mixture was cooled to -78°C and a solution of phenyl magnesium bromide (0.50 mL, 0.50 mmol, 1M in THF) added in one portion while the solution went dark brown. The solution was stirred for a further 1 hour while warming to room temperature where the solution turned orange. Diethyl ether (20 mL) was added, the solution filtered through a pad of neutral alumina, and the solvent removed in vacuo to yield an orange oil. Purification by silica gel column (100% light petroleum) gave 66 as a colourless oil. (0.0040 g, 16%). \(^1\)H NMR (400MHz, CDCl\textsubscript{3}) \(\delta 0.73-0.78 \text{ (m, 2H, CH} \text{H', CH} \text{H')}, 1.05-1.09 \text{ (m, 2H, CH} \text{H', CH} \text{H')}, 4.59 \text{ (dd, 1H, J=17.2, 1.4, CH} \text{=CH}_2), 4.90 \text{ (dd, 1H, J=10.4, 1.4, CH} \text{=CH}_2), 5.73 \text{ (dd, 1H, J=10.4, 17.2, CH} \text{=CH}_2), 7.58-7.61 \text{ (m, 5H, Ar} \text{H}). \(^{13}\)C NMR (100MHz, CDCl\textsubscript{3}) 12.8 (2xCH\textsubscript{2}), 26.8 (Q), 110.2 (CH\textsubscript{2}), 124.5 (2xCH), 126.3 (2xCH), 127.9 (CH), 139.3 (Q), 143.4 (CH). IR (thin film)/\text{cm}^{-1} 3150 \text{ (m), 2950 (m), 2922 (m), 1420 (m), 1377 (s), 1039 (s).}

All Spectroscopic data is consistent with that previously reported.  

160
Using palladium catalyst

![Chemical Structure](image)

To a solution of 65 (0.11 g, 0.40 mmol) in THF (4 mL) was added Pd(dba)$_2$ (5.1 mg, 8.9 μmol), followed by 1,2-bis(diphenylphosphino)ethane (4 mg, 10.1 μmol), and PhZnCl (1.10 mL, 1.91 mmol). The resulting solution was heated at 40°C for 4 hours. The yellow solution was quenched with diethyl ether (20 mL), the solid removed by filtration and the solvent removed in vacuo to yield a yellow viscous oil. Purification by silica gel column chromatography (100% Light petroleum) gave the product as a yellow oil (0.03 g, 48%). Spectral data match that obtained for 66.

1,1-Diphenyl cyclopropane (52)

![Chemical Structure](image)

To a solution of 73 (0.12 g, 0.40 mmol) in THF (4 mL) was added Pd(dba)$_2$ (0.0050 g, 0.0087 mmol), followed by 1,2-bis(diphenylphosphino)ethane (0.0032 g, 0.0080 mmol), and PhZnCl (1.10 mL, 1.91 mmol). The resulting solution was heated at 40°C for 4 hours. The yellow solution was quenched with diethyl ether (20 mL), the solid removed by filtration and the solvent removed in vacuo to yield a yellow viscous oil. Spectral data shows only starting material obtained.
1-(4-Methoxyphenyl)cyclopropan-1-ol (83)

To a solution of methyl p-anisate (1.02 g, 6.10 mmol) in toluene (20 mL) was added Ti(OiPr)$_4$ (1.80 mL, 6.10 mmol) followed by EtMgBr (6.00 mL, 18 mmol) over 1 hour. The resulting solution was stirred for 1 hour then poured into 10% aq. H$_2$SO$_4$ (200 mL) at 0°C. The organic layer was removed and the aqueous layer extracted with diethyl ether (3x50 mL), dried (MgSO$_4$), filtered, and the solvent removed in vacuo to yield a dark orange oil. Purification by silica gel column (10% ethyl acetate in light petroleum) yielded the product as a cream solid (0.44 g, 44%, mp 55-58°C). $^1$H NMR (400 MHz, CDCl$_3$) δ 0.95-0.98 (m, 2H, C$H_H$, C$H_H$), 1.18-1.21 (m, 2H, CH$H$, CH$H$), 2.28 (s, 1H, OH), 3.80 (s, 3H, OCH$_3$), 6.86-6.89 (m, 2H, Ar$H$), 7.25-7.28 (m, 2H, Ar$H$). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 16.7 (2xCH$_2$), 55.3 (CH$_3$), 56.7 (Q), 113.8 (2xCH), 126.4 (2xCH), 136.1 (Q), 158.4 (Q). IR (thin film)/cm$^{-1}$ 3582 (br, s), 3054 (s), 2986 (m), 1515 (s), 1265 (s).
Chapter 2 experimental
Representative procedure

To a solution of ketone (0.80 mmol) in toluene (20 mL) was added Ti(O\text{Pr})_4 (0.24 mL, 0.80 mmol) followed by EtMgBr (2.40 mL, 7.20 mmol) over 1 hour via syringe pump. The resulting solution was then stirred for 1 hour and quenched with NaHCO_3 (10 mL). The resulting solid was removed by filtration, the organic layer removed, and the aqueous layer extracted with diethyl ether (3x20 mL). The combined extracts were washed with NaHCO_3 (10 mL), brine (10 mL), dried (MgSO_4), filtered, and the solvent removed in vacuo. Purification by silica gel column chromatography (5% ethyl acetate in light petroleum) afforded the target compound.

1,1,2,2-Tetra(4-fluorophenyl)ethene (115)

Prepared using the representative procedure from 4,4’-difluorobenzophenone (0.17 g, 0.80 mmol) yielding a white solid (0.12 g, 71%, mp 193.6-194.3°C). ^1H NMR (400MHz, CDCl_3) δ 6.70-6.80 (m, 2H, ArH), 6.84-6.93 (m, 2H, ArH). ^13C NMR (100MHz, CDCl_3) δ 114.9 (2xCH, d, ^2J_{CF}=21), 122.8 (Q), 132.7 (2xCH, d, ^3J_{CF}=8), 139.1 (Q, d, ^4J_{CF}=3), 161.5 (Q, d, ^1J_{CF}=245). ^19F (CDCl_3) 47.10-47.18 (m, 4F). MS (ESI): [M+H]^+ requires 405.1266 found 405.1262. IR (thin film) cm^{-1} 3054 (m), 2986 (m), 1602 (s), 1507 (s), 1157 (s).
1,1,2,2-Tetra(4-bromophenyl)ethene (116)

Prepared using the representative procedure from 4,4’-dibromobenzophenone (0.27 g, 0.80 mmol) yielding a cream solid (0.093 g, 36%, mp 210.1-211.3°C). $^1$H NMR (400MHz, CDCl$_3$) $\delta$ 6.83-6.89 (m, 2H, ArH), 7.24-7.27 (m, 2H, ArH). $^{13}$C NMR (100MHz, CDCl$_3$) $\delta$ 120.2 (Q), 130.1 (2xCH), 131.8 (2xCH), 138.6 (Q), 140.4 (Q). MS (ESI): [M+Br$_2$]+ requires 648.8023 found 648.8025. IR (thin film)/cm$^{-1}$ 3054 (m), 2986 (m), 1487 (m), 1421 (m), 1265 (s).

(E/Z, 1:1)-1,2-Bis(4-fluorophenyl)-1,2-diphenylethene (117)

Prepared using the representative procedure from 4-fluorobenzophenone (0.16 g, 0.80 mmol) yielding a white solid (0.07 g, 52%, mp 183.9-185.1°C). $^1$H NMR (400MHz, CDCl$_3$) $\delta$ 6.75-6.84 (m, 2H, ArH), 6.94-7.03 (m, 4H, ArH), 7.07-7.13 (m, 3H, ArH). $^{13}$C NMR (100MHz, CDCl$_3$) $\delta$ 114.7 (2xCH, $^2$J$_{CF}$=22), 126.6 (2xCH), 127.8 (2xCH), 131.2 (CH), 132.7 (2xCH, d, $^3$J$_{CF}$=7), 139.4 (Q), 140.0 (Q), 143.3 (Q, d, $^4$J$_{CF}$=3), 161.4 (Q, d, $^1$J$_{CF}$=245). $^{19}$F (CDCl$_3$) 46.59-46.56 (m, 1F), 46.60-46.69 (m, 1F). MS (ESI): [M+H]$^+$ requires 369.1455 found 369.1457. IR (thin film)/cm$^{-1}$ 3583 (m), 3054 (m), 2923 (m), 1601 (s).
(E/Z, 1:1)-1,2-Bis(4-bromophenyl)-1,2-diphenylethene (118)

![Chemical Structure Image]

Prepared using the representative procedure from 4-bromobenzophenone (0.21 g, 0.80 mmol) yielding an orange oil (0.08 g, 41%). $^1$H NMR (400MHz, CDCl$_3$) δ 6.89-6.97 (m, 2H, ArH), 7.01-7.08 (m, 2H, ArH), 7.12-7.17 (m, 3H, ArH), 7.30-7.33 (m, 2H, ArH). $^{13}$C NMR (100MHz, CDCl$_3$) δ 119.6 (Q), 125.5 (2xCH), 126.8 (2xCH), 129.8 (2xCH), 130.1 (2xCH), 131.9 (CH), 139.2 (Q), 141.2 (Q), 141.8 (Q). MS (ESI): [MBr$^{+}$]+ requires 488.9853 found 488.9848. IR (thin film)/cm$^{-1}$ 3054 (m), 2957 (m), 2932 (m), 1609 (s).

4,4',4''',4'''-(Ethene-1,1,2,2-tetrayl)tetra(N,N-dimethylaniline) (119)

![Chemical Structure Image]

Prepared using the representative procedure from 4,4'-bis(dimethylamino)benzophenone (0.22 g, 0.80 mmol) yielding a green oil (0.14 g, 71%). $^1$H NMR (400MHz, CDCl$_3$) δ 2.94 (s, 6H, 2xC$_3$H$_6$), 6.74-6.76 (m, 2H, ArH), 7.04-7.09 (m, 2H, ArH). $^{13}$C NMR (100MHz, CDCl$_3$) δ 14.7 (CH$_3$), 121.9 (2xCH), 129.6 (2xCH), 133.2 (Q), 141.1 (Q), 151.4 (Q). MS (ESI): [M+H]$^+$ requires 505.3331 found 505.3339. IR (thin film)/cm$^{-1}$ 3056 (m), 2983 (m), 2922 (m), 1614 (s), 1333 (m), 1132 (m).
4,4',4'',4'''-Ethene-1,1,2,2-tetrayl)teta(N,N-diethylaniline) (120)

Prepared using the representative procedure from 4,4'-bis(diethylamino)benzophenone (0.26 g, 0.80 mmol) yielding a bright green solid (0.14 g, 57%, mp 190.4-191.7°C). \(^1\)H NMR (400MHz, CDCl\(_3\)) \(\delta\) 1.07 (t, 3H, J= 7.2, CH\(_2\)CH\(_3\)), 3.22 (q, 2H, J= 6.8, CH\(_2\)CH\(_3\)), 6.46 (d, 2H, J= 9.2, ArH), 7.02 (d, 2H, J= 9.2, ArH). \(^{13}\)C NMR (100MHz, CDCl\(_3\)) \(\delta\) 11.6 (CH\(_3\)), 43.3 (CH\(_2\)), 110.3 (2xCH), 127.9 (Q), 128.2 (2xCH), 138.9 (Q), 144.5 (Q). MS (ESI): [M+H]\(^+\) requires 617.4583 found 617.4573. IR (thin film)/cm\(^{-1}\) 3054 (m), 2986 (m), 1607 (s), 1421 (m).

1,1,2,2-Tetra(4-((tert-butyldimethylsilyl)oxy)phenyl)ethene (121)

Prepared using the representative procedure from 1,1,2,2-tetrakis(4-((tert-butyldimethylsilyl)oxy)phenyl)ethane (0.36 g, 0.80 mmol) yielding a white solid (0.26 g, 75%, mp 205.8-207.4°C). \(^1\)H NMR (400MHz, CDCl\(_3\)) \(\delta\) 0.17 (s, 6H, 2xOSiCH\(_3\)), 0.97 (s, 9H, OSiCCH\(_3\) x3), 6.57 (d, 2H, J= 8.8, ArH), 6.86 (d, 2H, J= 8.8, ArH). \(^{13}\)C NMR (100MHz, CDCl\(_3\)) \(\delta\) -5.4 (CH\(_3\)), 17.2 (Q), 24.6 (CH\(_3\)), 118.1 (2xCH), 131.5 (2xCH), 136.4 (Q), 137.6 (Q), 152.8 (Q). MS (ESI): [M+Na]\(^+\) requires 875.4718 found 875.4702. IR (thin film)/cm\(^{-1}\) 3054 (s), 2986 (m), 2931 (m), 1603 (s), 1264 (s), 896 (s).
**1,1,2,2-Tetraphenylethene (105)**

![1,1,2,2-Tetraphenylethene (105)](image)

Prepared using the representative procedure from benzophenone (0.15 g, 0.80 mmol) yielding a white solid (0.13 g, 99%, mp 203.9-205.2°C). $^1$H NMR (400MHz, CDCl$_3$) δ 6.93-6.96 (m, 2H, ArH), 6.97-7.00 (m, 3H, ArH). $^{13}$C NMR (100MHz, CDCl$_3$) δ 125.3 (2x CH), 126.6 (2x CH), 130.2 (CH), 139.9 (Q), 142.6 (Q). MS (ESI): [M+Na]$^+$ requires 355.1463 found 355.1453. IR (thin film)/cm$^{-1}$ 3054 (s), 2986 (s), 2905 (m), 1600 (s).

**1,1,2,2-Tetra(4-methoxyphenyl)ethene (110)**

![1,1,2,2-Tetra(4-methoxyphenyl)ethene (110)](image)

Prepared using the representative procedure from 4,4' -dimethoxybenzophenone (0.19 g, 0.80 mmol) yielding a yellow solid (0.16 g, 90%, mp 178.7-180.2°C). $^1$H NMR (400MHz, CDCl$_3$) δ 3.74 (s, 3H, OCH$_3$), 6.64 (d, 2H, J= 6.4, ArH), 6.92 (d, 2H, J= 6.4, ArH). $^{13}$C NMR (100MHz, CDCl$_3$) δ 55.1 (CH$_3$), 113.0 (2x CH), 132.5 (2x CH), 136.9 (Q), 138.4 (Q), 157.7 (Q). MS (ESI): [M+H]$^+$ requires 453.2066 found 453.2063. IR (thin film)/cm$^{-1}$ 3054 (m), 2986 (m), 1606 (s), 1263 (s).
(E/Z, 1:1)-1,2-Bis(4-methoxyphenyl)-1,2-diphenylethene (122)

Prepared using the representative procedure from 4-methoxybenzophenone (0.17 g, 0.80 mmol) yielding a white solid (0.13 g, 80%, mp 183.9-185°C). \(^1\)H NMR (400MHz, CDCl\(_3\)) \(\delta\) 3.76 (s, 3H, OCH\(_3\)), 6.63-6.69 (m, 2H, ArH), 6.92-6.97 (m, 2H, ArH), 7.03-7.06 (m, 5H, ArH). \(^1^3\)C NMR (100MHz, CDCl\(_3\)) \(\delta\) 54.1 (CH\(_3\)), 112.0 (2xCH), 125.2 (2xCH), 126.5 (2xCH), 130.3 (2xCH), 131.5 (CH), 135.3 (Q), 138.6 (Q), 143.2 (Q), 156.9 (Q). MS (ESI): [M+H]\(^+\) requires 393.1854 found 393.1846. IR (thin film)/cm\(^{-1}\) 3054 (m), 2986 (m), 2955 (m), 2930 (m), 2835 (m), 1605 (s).

(E/Z, 1:1)-But-2-ene-2,3-diyldibenzene (123)

Prepared using the representative procedure from acetophenone (0.09 mL, 0.80 mmol) yielding a colorless oil (0.05 g, 65%). \(^1\)H NMR (400MHz, CDCl\(_3\)) \(\delta\) 2.09 (s, 3H, CH\(_3\)), 6.86-6.88 (m, 2H, ArH), 6.94-6.96 (m, 2H, ArH), 7.7-7.28 (m, 1H, ArH). \(^1^3\)C NMR (100MHz, CDCl\(_3\)) \(\delta\) 21.8 (CH\(_3\)), 119.1 (2xCH), 127.5 (2xCH), 132.8 (CH), 136.6 (Q), 151.6 (Q). MS (ESI): [M+H]\(^+\) requires 209.1325 found 209.1324. IR (thin film)/cm\(^{-1}\) 3054 (s), 2984 (s), 2937 (s), 1601 (s), 1446 (s).
1,2-Diphenylcyclopent-1-ene (124)

Prepared using the representative procedure from 1,3-dibenzoylpropane (0.20 g, 0.80 mmol) yielding a colourless oil (0.03 g, 14%). $^1$H NMR (400MHz, CDCl$_3$) $\delta$ 2.02-2.09 (m, 2H, CH$_2$C$_6$H$_2$CH$_2$), 2.89-2.94 (m, 4H, CH$_2$C$_6$H$_2$CH$_2$), 7.15-7.25 (m, 10H, ArH). $^{13}$C NMR (100MHz, CDCl$_3$) $\delta$ 22.2 (2xCH$_2$), 39.2 (CH$_2$), 126.6 (2xCH), 128.1 (2xCH), 128.2 (CH), 137.6 (Q), 138.5 (Q). MS (ESI): [M+H]$^+$ requires 221.1330 found 221.1326. IR (thin film)/cm$^{-1}$ 3053 (m), 2955 (m), 2843 (m), 1598 (s).
Chapter 3 experimental
4-Bromobut-3-yn-1-ol (210)$^{85}$

To a solution of potassium hydroxide (11.49 g, 206.80 mmol) in H$_2$O (200 mL) was added bromine (3.00 mL, 56.90 mmol) and the solution cooled to 0°C. The flask was covered with foil and 3-butyn-1-ol (3.85 mL, 51.70 mmol) added. The mixture was stirred for 24 hours at room temperature then extracted with diethyl ether (3x50 mL), dried (MgSO$_4$), filtered, and the solvent removed in vacuo to yield a yellow oil (6.73 g, 87%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.87 (s, 1H, OH), 2.49 (t, 2H, J=6, CH$_2$CH$_2$OH), 3.74 (t, 2H, J=6.4, CH$_2$CH$_2$OH). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 24.0(CH$_2$), 40.1 (Q), 60.8 (CH$_2$), 89.4 (Q). MS (ESI): [MBr$_79$-OH]$^+$ requires 130.9496 found 130.9499. IR (thin film)/cm$^{-1}$ 3367 (br s), 2946 (s), 2886 (s), 2218 (m), 1051(s).

(Z)-4-Bromobut-3-en-1-ol (211)$^{85}$

To a solution of 210 (1.26 g, 8.42 mmol) in THF/H$_2$O (50 mL, 1:1) was added p-toluenesulfonyl hydrazide (3.16 g, 16.90 mmol) and sodium acetate (2.06 g, 25.10 mmol). The resulting solution was heated at reflux for 24 hours, then allowed to cool to room temperature before being extracted in to DCM (3x50 mL). The combined extracts were dried (MgSO$_4$), filtered, and the solvent removed in vacuo to yield a yellow oil (1.21g, 95%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.99 (s, 1H, OH), 2.48 (dt, 2H, J=6.4, 2.2, CH$_2$CH$_2$OH), 3.73 (t, 2H, J=6.4, CH$_2$CH$_2$OH), 6.19 (dt, 1H, J=6.8, 2.2, CH=CHCH$_2$), 6.29 (d, 1H, J=6.8, CH=CHCH$_2$). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 33.2 (CH$_2$), 61.0 (CH$_2$), 109.9 (CH), 131.1 (CH). IR (thin film)/cm$^{-1}$ 3350 (br s), 2950 (s), 2883 (s).
(Z)-4-Bromobut-3-en-1-yl methanesulfonate (212)$^{85}$

To a solution of 211 (1.33 g, 8.83 mmol) in DCM (5 mL) was added triethylamine (1.35 mL, 9.68 mmol) and the solution cooled to 0°C. Methanesulfonyl chloride (0.69 mL, 8.89 mmol) was then added dropwise and the resulting viscous orange solution was stirred overnight while warming to room temperature. The reaction was quenched by addition of H$_2$O (30 mL) and sodium bicarbonate (20 mL). The organics were extracted in to DCM (3x20 mL), dried (MgSO$_4$), filtered, and the solvent removed in vacuo. Purification by silica gel column (50% ethyl acetate in light petroleum) yielded 60 as a yellow oil (1.12 g, 74%). $^1$H NMR (400 MHz, CDCl$_3$) δ 2.67 (dt, 2H, J=6.4, 2.6, CH$_2$CH$_2$OMs), 3.03 (s, 3H, SO$_2$CH$_3$), 4.30 (t, 2H, J=6.4, CH$_2$CH$_2$OMs), 6.18 (dt, 1H, J=6.8, 2.6, CH=CHCH$_2$), 6.36 (d, 1H, J=6.8, CH=CHCH$_2$). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 29.88 (CH$_2$), 37.5 (CH$_3$), 67.4 (CH$_2$), 111.4 (CH), 128.9 (CH). IR (thin film)/cm$^{-1}$ 3055 (br s), 2987 (s), 1359 (s), 1175 (s), 736 (s).
Sodium iodide (8.16 g, 54.41 mmol) and 212 (0.83 g, 3.63 mmol) were added to acetone (75 mL) and heated under reflux for 24 hours. The solution was cooled to room temperature and the resulting precipitate filtered through a pad of celite. The filtrate was removed in vacuo to yield yellow solid. This was triturated with diethyl ether (5x20 mL), and the solvent removed in vacuo to yield 61 as a yellow oil (0.74 g, 78%). $^1$H NMR (400 MHz, CDCl$_3$) δ 2.81 (dt, 2H, J=6.8, 2.6, CH$_2$CH$_2$I), 3.20 (t, 2H, J=6.8, CH$_2$CH$_2$I), 6.14 (dt, 1H, J=6.4, 2.6, CH=CHCH$_2$), 6.36 (d, 1H, J=6.4, CH=CHCH$_2$). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 20.0 (CH$_2$), 31.0 (CH$_2$), 107.5 (CH), 130.8 (CH). MS (ESI): [MBr$_{79}$-I]$^+$ requires 132.9653, found 132.9647.
A solution of **213** (0.74 g, 2.84 mmol) and potassium phthalimide (1.05 g, 5.68 mmol) in 2-butanone (40 mL) was heated at reflux under N₂ for 24 hours. After cooling to room temperature the resulting residue was diluted with EtOAc (40 mL) and the solids filtered. The organic phase was washed with water (3x30 mL), dried (MgSO₄), filtered, and concentrated in vacuo to yield an orange solid. Purification by silica gel column (30% ethyl acetate in light petroleum) yielded the product as a yellow solid (0.49 g, 62%). ¹H NMR (400 MHz, CDCl₃) δ 2.62 (dt, 2H, J=6.8, 1.6, CH₂CH₂N), 3.82 (t, 2H, J=1.6, CH₂CH₂N), 6.15 (dt, 1H, J=6.8, 1.6, CH=CHCH₂), 6.24 (d, 1H, J=6.8, CH=CHCH₂), 7.69-7.74 (m, 2H, ArH), 7.83-7.88 (m, 2H, ArH). ¹³C NMR (100 MHz, CDCl₃) δ 29.2 (CH₂), 36.1 (CH₂), 110.6 (CH), 123.3 (2xCH), 130.8 (2xCH), 132.1 (2xQ), 133.9 (CH), 168.3 (2xQ). IR (thin film)/cm⁻¹ 3054 (m), 2986 (m), 1715 (s), 1265 (s), 739 (s).
(Z)-4-Bromobut-3-en-1-amine (208)$^{85}$

A solution of 214 (0.26 g, 0.95 mmol) in ethanol (40 mL) was treated with hydrazine monohydrate (0.05 mL, 0.95 mmol). The reaction mixture was refluxed for 24 hours then cooled to room temperature, the resulting solids filtered and washed with ethanol (3×10 mL). Filtrate was evaporated to give a white precipitate which was treated with water (20 mL), and 2M aq. HCl (pH 1-2). The solution was then filtered and the solids washed with water (2×10 mL). The pH of the filtrate was adjusted using NaOH (2M) to between pH 12-14, then extracted with DCM (5×10 mL). The combined extracts were dried (MgSO$_4$), filtered, and concentrated in vacuo to yield an orange oil (0.20 g, 38%). $^1$H NMR (400 MHz, CDCl$_3$) δ 1.25 (br s, 2H, NH$_2$), 2.52 (dt, 2H, J=6.4, 1.6, CH$_2$CH$_2$NH$_2$), 3.49 (t, 2H, J=6.4, CH$_2$CH$_2$NH$_2$), 6.18 (dt, 1H, J=6.8, 1.6, CH=CCH$_2$), 6.36 (d, 1H, J=6.8, CH=CHCH$_2$). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 34.0 (CH$_2$), 40.7 (CH$_2$), 109.6 (CH), 132.3 (CH). IR (thin film)/cm$^{-1}$ 3375 (br, m), 2938 (m), 2871 (m), 1622 (m), 1422 (m), 740 (s).
Dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (218)^[70]

\[
\text{MeO} \quad \text{CO}_2\text{Me} + \text{Br-} - \text{CH=CHBr} \xrightarrow{\text{NaOMe, MeOH}} \text{CO}_2\text{Me}
\]

To a stirred solution of sodium methoxide, prepared from sodium (1.14 g, 49.50 mmol) and methanol (20 mL), was added dimethyl malonate (5.84 mL, 51.10 mmol), followed by a solution of \textit{trans}-1,4-dibromobut-2-ene (5.30 g, 24.78 mmol) in methanol (20 mL). The resulting mixture was refluxed for 2.5 hours, then cooled to room temperature, and the resulting white precipitate filtered off. The filtrate was concentrated in vacuo, and the crude mixture then partitioned between diethyl ether (30 mL) and H\textsubscript{2}O (30 mL). The layers were separated and the organic layer washed with water (2 \times 30 mL), dried (MgSO\textsubscript{4}), filtered, and the solvent removed in vacuo to obtain a yellow oil. Purification by silica gel column (15% diethyl ether in light petroleum) to yield the product as a colourless oil (3.03 g, 66%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 1.58 (m, 1H, CH\textsuperscript{H'}), 1.73 (m, 1H, CH\textsubscript{H}), 2.58 (q, 1H, J=8.4, CH\textsubscript{CCO\textsubscript{2}Me}), 3.74 (s, 6H, CO\textsubscript{2}CH\textsubscript{3}), 5.14 (dd, 1H, J=10.4, 1.2, CH\textsubscript{2}=CH), 5.29 (dd, 1H, J=17.2, 1.2, CH\textsubscript{2}=CH), 5.43 (m, 1H, CH\textsubscript{2}=CH). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) δ 23.9 (CH\textsubscript{2}), 32.9 (Q), 40.2 (CH), 53.2 (2xCH\textsubscript{3}), 121.3 (CH\textsubscript{2}), 131.9 (CH), 170.3 (Q), 174.2 (Q). IR (thin film)/cm\textsuperscript{-1} 3055 (m), 2987 (m), 2955 (m), 2848 (w), 1726 (s), 1438 (s), 1265 (s).
To a stirred solution of 218 (1.01 g, 5.50 mmol) in THF/H$_2$O (1:1, 40 mL), was added lithium hydroxide (0.14 g, 5.82 mmol). The resulting mixture was stirred for 2 hours then acidified with 2M aq. HCl (pH 2), extracted with Et$_2$O (3x15 mL), washed with brine (3x15 mL), the combined extracts dried (MgSO$_4$), filtered, and the solvent removed in vacuo to yield a colourless oil (0.70 g, 75%). $^1$H NMR (400 MHz, CDCl$_3$) δ 1.99 (m, 1H, $\text{CH}_2$), 2.14 (m, 1H, $\text{CH}_2$), 2.76 (q, 1H, J=8.8, $\text{CHCCO}_2\text{Me}$), 3.79 (s, 1H, OH), 3.83 (s, 3H, $\text{CO}_2\text{CH}_3$), 5.25 (dd, 1H, J=10.4, 1.2, $\text{CH}_2$=CH), 5.41 (dd, 1H, J=17.2, 1.2, $\text{CH}_2$=CH), 5.67 (m, 1H, $\text{CH}_2$=CH). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 23.6 (CH$_2$), 33.2 (Q), 38.5 (CH), 53.2 (CH$_3$), 120.9 (CH$_2$), 132.1 (CH), 171.1 (Q), 173.2 (Q). IR (thin film)/cm$^{-1}$: 3206 (br s), 2989 (m), 2953 (m), 1734 (s), 1445 (s), 1266 (s).
Representative amide coupling procedure

**Methyl-1-(benzylcarbamoyl)-2-vinylcyclopropanecarboxylate (220)**

![Chemical Structure](image)

To a stirred solution of 200 (0.15 g, 0.89 mmol) in anhydrous EtOAc (10 mL) was added DIPEA (0.31 mL, 1.78 mmol) followed by T3P (0.80 mL, 1.96 mmol) and the mixture stirred for 10 minutes. Benzylamine (0.11 mL, 1.01 mmol) was then added and the reaction stirred for 17 hours at room temperature. The reaction was diluted with DCM (10 mL), and washed with 2M aq. HCl (10 mL), followed by aq. NaHCO₃ (20 mL). Both layers were re-extracted into DCM (3x20 mL), the organics combined, dried (MgSO₄), filtered, and the solvent removed in vacuo (0.20 g, 88%), no further purification was required. ¹H NMR (400 MHz, CDCl₃) δ 1.77 (m, 1H, CHH”), 1.98 (m, 1H, CHF), 2.48 (q, 1H, J=6.4, CHCCO₂Me), 3.58 (s, 3H, CO₂CH₃), 4.32-4.45 (m, 2H, NHCH₂), 5.02 (dd, 1H, J=1.2, 10.4, CH₂=CH), 5.23 (dd, 1H, J=1.2, 17.2, CH₂=CH), 5.53 (m, 1H, CH₂=CH), 7.13-7.24 (m, 5H, ArH), 8.62 (br s, 1H, CONHCH₂). ¹³C NMR (100 MHz, CDCl₃) δ 21.2 (CH₂), 33.8 (Q), 37.1 (CH), 44.0 (CH₂), 52.5 (CH₃), 119.7 (CH₂), 127.3 (CH), 127.4 (CH), 128.6 (2xCH), 133.2 (2xCH), 138.3 (Q), 167.8 (Q), 171.8 (Q). MS (ESI): [M+H]⁺ requires 260.1281 found 260.1274.
(Z)-Methyl-1-((4-bromobut-3-en-1-yl)carbamoyl)-2-vinyl cyclopropanecarboxylate (207)

Following the representative amide coupling procedure; to 200 (0.15 g, 0.89 mmol) in anhydrous EtOAc (10 mL) was added DIPEA (0.31 mL, 1.78 mmol), T3P (0.80 mL, 1.96 mmol), and 208 (0.20 g, 1.36 mmol) to yield the product as a yellow oil (0.24 g, 88%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.79-1.81 (m, 1H, CHH'), 1.98-2.02 (m, 1H, CHH), 2.38 (qd, 2H, J=6.8, 1.6, CH\(_2\)CH\(_2\)NH), 2.47 (m, 1H, CHCO\(_2\)Me), 3.40-3.47 (m, 2H, CH\(_2\)CH\(_2\)NH), 3.75 (s, 3H, CO\(_2\)CH\(_3\)), 5.19 (dd, 1H, J=10.4, 1.2, CH\(_2\)=CH), 5.38 (dd, 1H, J=17.2, 1.2, CH\(_2\)=CH), 5.61 (m, 1H, CH\(_2\)=CH), 6.14 (q, 1H, J=6.8, BrCH=CH\(_2\)), 6.31 (dt, 1H, J=1.2, 6.8, BrCH=CH\(_2\)), 8.39 (br s, 1H, NH). \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 21.3 (CH\(_2\)), 30.0 (CH\(_2\)), 34.4 (Q), 37.1 (CH), 38.2 (CH\(_2\)), 52.1 (CH\(_3\)), 110.2 (CH), 119.7 (CH\(_2\)), 131.5 (CH), 133.3 (CH), 167.9 (Q), 171.8 (Q). MS (ESI): [M+Na\(^{81}\)] requires 326.0191 found 326.0181. IR (thin film)/cm\(^{-1}\) 3054 (m), 2986 (m), 1708 (m), 1653 (m), 1535 (m), 1145 (m), 896 (m).
Methyl-1-((2-iodophenyl)carbamoyl)-2-vinylcyclopropane carboxylate (246)

Following the representative amide coupling procedure; to 200 (0.51 g, 2.99 mmol) in anhydrous EtOAc (20 mL) was added DIPEA (1.04 mL, 5.98 mmol), T3P (2.67 mL, 4.49 mmol) and 2-iodoaniline (0.72 g, 3.29 mmol) to yield the product as a yellow oil (0.66 g, 60%). $^1$H NMR (400 MHz, CDCl$_3$) δ 2.03-2.05 (m, 1H, $CHH^\prime$), 2.19-2.23 (m, 1H, $CHH^\prime$), 2.67 (q, 1H, J=6.4, CHCH=CH$_2$), 3.85 (s, 3H, CO$_2$CH$_3$), 5.23 (dd, 1H, J=0.8, 10.4, CH$_2$=CH), 5.42 (dd, 1H, J=16.8, 0.8, CH$_2$=CH), 5.66-5.75 (m, 1H, CH$_2$=CH), 6.86 (td, 1H, J=7.6, 1.2, ArH), 7.34 (td, 1H, J=7.6, 1.2, ArH), 7.84 (dd, 1H, J=8, 1.6, ArH), 8.18 (dd, 1H, J=8, 1.6, ArH), 10.55 (br s, 1H, NH$^\prime$). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 22.1 (CH$_2$), 38.4 (CH), 52.7 (CH$_3$), 89.8 (Q), 120.3 (CH$_2$), 122.9 (CH), 126.0 (CH), 128.8 (CH), 132.9 (CH), 133.1 (Q), 139.2 (CH), 166.4 (Q), 170.03 (Q), 171.2 (Q). MS (ESI): [M+H]$^+$ requires 372.0097 found 372.0081. IR (thin film)/cm$^{-1}$: 3356 (m), 3054 (m), 2986 (m), 2955 (m), 1707 (s), 1655 (s), 1529 (s), 1439 (s), 1145 (m).
2-Iodobenzylamine (241)

To a solution of 7M ammonia in methanol (4 mL) was added 2-iodobenzyl bromide (0.26 g, 0.86 mmol) dissolved in methanol (9 mL) slowly via dropping funnel over 10 minutes. Once addition was complete the resulting mixture was stirred at room temperature for 17 hours then the solvent removed in vacuo. The resulting solid was refluxed in EtOAc (20 mL) for 5 minutes, hot filtered, and the resulting solid washed with cold EtOAc (10 mL), followed by cold hexane (10 mL) to yield the product as a white solid (0.15 g, 76%, mp 241.6-242.9°C). $^1$H NMR (400 MHz, (CD$_3$)$_2$SO) δ 4.10 (s, 2H, CH$_2$), 7.13-7.17 (m, 1H, ArH), 7.48-7.55 (m, 2H, ArH), 7.72 (br s, 2H, NH$_2$), 7.94-7.96 (m, 1H, ArH). $^{13}$C NMR (100 MHz, (CD$_3$)$_2$SO) δ 46.9 (CH$_2$), 100.4 (Q), 128.6 (CH), 129.3 (CH), 130.4 (CH), 136.3 (Q), 139.3 (CH). MS (ESI): [M+H]$^+$ requires 223.9779 found 233.9773. IR (thin film)/cm$^{-1}$ 3420 (m), 2536 (w), 2160 (m), 2032 (m), 1574 (m).
Methyl 1-((2-iodobenzyl)carbamoyl)-2-vinylcyclopropanecarboxylate (309)

Following the representative amide coupling procedure; to 200 (0.10 g, 0.59 mmol) in anhydrous DMF/EtOAc (3:1, 8 mL) was added DIPEA (0.21 mL, 1.19 mmol), T3P (0.53 mL, 0.89 mmol) and 2-iodobenzyl amine (0.15 g, 0.65 mmol) to yield the product as an orange oil (0.11 g, 45%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.89-1.92 (m, 1H, CHH'), 2.09-2.12 (m, 1H, CHH'), 2.57 (q, 1H, J=6.4, CHCHCH$_2$), 3.76 (s, 3H, CO$_2$CH$_3$), 4.45-4.52 (m, 2H, NHCH$_2$), 5.19 (dd, 1H, J=10, 0.8, CH$_2$=CH), 5.37 (dd, 1H, J=17.2, 0.8, CH$_2$=CH), 5.60-5.69 (m, 1H, CH$_2$=CH), 6.97-7.01 (m, 1H, ArH), 7.31-7.39 (m, 2H, ArH), 7.84-7.86 (m, 1H, ArH), 8.92 (br s, 1H, NH). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 21.6 (CH$_2$), 34.5 (Q), 37.2 (CH), 48.6 (CH$_2$), 52.6 (CH$_3$), 99.1 (Q), 119.8 (CH$_2$), 128.5 (CH), 129.0 (CH), 129.5 (CH), 133.2 (CH), 139.4 (CH), 140.4 (Q), 167.8 (Q), 171.6 (Q). MS (ESI): [M+H]$^+$ requires 386.0253 found 386.0240. IR (thin film)/cm$^{-1}$ 3356 (m), 3054 (m), 2986 (m), 2955 (m), 1707 (s), 1655 (s), 1529 (s), 1439 (m), 1145 (m).
To a solution of methyl vinyl ketone (0.15 mL, 1.70 mmol) in DMF (10 mL) was added dimethyl bromomalonate (0.19 mL, 1.45 mmol), and potassium carbonate (0.40 g, 2.90 mmol). The reaction was stirred at room temperature for 2 hours then quenched by addition of 2M aq. HCl (2 mL). The reaction mixture was extracted into CH₂Cl₂ (10 mL), the organics washed with water (2x10 mL), brine (3x10 mL), dried (MgSO₄), filtered, and concentrated in vacuo. Purification by silica gel column (35% ethyl acetate in light petroleum) to yield the product as a colourless oil (0.19 g, 69%).

**1H NMR** (400 MHz, CDCl₃) δ 1.60-1.63 (m, 1H, CH'H'), 1.94-1.96 (m, 1H, CH'H'), 2.34 (s, 3H, CH₃), 2.84 (t, 1H, J=6.4, COCH'), 3.70 (s, 3H, CO₂CH₃), 3.64 (s, 3H, CO₂CH₃). **13C NMR** (100 MHz, CDCl₃) δ 19.7 (CH₂), 30.5 (CH₃), 33.1 (CH), 51.8 (CH₃), 52.1 (CH₃), 134.3 (Q), 165.3 (Q), 168.2 (Q), 202.1 (Q). MS (ESI): [M+Na]+ requires 223.0582 found 223.0577. IR (thin film)/cm⁻¹ 3056 (m), 2955 (m), 1736 (s), 1712 (s), 1438 (s).
Dimethyl 2-(prop-1-en-2-yl)cyclopropane-1,1-dicarboxylate (222)

To a suspension of methyltriphenylphosphonium bromide (0.89 g, 2.50 mmol) in anhydrous diethyl ether (25 mL), was added n-BuLi (1.74 mL, 1.44M, 2.50 mmol). After 60 minutes 232 (0.50 g, 2.50 mmol) was added and the mixture stirred at room temperature for 24 hours. Water (20 mL) was added, the organics removed and the aqueous layer extracted with diethyl ether (3x20 mL). The combined organic extracts then washed brine (20 mL), dried (MgSO₄), filtered, and the solvent removed in vacuo. Purification by silica gel column (20% ethyl acetate in light petroleum) to yield the product as a colourless oil (0.22 g, 44%). ¹H NMR (400 MHz, CDCl₃) δ 1.47-1.50 (m, 1H, CHH), 1.70 (s, 3H, CH₃), 1.86-1.90 (m, 1H, CHH), 2.50 (t, 1H, J=8.4, CHCCC₃), 3.69 (s, 3H, CO₂CH₃), 3.76 (s, 3H, CO₂CH₃), 4.72 (d, 1H, J=0.8, CH₂=CH₃), 4.88 (d, 1H, J=0.8, CH₂=CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 18.5 (CH₂), 22.7 (CH₃), 33.9 (CH), 36.2 (Q), 52.5 (CH₂), 52.8 (CH₃), 112.8 (CH₂), 139.3 (Q), 167.6 (Q), 170.9 (Q). IR (thin film)/cm⁻¹ 1730 (s), 1651 (m), 1438 (s), 1333 (s), 1268 (s), 1132 (s), 902 (m). MS (ESI): [M+Na]⁺ requires 221.0789 found 221.0784.
1-(Methoxycarbonyl)-2-(prop-1-en-2-yl)cyclopropanecarboxylic acid (230)

To a stirred solution of 222 (0.19 g, 0.96 mmol) in THF/H$_2$O (1:1, 8 mL), was added lithium hydroxide (0.02 g, 0.96 mmol). The resulting mixture was stirred for 2 hours then acidified with 2M aq. HCl (pH 2), extracted with Et$_2$O (3x5 mL), washed with brine (3x5 mL), the combined extracts dried (MgSO$_4$), filtered, and the solvent removed in vacuo to yield a colourless solid (0.16 g, 91%, mp 66.8-68.1°C). $^1$H NMR (400 MHz, CDCl$_3$) δ 1.76 (s, 3H, CH$_3$), 2.06-2.10 (m, 1H, CHH'), 2.12-2.15 (m, 1H, CHH'), 2.71 (t, 1H, J=6.4, CHCCH$_3$), 3.29 (s, 1H, OH), 3.75 (s, 3H, CO$_2$CH$_3$), 4.93 (d, 1H, J=0.8, CH$_2$=CCH$_3$), 5.04 (d, 1H, J=0.8, CH$_2$=CCH$_3$). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 21.8 (CH$_2$), 22.4 (CH$_3$), 32.4 (Q), 42.4 (CH), 52.8 (CH$_3$), 115.4 (CH$_2$), 138.1 (Q), 170.6 (Q), 174.0 (Q). IR (thin film)/cm$^{-1}$ 3353 (br s), 1755 (s), 1673 (s), 1446 (s), 1421 (s), 1354 (s), 1265 (s), 897 (m). MS (ESI): [M+Na]$^+$ requires 207.0633 found 207.0627.
(Z)-Methyl 1-((4-bromobut-3-en-1-yl)carbamoyl)-2-(prop-1-en-2-yl)cyclopropanecarboxylate (233)

Following the representative amide coupling procedure 230 (0.07 g, 0.36 mmol) in anhydrous EtOAc (10 mL) was added DIPEA (0.12 mL, 0.72 mmol), T3P (0.32 mL, 0.90 mmol) and 208 (0.20 g, 1.36 mmol) to yield the product as an orange oil (0.09 g, 75%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.75 (s, 3H, $CH_3$), 1.96-2.00 (m, 2H, $CHH'$, $CHH$), 2.44-2.52 (m, 2H, $CH_2CH_2NH$), 3.12 (t, 1H, $J$=7.6, $CHCCH_3$), 3.39-3.47 (m, 2H, $CH_2CH_2NH$), 3.65 (s, 3H, $CO_2CH_3$), 4.84 (d, 1H, $J$=0.8, $CH_2=CCH_3$), 4.90 (d, 1H, $J$=0.8, $CH_2=CCH_3$), 6.13-6.18 (m, 1H, Br$CH=CHCH_2$), 6.31 (d, 1H, $J$=7.2, Br$CH=CHCH_2$), 8.40 (br s, 1H, $NH$). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 8.6 (Q), 18.9 (CH$_2$), 22.6 (CH$_3$), 30.1 (CH$_2$), 34.2 (Q), 38.2 (CH$_2$), 39.1 (CH), 40.1 (Q), 51.8 (CH$_3$), 110.1 (CH), 114.0 (CH$_2$), 131.5 (CH), 139.3 (Q). IR (thin film)/cm$^{-1}$ 3361 (m), 2253 (m), 1702 (m), 1654 (m), 1536 (m), 1148 (m), 908 (s), 734 (s).
Methyl 1-((2-iodophenyl)carbamoyl)-2-(prop-1-en-2-yl)cyclopropanecarboxylate (310)

Following the representative amide coupling procedure 230 (0.05 g, 0.29 mmol) in anhydrous EtOAc (10 mL) was added DIPEA (0.10 mL, 0.59 mmol), T3P (0.26 mL, 0.44 mmol) and 2-iodoaniline (0.07 g, 0.32 mmol) to yield the product as an orange oil (0.07 g, 64%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.82 (s, 3H, CH$_3$), 2.08-2.14 (m, 2H, CHH', CHH), 2.54 (t, 1H, J=8.8, CHCCH$_3$), 3.77 (s, 3H, CO$_2$CH$_3$), 4.91 (d, 1H, J=0.8, CH$_2$=CCH$_3$), 5.01 (d, 1H, J=0.8, CH$_2$=CCH$_3$), 6.86 (td, 1H, J=7.2, 1.2, ArH), 7.35 (td, 1H, J=8.4, 1.2, ArH), 7.84 (dd, 1H, J=8, 1.2, ArH), 8.15 (dd, 1H, J=8, 1.2, ArH), 10.48 (br s, 1H, NH). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 18.3 (CH$_2$), 21.6 (CH$_3$), 34.2 (Q), 39.4 (CH), 51.3 (CH$_3$), 89.1 (Q), 113.4 (CH$_2$), 118.9 (Q), 122.0 (CH), 125.0 (CH), 127.8 (CH), 128.3 (Q), 138.2 (CH), 165.8 (Q), 170.0 (Q). IR (thin film)/cm$^{-1}$ 3054 (m), 2987 (m), 1707 (m), 1669 (m), 1527 (m), 1435 (m), 1422 (m).
Methyl 1-((2-iodobenzyl)carbamoyl)-2-(prop-1-en-2-yl)cyclopropanecarboxylate (311)

Following the representative amide coupling procedure; to 230 (0.05 g, 0.26 mmol) in anhydrous DMF/EtOAc (3:1, 8 mL) was added DIPEA (0.09 mL, 0.52 mmol), T3P (0.23 mL, 0.39 mmol) and 241 (0.07 g, 0.29 mmol) to yield the product as a yellow oil (0.08 g, 73%). \( ^1 \text{H NMR (400 MHz, CDCl}_3 \) \( \delta \) 1.75 (s, 3H, \( \text{CH}_3 \)), 1.97-2.02 (m, 2H, \( \text{CHH'} \), \( \text{CHH}'' \)), 2.50 (t, 1H, J=8.4, \( \text{CHCH}_3 \)), 3.65 (s, 3H, \( \text{CO}_2\text{CH}_3 \)), 4.55-4.59 (m, 2H, \( \text{NHCCH}_2 \)), 4.85 (d, 1H, J=1.2, \( \text{CH}_2=\text{CCH}_3 \)), 4.96 (d, 1H, J=1.2, \( \text{CH}_2=\text{CCH}_3 \)), 7.69 (td, 1H, J=2, 8, \( \text{ArH} \)), 7.33 (m, 2H, \( \text{ArH} \)), 7.85 (dd, 1H, J=8, 2, \( \text{ArH} \)), 8.85 (br s, 1H, \( \text{NH} \)). \( ^{13} \text{C NMR (100 MHz, CDCl}_3 \) \( \delta \) 18.1 (\( \text{CH}_2 \)), 21.6 (\( \text{CH}_3 \)), 33.3 (Q), 38.4 (CH), 47.6 (\( \text{CH}_2 \)), 50.9 (\( \text{CH}_3 \)), 97.9 (Q), 113.1 (\( \text{CH}_2 \)), 127.5 (CH), 128.1 (CH), 128.3 (CH), 138.1 (Q), 138.4 (CH), 139.4 (Q), 167.2 (Q), 170.6 (Q). IR (thin film)/cm\(^{-1} \) 3054 (m), 2986 (m), 1703 (m), 1655 (m), 1439 (m), 1422 (m).
Representative cyclisation procedure

(Z)-Methyl 1-(4-bromobut-3-en-1-yl)-2-oxo-5-vinylpyrrolidine-3-carboxylate (221)

\[
\begin{align*}
\text{(233)} & \quad \text{CO}_2\text{Me} \\
\text{Br} & \quad \text{H} \\
\text{Me} & \quad \text{N}
\end{align*}
\]

\[
\begin{align*}
\text{(221)} & \quad \text{CO}_2\text{Me} \\
\text{Br} & \quad \text{H}
\end{align*}
\]

To a stirred solution of 233 (0.05 g, 0.16 mmol) in MeOH (3 mL) was added tetrakis(triphenylphosphine)palladium (0.02 g, 0.02 mmol). The reaction was stirred at room temperature for 17 hours then the solvent removed in vacuo. The resulting solid was redissolved in EtOAc, filtered through a pad of celite, and the solvent removed in vacuo. Purification by silica gel column (25% ethyl acetate in light petroleum) yielded the target compound as an orange oil (0.02 g, 42%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.90-2.14 (m, 1H, CH\(_2\)CHCO\(_2\)Me), 2.35-2.39 (m, 2H, NCH\(_2\)CH\(_2\)), 2.50-2.52 (m, 1H, CH\(_2\)CHCO\(_2\)Me), 2.94-2.99 (m, 2H, NCH\(_2\)CH\(_2\)), 3.36-3.43 (m, 1H, CH\(_2\)CHCO\(_2\)Me), 3.67 (s, 3H, CO\(_2\)CH\(_3\)), 4.18-4.20 (m, 1H, CHCH=CH\(_2\)), 5.21-5.34 (m, 2H, CH\(_2\)=CH), 5.53-5.69 (m, 1H, CH\(_2\)=CH), 6.01-6.04 (m, 1H, BrCH=CHCH\(_2\)), 6.15-6.18 (m, 1H, BrCH=CHCH\(_2\)). IR (thin film)/cm\(^{-1}\) 2936 (m), 2872 (m), 1752 (s), 1676 (s), 1265 (m), 740 (m). MS (ESI): [MBr\(^{79}\)+H]\(^+\) requires 302.0392 found 302.0395.
Representative Heck coupling procedure

Methyl 9-methylene-3-oxo-2,3,5,6,9,9a-hexahydro-1H-pyrrolo[1,2-a]azepine-2-carboxylate (203)

To a stirred solution of 221 (0.05 g, 0.16 mmol) in MeOH (3 mL) was added tetrakis(triphenylphosphine)palladium (0.02 g, 0.016 mmol), followed by triethylamine (0.06 mL, 0.4 mmol). The reaction was stirred at reflux for 24 hours then the solvent removed in vacuo. The resulting solid was redissolved in EtOAc, filtered through a pad of celite, and the solvent removed in vacuo. Purification by silica gel column (50% ethyl acetate in light petroleum) yielded the target compound as an orange oil (0.02 g, 45%), in a 1:1 ratio of diastereoisomers. $^1$H NMR (400 MHz, CDCl$_3$) δ 2.07-2.12 (m, 1H, CH$_2$CHCO$_2$Me), 2.49 (m, 1H, CH$_2$CHCO$_2$Me), 3.24-3.29 (m, 2H, NCH$_2$CH$_2$), 3.38-3.47 (m, 1H, CH$_2$CHCO$_2$Me), 3.74 (s, 3H, CO$_2$CH$_3$), 3.78-3.82 (m, 2H, NCH$_2$CH$_2$), 4.66 (t, 1H, J=7.2, NCHCH$_2$), 5.06 (d, 1H, J=2.4, CH$_2$=C), 5.12 (d, 1H, J=2.4, CH$_2$=C), 5.59-5.63 (m, 1H, CH$_2$CH=CH), 6.06-6.11 (m, 1H, CH$_2$CH=CH). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 29.3 (CH$_2$), 30.3 (CH$_2$), 39.5 (CH$_2$), 47.1 (CH), 51.7 (CH$_3$), 61.6 (CH), 115.3 (CH$_2$), 127.1 (CH), 129.3 (CH), 144.4 (Q), 167.8 (Q), 169.5 (Q). IR (thin film)/cm$^{-1}$ 3054 (m), 2987 (m), 1740 (m), 1692 (m), 1422 (m), 896 (m). MS (ESI): [M+Na]$^+$ requires 244.0949 found 244.0942.
Representative cyclisation, Heck cascade procedure

**Methyl 9-methylene-3-oxo-2,3,5,6,9,9a-hexahydro-1H-pyrrolo[1,2-a]azepine-2-carboxylate (203)**

To a stirred solution of 233 (0.05 g, 0.17 mmol) in MeOH (3 mL) was added tetrakis(triphenylphosphine)palladium (0.02 g, 0.02 mmol), followed by triethylamine (0.06 mL, 0.43 mmol). The reaction was stirred at reflux for 24 hours then the solvent removed in vacuo. The resulting solid was redissolved in EtOAc, filtered through a pad of celite, and the solvent removed in vacuo. Purification by silica gel column (50% ethyl acetate in light petroleum) yielded the target compound as an orange oil (0.03 g, 52%), in a 1:1 ratio of diastereoisomers. All spectral data matches that reported in the representative Heck coupling procedure.
Representative Heck, carbonylation cascade procedure

Methyl 9-(2-methoxy-2-oxoethyl)-3-oxo-2,3,5,6,9,9a-hexahydro-1H-pyrrolo[1,2-a]azepine-2-carboxylate (205)

To a stirred solution of 233 (0.05 g, 0.16 mmol) in MeOH (3 mL) was added tetrakis(triphenylphosphine)palladium (0.02 g, 0.02 mmol), followed by triethylamine (0.06 mL, 0.40 mmol). The reaction vessel was then placed under a CO atmosphere using 3 cycles of a freeze, evacuate, and thaw technique. The reaction was stirred at reflux for 24 hours then the solvent removed in vacuo. The resulting solid was redissolved in EtOAc, filtered through a pad of celite, and the solvent removed in vacuo. Purification by silica gel column (50% ethyl acetate in light petroleum) yielded the target compound as an orange oil (0.03 g, 52%), in a 1:1 ratio of diastereoisomers. $^1$H NMR (400 MHz, CDCl$_3$) δ 1.97-1.99 (m, 1H, CH$_2$CO$_2$Me), 2.41-2.48 (m, 2H, CH$_2$CH$_2$N), 2.58-2.60 (m, 1H, CH$_2$CHCO$_2$Me), 3.02-3.07 (m, 2H, CH$_2$CH$_2$N), 3.44-3.51 (m, 1H, CH$_2$CHCO$_2$Me), 3.77 (s, 3H, CH$_2$CO$_2$C$_3$H$_3$), 3.79 (s, 3H, CH$_2$CHCO$_2$C$_3$H$_3$), 4.26-4.28 (m, 1H, HN), 5.29-5.41 (m, 2H, CHC=CHCH$_2$CO$_2$Me), 5.61-5.79 (m, 1H, CHCH$_2$CO$_2$Me), 6.09-6.12 (m, 1H, CH=CHCH$_2$), 6.22-6.25 (m, 1H, CH=CHCH$_2$). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 28.2 (CH$_2$), 28.7 (CH$_2$), 38.0 (CH$_2$), 46.6 (CH), 51.7 (2xCH$_3$), 61.0 (CH), 109.0 (CH), 118.3 (CH$_2$), 130.3 (CH), 135.8 (CH), 165.6 (Q), 168.8 (Q), 169.5 (Q). IR (thin film)/cm$^{-1}$ 3054 (m), 2987 (m), 2954 (m), 1739 (s), 1721 (s), 1692 (s), 1437 (m), 1422 (m). MS (ESI): [M+Na]$^+$ requires 304.1161 found 304.1150.
Methyl 9-(2-methoxy-2-oxoethyl)-3-oxo-2,3,9,9a-tetrahydro-1H-pyrrolo[1,2-a]indole-2-carboxylate (245)

Following the representative Heck, carbonylation cascade procedure; to 246 (0.07 g, 0.18 mmol) in MeOH (3mL) was added tetrakis(triphenylphosphine)palladium (0.02 g, 0.02 mmol), and triethylamine (0.06 mL, 0.44 mmol) to yield the target compound as an orange oil (0.02 g, 36%), as a mixture of diastereoisomers. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.58-2.66 (m, 1H, CH$_2$CHCHO$_2$Me), 3.06-3.13 (m, 1H, CH$_2$CHCO$_2$Me), 3.58-3.64 (m, 1H, CH$_2$CHCO$_2$Me), 3.66-3.72 (m, 2H, CH$_2$CO$_2$Me), 3.77 (s, 3H, CH$_2$CO$_2$C$_3$H$_7$), 3.83 (s, 3H, CH$_2$CHCO$_2$CH$_3$), 3.88-3.94 (m, 1H, CHCH$_2$CO$_2$Me), 4.29-4.31 (m, 1H, CHNCO), 7.09-7.17 (m, 2H, ArH), 7.27-7.31 (m, 1H, ArH), 7.61-7.64 (m, 1H, ArH). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 37.3 (CH$_2$), 44.9 (CH), 47.2 (CH$_2$), 52.9 (CH$_3$), 53.8 (CH$_3$), 56.4 (CH), 65.3 (CH), 115.2 (CH), 123.8 (CH), 125.1 (CH), 128.5 (CH), 137.5 (Q), 138.6 (Q), 165.8 (Q), 169.3 (Q), 171.2 (Q). MS (ESI): [M+H]$^+$ requires 304.1185 found 304.1180. IR (thin film)/cm$^{-1}$ 3055 (m), 2987 (m), 2954 (m), 1741 (s), 1725(s), 1702 (s), 1485 (m), 1172 (m).
Methyl 9-(2-methoxy-2-oxoethyl)-9-methyl-3-oxo-2,3,5,6,9,9a-hexahydro-1H-pyrrolo[1,2-a]azepine-2-carboxylate (235)

Following the representative Heck, carbonylation cascade procedure to 233 (0.04 g, 0.13 mmol), in MeOH (3 mL) was added tetrakis(triphenylphosphine)palladium (0.02 g, 0.01 mmol), and triethylamine (0.05 mL, 0.33 mmol) to yield the target compound as an orange oil (0.01 g, 28%), as a mixture of diastereoisomers. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.66 (s, 3H, CH\(_3\)), 2.04-2.08 (m, 1H, CH\(_2\)CHCO\(_2\)Me), 2.51-2.57 (m, 1H, CH\(_2\)CHCO\(_2\)Me), 2.71-2.88 (m, 2H, CH\(_2\)CH\(_2\)N), 3.01-3.12 (m, 2H, CH\(_2\)CH\(_2\)N), 3.44-3.55 (m, 1H, CH\(_2\)CHCO\(_2\)Me), 3.73 (s, 3H, CH\(_2\)CO\(_2\)CH\(_3\)), 3.80 (s, 3H, CH\(_2\)CHCO\(_2\)Me), 4.30-4.33 (m, 1H, CH\(_2\)N), 5.01-5.12 (m, 2H, CH\(_2\)CO\(_2\)Me), 5.86 (d, 1H, J=11.6, CH=CHCH\(_2\)), 6.20-6.27 (m, 1H, CH=CHCH\(_2\)). \(^1\)\(^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 16.9 (CH\(_3\)), 27.7 (CH\(_2\)), 29.7 (CH\(_2\)), 39.6 (CH\(_2\)), 47.85 (CH), 51.2 (CH\(_3\)), 52.7 (CH\(_3\)), 61.8 (CH), 115.0 (CH\(_2\)), 121.4 (CH), 142.3 (Q), 146.3 (CH), 166.6 (Q), 170.2 (Q), 170.6 (Q). IR (thin film)/cm\(^{-1}\) 3055 (m), 2987 (m), 2954 (m), 1741 (s), 1719 (s), 1691 (s), 1437 (m), 1199 (m), 1178 (m). MS (ESI): [M+Na]\(^+\) requires 318.1317 found 318.1312.
Methyl 10-(2-methoxy-2-oxoethyl)-10-methyl-3-oxo-1,2,3,5,10,10a-hexahydropyrrolo[1,2-b]isoquinoline-2-carboxylate (242)

Following the representative Heck, carbonylation cascade procedure; to 311 (0.04 g, 0.09 mmol) in MeOH (3 mL) was added tetrakis(triphenylphosphine)palladium (0.01 g, 0.01 mmol), and triethylamine (0.03 mL, 0.02 mmol) to yield the target compound as an orange oil (0.02 g, 52%), as a mixture of diastereoisomers. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.65 (s, 3H, CH$_3$), 2.07-2.11 (m, 1H, CH$_2$CHCO$_2$Me), 2.61-2.64 (m, 1H, CH$_2$CHCO$_2$Me), 3.63-3.67 (m, 1H, CH$_2$CHCO$_2$Me), 3.84 (s, 3H, CH$_2$CO$_2$CH$_3$), 3.90 (s, 3H, CH$_2$CHCO$_2$CH$_3$), 4.04-4.07 (m, 1H, CH$_N$), 4.44-4.53 (m, 1H, CCH$_2$CO$_2$Me), 4.80-4.83 (m, 1H, NCH$_2$), 4.94-4.95 (m, 1H, NCH$_2$), 5.19-5.27 (m, 1H, CCH$_2$CO$_2$Me), 7.34-7.37 (m, 2H, ArH), 7.51-7.53 (m, 1H, ArH), 7.94-7.96 (m, 1H, ArH). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 17.4 (CH$_3$), 27.9 (CH$_2$), 42.6 (CH$_2$), 47.6 (CH), 52.2 (CH$_3$), 52.8 (CH$_2$), 61.8 (CH), 114.5 (CH$_2$), 127.3 (CH), 129.3 (CH), 129.8 (Q), 130.8 (CH), 132.6 (CH), 137.4 (Q), 142.4 (Q), 167.6 (Q), 170.4 (Q), 171.0 (Q). IR (thin film)/cm$^{-1}$ 3057 (m), 2961 (m), 2916 (m), 2849 (m), 1691 (m), 1718 (m), 1736 (m), 1433 (m), 1084 (m). MS (ESI): [M+Na]$^+$ requires 331.1420 found 331.1423.
Representative Krapcho decarboxylation procedure\textsuperscript{99}

Methyl 2-(3-oxo-2,3,9,9a-tetrahydro-1H-pyrrolo[1,2-a]indol-9-yl)acetate (312)

To a solution of 245 (0.02 g, 0.29 mmol) in DMF (1 mL) was added LiCl (approx. 2 mg) and water (1 drop). This was microwaved at 180°C for 10 minutes then diluted with diethyl ether (10 mL) washed with water (10 mL), brine (3x10 mL), dried (MgSO\textsubscript{4}), filtered, and the solvent removed in vacuo to yield the product as an orange oil. (0.008 g, 60%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 2.05-2.14 (m, 1H, \(\text{CH}_2\text{CHN}\)), 2.49-2.54 (m, 1H, \(\text{CH}_2\text{CHN}\)), 2.58 (dd, 1H, \(J=16.8\,8\), \(\text{CH}_2\text{CON}\)), 2.59 (dd, 1H, \(J=16.4\,10.4\) \(\text{CH}_2\text{COOCH}_3\)), 2.76-2.86 (m, 1H, \(\text{CH}_2\text{CON}\)), 3.03 (dd, 1H, \(J=16.4\,4.4\) \(\text{CH}_2\text{COOCH}_3\)), 3.55-3.61 (m, 1H, \(\text{CHCH}_2\text{CO}_2\text{CH}_3\)), 3.75 (s, 3H, \(\text{CO}_2\text{CH}_3\)), 4.28-4.34 (m, 1H, \(\text{CHNCO}\)), 7.05-7.24 (m, 2H, \(\text{ArH}\)), 7.44-7.48 (m, 1H, \(\text{ArH}\)), 7.53-7.57 (m, 1H, \(\text{ArH}\)). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 29.2 (\(\text{CH}_2\)), 36.2 (\(\text{CH}_2\)), 37.5 (\(\text{CH}_2\)), 44.8 (CH), 52.0 (CH\textsubscript{3}), 69.9 (CH), 115.1 (CH), 123.9 (CH), 124.4 (CH), 132.1 (CH), 136.2 (Q), 139.0 (Q), 171.7 (Q), 172.3 (Q). IR (thin film)/cm\textsuperscript{-1} 3054 (m), 2985 (m), 1721 (m), 1644 (m), 1434 (m), 1421 (m). MS (ESI): [M+Na]\textsuperscript{+} requires 245.1052 found 245.1055.
Chapter 4 experimental
**4-Bromo-2,2-dimethyl-dihydrobenzo-1,3-dioxole (281)**

To a stirred solution of (1S,2S)-3-bromocyclohexa-3,5-diene-1,2-diol (1.18 g, 6.20 mmol) in CH₂Cl₂ (40 mL) was added 2,2-dimethoxypropane (0.84 mL, 6.82 mmol), and tosic acid (0.12 g, 0.620 mmol). The reaction was stirred at room temperature for 1h then was quenched by addition of aqueous NaHCO₃ (40 mL). The reaction mixture was extracted into CH₂Cl₂ (3x15mL), the organics combined, dried (MgSO₄), filtered, and concentrated in vacuo to yield the product as a pale brown oil (1.28 g, 89%).

**¹H NMR** (400 MHz, CDCl₃) δ 1.45 (s, 3H, OCC₃H₃), 1.46 (s, 3H, OCC₃H₃), 4.75-4.76 (m, 2H, 2xCHOC), 5.88-5.93 (m, 1H, OCHCH=CH), 5.98-6.02 (m, 1H, OCHCH=CH), 6.36 (d, 1H, J=6, BrC=CH). **¹³C NMR** (100 MHz, CDCl₃) δ 24.51 (CH₃), 26.40 (CH₃), 71.85 (CH), 74.79 (CH), 104.79 (Q), 123.43 (CH), 124.06 (Q), 124.89 (CH), 125.78 (CH). **IR** (thin film)/cm⁻¹ 2990 (w), 2934 (w), 2253 (m), 908 (s).
**Dimethyl 2-diazomalonate (280)**

![Equation](image)

To a stirred solution of dimethyl malonate (2.43 mL, 21.22 mmol) and 4-acetamidobenzenesulfonyl azide (4.99 g, 20.80 mmol) in acetonitrile (60 mL) at 0°C was added triethylamine (8.70 mL, 62.4 mmol). The mixture was allowed to warm to room temperature then stirred for 17 hours. The solvent was removed in vacuo, producing a solid which was triturated with ether/i-hexane (1:1). The solvent was removed in vacuo to yield an orange oil (3.03 g, 92%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.86 (s, 6H, OCH\(_3\)). \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 52.53 (2xCH\(_3\)), 130.9 (Q), 161.8 (2xQ). IR (thin film)/cm\(^{-1}\) 3006 (m), 2958 (s), 2138 (s), 1739 (s), 1697 (s). LC-MS: RT 0.62 mins; MS m/z 159.4 [M+H]\(^+\).
To a solution of 281 (1.18 g, 5.11 mmol), and diacetoxyrhodium (0.02 g, 0.036 mmol) in 1,2-dichloroethane (5 mL) was added dimethyl 2-diazomalonate (0.57 g, 3.57 mmol) diluted in 1,2-dichloroethane (10 mL) via dropping funnel over 30 min and the resulting mixture was then stirred at room temperature for 72 hours. The reaction mixture was concentrated in vacuo to yield a brown viscous oil. Purification by flash column chromatography using the ISCO combiflash Rf, (0-30% ethyl acetate in i-hexane) over 15 mins to yield the product as a pale yellow oil (0.39 g, 21%).  

$^1$H NMR (400 MHz, CDCl$_3$) δ 1.43 (s, 3H, OCC$_3$H$_3$), 1.49 (s, 3H, OCC$_3$H$_3$), 2.32-2.33 (m, 1H, CCHCHO), 2.45-2.48 (m, 1H, CCHCH=CBr), 3.74 (s, 3H, CO$_2$C$_3$H$_3$), 3.76 (s, 3H, CO$_2$C$_3$H$_3$), 4.30 (d, 1H, J=6.9, CCHCHO), 5.11 (d, 1H, J=6.9, BrCCHO), 6.30 (d, 1H, J=5.4, BrC=CH$_3$). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 24.8 (CH$_3$), 25.7 (CH$_3$), 25.9 (CH$_3$), 27.4 (CH$_3$), 39.8 (Q), 53.0 (CH), 53.1 (CH), 71.3 (CH), 73.8 (CH), 110.1 (Q), 124.9 (CH), 166.8 (Q), 168.8 (Q), 171.1 (Q). MS (ESI): [MBr$^{79}$+H]$^+$ requires 361.0287 found 361.0289.
(3aS,5aS,6aS,6bS) 4-Bromo-6-(methoxycarbonyl)-2,2-dimethyl-5a,6,6a,6b-tetrahydro-3aH-cyclopropa[3,4]benzo[1,2-d][1,3]dioxole-6-carboxylic acid (284).\(^{70}\)

![Chemical structure diagram]

To a stirred solution of 282 (0.37 g, 1.04 mmol) in THF (6 mL) and water (6 mL), was added LiOH (0.03 g, 1.10 mmol) and the reaction left stirring for 2 hours at room temp. The reaction mixture was acidified to pH 2 with 1M aq. HCl and extracted with Et\(_2\)O (2x20 mL), the ether layers combined, dried (MgSO\(_4\)), filtered, and concentrated in vacuo to give a yellow oil (0.31 g, 85%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.43 (s, 3H, OCH\(_3\)), 1.48 (s, 3H, OCH\(_3\)), 2.43-2.45 (m, 1H, CCHCHO), 2.49-2.53 (m, 1H, CCHCH=CHBr), 3.22 (s, 1H, OH), 3.77 (s, 3H, CO\(_2\)CH\(_3\)), 4.33 (d, 1H, J=7, BrC=CH), 5.11 (d, 1H, J=7, BrC=CH), 6.31 (d, 1H, J=5.3, BrC=CH). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 25.5 (CH\(_3\)), 27.3 (CH\(_3\)), 27.3 (CH\(_3\)), 39.2 (Q), 53.2 (CH), 71.2 (CH), 73.97 (CH), 110.2 (Q), 124.3 (CH), 125.3 (CH), 166.9 (Q), 168.8 (Q), 172.9 (Q). MS (ESI): [MBr\(^{79}\)+H]\(^+\) requires 347.0131 found 347.0129.
(3aS,5aR,6aR,6bS) Methyl 6-(benzylcarbamoyl)-4-bromo-2,2-dimethyl-5a,6a,6b-tetrahydro-3aH-cyclopropa[3,4]benzo[1,2-d][1,3]dioxole-6-carboxylate (285).

To a stirred solution of 284 (0.32 g, 1.63 mmol) in EtOAc (5 mL) was added DIPEA (0.31 mL, 1.79 mmol), T3P (1.45 mL, 2.44 mmol) and allowed to stir for 10 mins. Benzyl amine (0.18 mL, 1.63 mmol) then added and the solution stirred overnight. Reaction was diluted with DCM (15 mL), and washed with 2M aq. HCl (10 mL) followed by aq. NaHCO₃ (2x10 mL), then both aqueous layers re-extracted into DCM (3x15 mL). The combined DCM extracts then dried (MgSO₄), filtered, and solvent removed in vacuo to yield a yellow oil. Reaction was purified by flash column chromatography using the ISCO combiflash Rf, (0-30% ethyl acetate in i-hexane) over 15 mins to yield the product as a pale yellow oil (0.39 g, 86%). ¹H NMR (400 MHz, CDCl₃) δ 1.39 (s, 3H, OCC₃H₃), 1.50 (s, 3H, OCCH₃), 2.43-2.46 (m, 1H, CCHCHO), 2.67 (d, 1H, J=8.6, CCHCH=CBr), 3.70 (s, 3H, CO₂CH₃), 4.38 (d, 1H, J=7.3, CCHCHO), 4.45-4.49 (m, 2H, NHCH₂Ph), 5.03 (d, 1H, J=7.3, BrCCHO), 6.23 (d, 1H, J=5.2, BrC=CH₂), 7.25-7.34 (m, 5H, ArH), 7.47 (t, 1H, J=5.7, CONH₂). LCMS: RT 1.20 mins; MS m/z 438.4 [M+H]⁺, 436.4 [M-H]⁻. IR (thin film)/cm⁻¹ 3054 (m), 2987 (m), 1657 (br, m), 1421 (m), 1265(s).
(3aS,8bS)-Methyl 6-benzyl-4-bromo-2,2-dimethyl-7-oxo-5a,6,7,8,8a,8b-hexahydro-3aH-[1,3]dioxolo[4,5-e]indole-8-carboxylate (286).

Room temperature reaction

To a stirred solution of 285 (0.17 g, 0.38 mmol), in methanol (10 mL) was added Pd(PPh₃)₄ (0.04 g, 0.04 mmol) and the reaction allowed to stir at room temperature for 17 hrs. The solvent was removed and the resulting solid re-dissolved in EtOAc (20 mL) and filtered through a plug of silica to remove the palladium. The provisionally interpreted ¹H spectra and LCMS data shows none of the expected protected product formed. Only observed starting material from the reaction.

Microwave reaction

To a 0.5-2mL microwave vial was added 285 (0.05 g, 0.12 mmol), methanol (1 mL) and tetrakis palladium (0.01 g, 0.012 mmol), the vial flushed with N₂ and heated in the biotage initiator microwave oven at 120°C for 15 mins. A colour change from yellow to dark orange was observed. Solvent was removed in vacuo and the resulting solid redissolved in EtOAc and filtered through a pad of celite and evaporated in vacuo to yield a yellow oil. The provisionally interpreted ¹H spectra shows the expected 286 was not formed. Only observed starting material. LCMS: RT 1.27 mins; MS m/z 438.1 [M+H]+ - consistent with starting material.
2,2-Dimethyl-dihydrobenzo-1,3-dioxole (292)

\[
\begin{align*}
\text{Br} & \quad \text{Et}_2\text{O}, -78^\circ\text{C} \quad \text{Li} \\
\text{(281)} & \quad \rightarrow \quad \text{(292)} \\
\end{align*}
\]

To a stirred solution of 281 (1.02 g, 4.40 mmol) in diethyl ether (5 mL) at -78°C was added BuLi (3.22 mL, 4.84 mmol) dropwise. Colour change from colourless to yellow was observed. Once addition was complete solution was allowed to stir for 10 mins then removed from the cold bath and allowed to warm to approx. -20°C for 5 mins where the colour went darker yellow/brown. Solution then cooled back down to -78°C and quenched with water (5mL) and the flask allowed to warm to room temp.

Reaction mixture was extracted in to diethyl ether (3x10mL), washed with brine (10mL), dried (MgSO\(_4\)), filtered, and evaporated to a yellow oil. The provisionally interpreted \(^1\)H spectra show only starting material obtained from the reaction.
(3aR,5aS,6aR,6bS) Methyl 6-(benzylcarbamoyl)-2,2,4-trimethyl-5a,6,6a,6b-tetrahydro-3aH-cyclopropa[3,4]benzo[1,2-d][1,3]dioxole-6-carboxylate (294)

To a solution of 285 (0.10 g, 0.233 mmol), anhydrous toluene (5 mL) and Pd(PPh₃)₄ (10.7 mg, 9.26 µmol) were added. The solution was allowed to stir at room temp for 2 hours then a solution of 1M methylmagnesium bromide (0.30 mL, 0.30 mmol) was added. The resulting solution was allowed to stir at room temperature overnight. Reaction was quenched with water (15 mL) and filtered through a pad of celite. The filtrate was extracted with diethyl ether (3x20 mL), the combined extracts dried (MgSO₄), filtered, and the solvent removed in vacuo to yield a yellow oil. Only observed starting material from the reaction. LCMS: RT 1.26 mins; MS m/z 438.1 [M+H]+ consistent with starting material.
Dimethyl iodonium ylide (283)\textsuperscript{101}

\begin{center}
\begin{tikzpicture}
\node at (-2,0) {\text{MeO}};
\node at (-1,0) {\text{\overset{\text{\textbullet}}{\text{\textbullet}}} \text{\overset{\text{\textbullet}}{\text{\textbullet}}}};
\node at (0,0) {\text{PhOAc}};
\node at (1,0) {\text{MeO}};
\node at (2,0) {\text{\overset{\text{\textbullet}}{\text{\textbullet}}} \text{\overset{\text{\textbullet}}{\text{\textbullet}}}};
\node at (3,0) {\text{Ph}};
\node at (4,0) {\text{Me}};\end{tikzpicture}
\end{center}

\text{MeO} \text{\overset{\text{\textbullet}}{\text{\textbullet}}} \text{\overset{\text{\textbullet}}{\text{\textbullet}}} \text{Me} \xrightarrow{\text{Ph(OAc)}_2, \text{KOH}} \text{MeO} \text{\overset{\text{\textbullet}}{\text{\textbullet}}} \text{\overset{\text{\textbullet}}{\text{\textbullet}}} \text{Me} \text{(283)}

To a solution of potassium hydroxide (1.04 g, 18.53 mmol) in acetonitrile (10 mL) under a nitrogen atmosphere was added dimethyl malonate (0.35 mL, 3.06 mmol). The mixture was cooled to 0°C and stirred vigorously for 5 mins, where the solution changed to a milky white colour. Iodobenzene diacetate (1.08 g, 3.35 mmol) was then added in one portion, and the solution continued vigorously stirring for 2 hours while remaining at 0°C. Mixture became a thick creamy mixture. Water (5 mL) was added and the mixture stirred for 1 minute and the suspension filtered. The solid was washed with water (2x5 mL), ensuring the solid is dry in between each wash, followed by Et\textsubscript{2}O (10 mL), and the off white solid dried under high vacuum. (0.82 g, 73%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \text{δ} 3.89 (s, 6H, OCH\textsubscript{3}), 7.11-7.15 (m, 2H, ArH), 7.34-7.37 (m, 1H, ArH), 7.73 (d, 2H, J=8, ArH). MS (ESI): [M+H]\textsuperscript{+} requires 334.9781 found 334.9782.

All Spectroscopic data is consistent with that previously reported\textsuperscript{101}
(3aR,7aS) 2,2,4-Trimethyl-3a,7a-dihydrobenzo[d][1,3]dioxole (294)

In a 2-5mL microwave vial was added 281 (0.20 g, 0.88 mmol), methylboronic acid (0.63 g, 10.45 mmol), potassium carbonate (0.36 g, 2.61 mmol), and PdCl$_2$(dpdf)-CH$_2$Cl$_2$ adduct (0.12 g, 0.15 mmol) in DMF (5 mL), and heated in the biotage microwave oven for 1 hour at 100°C. Colour changed from yellow to brown. Reaction mixture was combined with water (5 mL) and extracted into EtOAc (2x10 mL). The combined extracts were then washed with brine (10mL) and dried (MgSO$_4$), filtered, and concentrated in vacuo to yield a brown oil. Reaction was purified by flash chromatography using the ISCO combiflash Rf, (0-30% ethyl acetate in i-hexane) over 15 mins. NMR data shows no expected product or starting material obtained.

A solution of 281 (0.05 g, 0.22 mmol), methylboronic acid (0.10 g, 1.75 mmol), potassium carbonate (0.54 g, 3.93 mmol), and Pd(PPh$_3$)$_4$ (5.3 mg, 4.59 µmol) in DMF/H$_2$O (5:1, 30 mL) was stirred at room temperature for 72 hours. Reaction mixture diluted with EtOAc (10mL) and washed with water (20 mL), dried (MgSO$_4$), filtered, and evaporated to a yellow oil. Reaction was purified by flash column chromatography using the ISCO combiflash Rf, (0-25% ethyl acetate in i-hexane) over 15 mins on a 4g silica cartridge resulting in 2 main spots. The provisionally interpreted $^1$H spectra shows only starting material and a small amount of degraded material isolated from the reaction.
(1R,6S) 6-Hydroxycyclohex-3-en-1-yl acetate (296)$^{102}$

Cyclohexa-1,4-diene (0.59 mL, 6.24 mmol) was added to a stirred solution of potassium iodate (0.27 g, 1.25 mmol) and iodine (0.79 g, 3.12 mmol) in Acetic Acid (10 mL) at room temp. The resulting mixture was stirred at 60°C for 3 hours. After cooling, potassium acetate (0.61 g, 6.24 mmol), was added and the mixture heated at reflux for 3 hours. Reaction was cooled and water (2 mL) added. The solvent was removed in vacuo, Et$_2$O (10 mL) added and the organic layer washed with saturated aq. Na$_2$SO$_3$ (3x10 mL) to remove excess iodine, dried (MgSO$_4$), filtered, and the solvent removed in vacuo to give a colourless oil (0.47 g), which was used as a crude mixture.

(1R,2S) Cyclohex-4-ene-1,2-diol (297)$^{102}$

To the crude oil of 296 (0.47 g) was added amberlite IRA-400(OH)$^\circledR$ (3.03 g), MeOH (6 mL), and THF (3 mL) and the resulting suspension stirred at room temp for 17 hours. The amberlite IRA-400(OH)$^\circledR$ resin was initially prepared by stepwise washing on a sintered glass funnel with water, 5% NaOH (100 mL each), water until neutrality, EtOH, and Et$_2$O (50 mL each) and then dried in vacuo. Reaction mixture filtered through a plug of celite and the resin washed with hot methanol (40 mL). The solvent then removed in vacuo to yield a white solid (0.29 g, 42% overall yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 2.22-2.50 (m, 4H, CH$_2$), 3.05 (br s, 2H, OH), 4.27-4.30 (m, 2H, CHOCH), 5.72 (t, 2H, J=4, CH$_2$CH=CH$_2$). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 30.9 (2xCH$_2$), 68.9 (2xCH), 123.7 (2xCH). IR (thin film)/cm$^{-1}$ 3400 (br s).
To a solution of 297 (3.30 g, 28.90 mmol) in DCM (50 mL) was added imidazole (9.85 g, 145 mmol) and tert-butyl(dimethyl)silyl chloride (10.47 g, 69.40 mmol). The reaction mixture was then stirred under nitrogen for 17 hours. Water (5 mL) was added to the reaction and the layers separated. The aqueous layer was extracted with DCM (15 mL), and the combined organic extracts then washed with 1M aq. HCl (15 mL), water (15 mL), and finally brine (15 mL), dried (NaSO₄), filtered, and the solvent removed in vacuo to yield a pale yellow oil. (9.47 g, 96%).

**[4R,5S] 4,5-Bis((tert-butyl(dimethyl)silyl)oxy)cyclohex-1-ene (298)**

**1H NMR (400 MHz, CDCl₃)** δ 0.01 (s, 12H, Si(CH₃)₂), 0.85 (s, 18H, SiC(CH₃)₃), 2.01-2.19 (m, 4H, CH₂), 3.77-3.80 (m, 2H, CHOSi), 5.42-5.45 (2H, CH₂CH=CH). **13C NMR (100 MHz, CDCl₃)** δ 18.1 (2xQ), 25.7 (6xCH₃), 25.9 (4xCH₃), 32.6 (2xCH₂), 70.6 (2xCH), 124.0 (2xCH). IR (thin film)/cm⁻¹: 3029 (s), 2955 (s), 2929 (s), 2895 (s), 2857 (s), 1045 (s). MS (ESI): [M+H]+ requires 343.2489 found 343.2488.
To a solution of 298 (0.40 g, 1.17 mmol) in dry DCM (12 mL) at 0°C was added dropwise a solution of bromine (0.17 mL, 3.28 mmol) in DCM (8 mL) over a period of 1 hour. The reaction was then stirred for an additional 2 hours at room temp. The solvent was removed in vacuo to yield the product as an orange oil (0.50 g, 85%).

\(^{1}\mathrm{H}\ \text{NMR} \ (400\ \text{MHz, CDCl}_3)\ \delta\ 0.01 \ (s, 12\ \text{H, Si(CH}_3)_2),\ 0.83 \ (s, 18\ \text{H, SiC(CH}_3)_3),\ 1.83-1.91 \ (m, 1\ \text{H, CH}_2),\ 2.13-2.19 \ (m, 1\ \text{H, CH}_2),\ 2.37-2.40 \ (m, 1\ \text{H, CH}_2),\ 2.41-2.46 \ (m, 1\ \text{H, CH}_2),\ 3.50-3.55 \ (m, 1\ \text{H, CHOTBS}),\ 3.80-3.81 \ (m, 1\ \text{H, CHOTBS}),\ 3.96-3.99 \ (m, 1\ \text{H, CHBr}),\ 4.25-4.29 \ (m, 1\ \text{H, CHBr}).\ \text{IR (thin film)/cm}^{-1} 3053 \ (s),\ 2955 \ (s),\ 2930 \ (s),\ 2886 \ (s),\ 2857 \ (s),\ 1043 \ (s).\ \text{MS (ESI)}: \ [\text{MBr}^{79}+\text{H}]^+ \ \text{requires} \ 501.0855 \ \text{found} \ 501.0857.
(5R,6S) 5,6-Bis((tert-butyldimethylsilyl)oxy)cyclohexa-1,3-diene (312)³⁰³

To a solution of 299 (0.50 g, 0.99 mmol) in dry toluene (15 mL) was added DBU (1.19 mL, 7.92 mmol) at room temperature. The reaction mixture was then heated at 85°C for 6 hours. Reaction was cooled to room temp and the solid filtered off. The toluene was poured into water (20 mL) and extracted with diethyl ether (3x10 mL). The combined extracts were washed with saturated aq. NaHCO₃ (3x10 mL), dried (MgSO₄), filtered, and evaporated in vacuo to yield a pale yellow oil. The oil was purified by filtration through a plug of silica to yield a colourless oil. The provisionally interpreted spectra show only starting material obtained.
(3aR,7aS) 2,2-Dimethyl-3a,4,7,7a-tetrahydrobenzo[d][1,3]dioxole (302)

\[
\text{OH} \quad \text{MeO} \quad \text{MeO} \quad \text{Tosic acid} \\
(297) \quad \begin{array}{c}
\text{CH}_2\text{Cl}_2, \text{rt}, 1h \\
\end{array} \quad \text{(302)}
\]

To a solution of 297 (1.08 g, 9.48 mmol) in DCM (40 mL) was added 2,2-dimethoxypropane (11.66 mL, 95 mmol) followed by tosic acid (0.18 g, 0.95 mmol) and the solution stirred at room temperature for 1 hour then quenched with NaHCO\(_3\) (40 mL). The reaction mixture was extracted into DCM (3x15 mL), the combined extracts washed with brine (30 mL), dried (MgSO\(_4\)), filtered, and evaporated in vacuo to yield a pale yellow oil. (0.98 g, 67%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.27 (s, 3H, OCH\(_3\)), 1.37 (s, 3H, OCH\(_3\)), 2.19-2.21 (m, 4H, CH\(_2\)), 4.26-4.30 (m, 2H, CHO), 5.69-5.74 (m, 2H, CH=CH). \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 24.8 (CH\(_3\)), 27.0 (CH\(_3\)), 28.3 (2xCH\(_2\)), 73.1 (2xCH), 107.5 (Q), 125.5 (2xCH). IR (thin film)/cm\(^{-1}\) 2987 (m), 2937 (m), 2908 (m), 1380 (m), 1265 (s).

(3,5,6,7) 5,6-Dibromo-2,2-dimethylhexahydrobenzo[1,3]dioxole (303)

\[
\begin{array}{c}
(302) \quad \text{Br}_2 \\
\text{CH}_2\text{Cl}_2, \text{rt}, 2h \\
\end{array} \quad \text{(303)}
\]

To a solution of 302 (0.66 g, 4.30 mmol) in dry DCM (30 mL) at 0°C was added dropwise a solution of bromine (0.23 mL, 4.46 mmol) in DCM (20 mL) over a period of 1 hour. The reaction was then stirred for an additional 2 hours at room temp. The solvent was removed in vacuo to yield a brown oil. Initial interpretation of the \(^1\)H NMR shows none of the expected product has formed, some starting material and degraded material present in the NMR.
(3,7) 2,2-Di-tert-butyl-3,4,7,7tetrahydrobenzo[1,3,2]dioxasilole (313)\textsuperscript{104}

\[
\text{HO} \quad \xrightarrow{(t-\text{Bu})_2\text{Si(OTf)}_2} \quad \text{HO} \\
(297) \quad \text{CH}_2\text{Cl}_2, \text{pyridine, rt, 17h} \quad \text{Si} \\
(313)
\]

To a stirred solution of 297 (1.02 g, 8.95 mmol) and pyridine (2.17 mL, 26.90 mmol) under nitrogen at 0°C was added di-tert-butylsilanediyl bis(trifluoromethanesulfonate) (3.50 mL, 10.74 mmol). The resulting mixture was stirred for 2 minutes then allowed to warm to room temperature and continued stirring for 17 hours. The reaction mixture was filtered to remove solid that formed and the solvent removed in vacuo. Purification was achieved by flash column chromatography using the ISCO combiflash Rf, (0-10\% ethyl acetate in i-hexane) over 15 mins to yield the product as a colourless oil (0.63 g, 28\%). $^1$H NMR (400 MHz, DMSO) δ 0.99 (s, 9H, SiCCH$_3$), 1.01 (s, 9H, SiCCH$_3$), 1.97-1.99 (m, 1H, CH$_2$), 2.01-2.04 (m, 1H, CH$_2$), 2.32-2.34 (m, 1H, CH$_2$), 2.53-2.55 (m, 1H, CH$_2$), 4.19-4.21 (m, 2H, CHO), 5.79-5.81 (m, 2H, CH=CH). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 19.8 \textbf{(2xQ)}, 22.6 \textbf{(2xCH$_3$)}, 27.0 \textbf{(2xCH$_3$)}, 27.6 \textbf{(2xCH$_3$)}, 31.6 \textbf{(2xCH$_2$)}, 73.2 \textbf{(2xCH)}, 127.3 \textbf{(2xCH)}. MS (ESI): [M+H]$^+$ requires 255.1780 found 255.1781.
To a solution of 313 (0.63 g, 2.47 mmol) in dry DCM (20 mL) at 0°C was added dropwise a solution of bromine (0.13 mL, 2.54 mmol) in DCM (20 mL) over a period of 1 hour. The reaction was then stirred for an additional 2 hours at room temp. The solvent was removed in vacuo to yield an orange oil. Reaction was purified by flash column chromatography using the ISCO combiflash Rf, (0-15% ethyl acetate in i-hexane) over 20 mins to yield the product as an orange oil. (0.28 g, 27%). $^1$H NMR (400 MHz, CDCl$_3$) δ 1.04 (s, 18H, 2xSiC(CH$_3$)$_3$), 1.94-2.01 (m, 1H, CH$_2$), 2.37-2.43 (m, 1H, CH$_2$), 2.46-2.53 (m, 1H, CH$_2$), 2.73-2.77 (m, 1H, CH$_2$), 3.96-3.99 (m, 1H, CHO), 4.01-4.05 (m, 1H, CHO), 4.06-4.09 (m, 1H, CHBr), 4.35-4.42 (m, 1H, CHBr). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 14.2 (3xCH$_3$), 20.3 (2xQ), 21.0 (3xCH$_3$), 27.3 (CH), 51.9 (CH), 60.4 (2xCH$_2$), 69.8 (CH), 71.04 (CH). IR (thin film)/cm$^{-1}$ 2953 (w), 2861 (w), 2253 (m), 908 (s).
(3aR,7aS) 2,2-Di-tert-butyl-3a,7a-dihydrobenzo[d][1,3,2]dioxasilole (304)

To a solution of 314 (0.28 g, 0.67 mmol) in dry toluene (10 mL) was added DBU (0.81 mL, 5.38 mmol) at room temp. The reaction mixture was then heated at 85°C for 6 hrs. Reaction was cooled to room temp and the solid filtered off. The toluene was poured into water (20 mL) and extracted with diethyl ether (3x10 mL). The combined extracts were washed with saturated aq. NaHCO₃ (3x10 mL), dried (MgSO₄), filtered, and the solvent removed in vacuo. Purification by flash column chromatography using the ISCO combiflash Rf, (0-10% ethyl acetate in i-hexane) over 20 mins to yield the product as a colourless oil (0.14 g, 9%). ¹H NMR (400 MHz, CDCl₃) δ 1.01 (s, 18H, SiCH₃), 4.73-4.75 (m, 2H, CH₂O), 5.75-5.78 (m, 2H, CHCH=CH), 5.79-5.82 (m, 2H, CHCH=CH). IR (thin film)/cm⁻¹ 2935 (m), 2860 (m), 1596 (m), 1265 (m). [M+H]⁺ requires 253.1624 found 253.1625.
Chapter 8

References
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