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Carbenoid Insertions and Cyclometallations of Zirconacycles

By Louise Daisy Norman

Thesis for the degree of Doctor of Philosophy

November 2009
The synthesis of zirconacycles and further elaborations to produce a wide variety of carbocyclic and heterocyclic systems is well established. This thesis focuses on the insertion of chloro(aryl)methyllithiums (benzyl carbenoids) into a range of zirconacyclopentenes and zirconacyclopentanes.

Benzyl carbenoid insertion into a zirconacyclopentene generated the zirconacyclohexene via a 1,2-metalate rearrangement. A low temperature quench afforded the expected benzyl inserted product. Quenching at higher temperatures afforded a styrene containing product. It was proposed that the styrene product was formed via a novel endocyclic cyclometallation to afford a zirconocene $\eta^2$-alkene complex followed by decomplexation. A wide variety of zirconacyclopentenes and benzyl carbenoids have been investigated.

A range of benzyl carbenoids were inserted into a zirconacyclopentane to afford the expected benzyl inserted product. Double benzyl carbenoid insertion was also observed and afforded a mono-alkene product. It was speculated that the bis-inserted products were formed via a zirconacycloheptane followed by a novel endocyclic cyclometallation.

Having shown that zirconacyclohexenes underwent an endocyclic cyclometallation to afford a zirconocene $\eta^2$-alkene complex, the concept of intramolecular trapping of the zirconocene $\eta^2$-alkene complex, to generated bicyclic compounds, was investigated.
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Declaration

This thesis is based solely on the work carried out by the author whilst registered for the degree of Doctor of Philosophy in the School of Chemistry at the University of Southampton, except where specific citations of literature examples are indicated. All computational modelling reported in this thesis was carried out by Prof. R. J. Whitby.
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1 Introduction

1.1 Overview
The results described in this thesis focus on the insertion of chloro(aryl)methyllithiums (benzyl carbenoids) into zirconacycles. Work carried out by Fillery, within the Whitby group, demonstrated that benzyl carbenoids can be successfully inserted into zirconacycles. Chapter 1 gives a brief description of the formation of carbenoids, zirconacycles and elaboration of zirconacycles by inserting carbenoids. A more detailed discussion of benzyl carbenoids and previous work investigating their insertion into zirconacycles is described. The aim of the research was to extend the methodology and to gain a greater mechanistic understanding of the relevant reactions. The results of these investigations are reported in Chapters 2-4.

1.2 Background
Organozirconium chemistry has now been under investigation for over 50 years. The birth of organozirconium chemistry can be defined by the preparation of the first well characterised organozirconium compound, zirconocene dibromide (ZrCp₂Br₂) by Wilkinson and Birmingham in 1954. This discovery was of great significance to organozirconium chemistry as around 70-80% of the known organozirconium compounds are zirconocene derivatives.

There are several favourable properties which make zirconium of interest in organic chemistry. Zirconium occurs in the lithosphere to the extent of 0.022% and therefore is roughly as abundant as carbon. It is one of the least expensive transition metals and does not appear to be associated with acute or severe toxicity.

The chemistry of zirconocene complexes is dominated by the usual 16 electron configuration. The empty orbital remaining is not very Lewis acidic and therefore not filled by Lewis base coordination. The oxidation state is normally +4, though a few +2 complexes are known.
1.3 Carbenoids

The term carbenoid was first used by Closs and Moss to describe an intermediate which exhibited properties similar to those of carbenes.\(^5\) A carbenoid is a species which contains a metal atom (M) (or lone pair if ionised) and a leaving group (X) on the same carbon. (R’R’’CMX). This section focuses on lithium halocarbons (R’R’’CLiX) (hereafter referred to as carbenoids).

There are two main methods for forming carbenoids \(2\, (\text{Scheme 1})\).\(^6\)\(^-\)\(^8\) The easiest method is via deprotonation of the corresponding halogenated hydrocarbon \(1\) with a base.\(^6\),\(^7\) The optimum temperature for formation of the carbenoid \(2\) is between –120 and –70 °C. The temperature range is limited at the lower end by the rate of deprotonation and at the upper end by the rate of decomposition of the carbenoid. This is a major limitation of the method and many substrates will not deprotonate at the low temperatures required for stability of the carbenoid. The second method is halogen-metal exchange of the gem-dihalogen-compound \(3\).\(^6\),\(^7\) Halogen-metal exchange is a very fast process, even at low temperatures and therefore can often be used to make carbenoids that cannot be synthesised via the deprotonation method. However, one limitation of this method is competing side reactions such as α-metallation.

\[ \begin{align*}
\text{Scheme 1: Formation of carbenoids.}
\end{align*} \]

Carbenoids \(2\) are extremely thermally sensitive species. There are several pathways by which they can decompose. One important pathway is α-elimination to generate the carbene \(4\, (\text{Scheme 2})\).\(^6\)

\[ \begin{align*}
\text{Scheme 2: Decomposition of carbenoids to generate carbenes.}
\end{align*} \]
Carbenoids 2 can be described as being amphiphilic, meaning they have both nucleophilic and electrophilic properties. Nucleophilic reactions of carbenoids include alkylations, acylations and halogenations.\(^6\)\(^-\)\(^8\) Electrophilic reactions of carbenoids include reactions with alkyl metals (Scheme 3).\(^6\),\(^7\),\(^9\)

Scheme 3: Nucleophilic and electrophilic reactions of carbenoids.

1.4 Benzyl carbenoids

The reaction of benzyl chloride with \(n\)-BuLi is well known and is the basis for the extensively used Gilman-Haubein ‘double titration’ method for quantitative analysis of \(n\)-BuLi.\(^10\) Gilman and Haubein suggested that the reaction proceeded via halogen-lithium exchange to form benzyl lithium 5, which was rapidly consumed in subsequent cross-coupling reactions to give a mixture of bibenzyl 7 and pentyldibenzene 6 (Scheme 4).

Scheme 4: Gilman-Haubein ‘double titration’ method for quantitative analysis of \(n\)-BuLi.

Evidence for the benzyl lithium 5 as the intermediate was provided by the observed yellow colour, characteristic of benzyl lithium and the production of phenylacetic acid when the intermediate was treated with solid carbon dioxide.\(^10\)

Hoeg et al. also observed trans-stilbene 10, in 20% yield, when the reaction was carried out in THF rather than diethyl ether.\(^11\) The formation of the trans-stilbene 10 suggested that an alternative intermediate had formed, as 10 is unlikely to be produced from the benzyl lithium intermediate.
Hoeg et al. suggested that the mechanism was via α-metallation to give benzyl chloride 8. Subsequent reaction of the benzyl carbenoid 8 with benzyl chloride gave the α-chlorobibenzyl 9 which under-went a thermal dehydrochlorination to give the trans-stilbene 10 (Scheme 5).\(^{11}\)

![Scheme 5: Formation of benzyl carbenoid and subsequent reaction with benzyl chloride to form trans-stilbene.](image)

It was reported that this reaction was solvent dependant and trans-stilbene 10 was only observed when the reaction was carried out in THF. The yields of 10 were increased as the reaction temperature was reduced. An 80% yield is obtained when 2 equivalents of benzyl chloride and 1 equivalent of \(n\)-BuLi is used at –100 °C. Attempts to methylate the benzyl carbenoid after formation proved unsuccessful even at –100 °C, suggesting that the benzyl carbenoid 8 is a highly unstable species.\(^{11}\)

Since carbenoids are much more electrophilic than the parent halide due to ‘metal assisted ionisation’,\(^{12}\) it seems likely that carbenoid dimerisation to afford 11 followed by fast elimination of LiCl is occurring, to give trans-stilbene 10 (Scheme 6).

![Scheme 6: Benzyl carbenoid dimerisation.](image)

Benzyl carbenoid 8 has been used in the synthesis of arylcyclopropanes 13 (Scheme 7). The first published procedure was the reaction of benzyl chloride with \(n\)-BuLi in cyclohexene, which gave phenylnorcarane in a low 14% yield.\(^{13}\) Improvements in the yield were observed when LiTMP was used as the base. A large range of alkenes 12 have been successfully trapped by benzyl carbenoids 8 to yield arylcyclopropanes 13 (50-87% yield).\(^{14}\)
Scheme 7: Synthesis arylcyclopropanes via benzyl carbenoids.

The methodology was extended by trapping allene 14 with benzyl carbenoids to give arylmethylenecyclopropanes 15 (Scheme 8).\textsuperscript{15}

Scheme 8: Synthesis of arylmethylenecyclopropanes.

The \textit{in situ} trapping of benzyl carbenoid 8 was investigated by Wenkert \textit{et al.}\textsuperscript{16} Benzyl chloride was treated with 1 equivalent of LDA at –78 °C, followed by the addition of benzyl bromide 16. A mixture of α-chlorobiphenyl 9 and α-bromobiphenyl 17 was produced (Scheme 9).

Scheme 9: Self condensation of benzyl carbenoids.

Generation of the α-bromobiphenyl 17 can only occur if the deprotonation of the benzyl chloride was incomplete. Wenkert \textit{et al.} suggested the rate of alkylation of the benzyl carbenoid was greater than the rate of deprotonation of the benzyl chloride, resulting in complete consumption of the benzyl chloride before complete α-metallation could be achieved. The benzyl bromide 16 added to the reaction mixture was α-metallated using the remaining LDA to give bromo(phenyl)methyl lithium. Bromomethylphenyllithium was rapidly alkylated with the remaining benzyl bromide to give α-bromobiphenyl 17.

Brandsma \textit{et al.} attempted to trap the preformed carbenoid with trimethylsilyl chloride at –100 °C, however, only the self condensation product 9 was observed (Scheme 10).\textsuperscript{17}
Brandsma et al. overcame this by adding the trimethylsilyl chloride to the benzyl chloride prior to the very slow addition of LDA at –100 °C, which gave the desired product 18 in 84% yield. Even under these conditions traces of the self condensed product 9 was observed (Scheme 10).

Kabalka et al. reported the in situ reaction of benzyl carbenoids with trialkylboranes 19 and alkylboronic esters 22 to give the alkylarylcarbinols 21a in very good yield after oxidation (Scheme 11).

Deprotonation of the benzyl chloride generated the benzyl carbenoid 8. The carbenoid reacts with the trialkylborane 19 to form a borate complex 24 that gives a new trialkylborane 20 via a 1,2-metalate rearrangement (Scheme 12).
This method has been successfully applied to a wide range of trialkylboranes and alkylboronic esters and extended to included substituted benzyl chlorides. Benzyl carbenoids with \textit{para}-methyl, methoxy and chloro substituents have all successfully inserted into trialkylboranes. Significantly lower yields were observed when benzyl bromide was used as the carbenoid precursor, which was attributed to the more facile formation and greater stability of the lithium chloro-carbenoid compared to the lithium bromo-carbenoids.

In a related publication, Aggarwal \textit{et al.} reported the asymmetric lithiation of substituted benzylamines 25 and subsequent insertion into trialkylboranes, which after oxidation, gave the chiral secondary alcohols 21 with high enantioselectivity (Scheme 13).\textsuperscript{19}

Aggarwal \textit{et al.} has also reported the reaction of benzyl sulfonium salt 26 and trialkylboranes 19, which after oxidation gave the secondary alcohol 21 in excellent yield (Scheme 14).\textsuperscript{20}
Scheme 14: Insertion of sulfonium ylides into trialkylboranes.

Chiral sulfonium salts have also been successfully reacted with trialkylboranes to generate chiral organoboranes, which after quenching with either \( \text{H}_2\text{O} \) and NaOH or NH\(_2\)OSO\(_3\)H afforded the chiral secondary alcohol or amine in high enantioselectivity.\(^{19}\)

1.5 Synthesis of zirconacycles

The main method employed to synthesise zirconacycles is the co-cyclisation of dienes, enynes and diynes\(^{21, 22}\) using a ‘ZrCp\(_2\)’ equivalent (Scheme 15).\(^{3}\) Negishi et al. published the first co-cyclisation of an enyne with a ‘ZrCp\(_2\)’ equivalent generated by reducing ZrCp\(_2\)Cl\(_2\) with a magnesium amalgam.\(^{23}\) In view of the low chemoselectivity of the magnesium and the toxicity of the mercury this method has largely been replaced with a ‘ZrCp\(_2\)’ equivalent formed \textit{in situ} by treating ZrCp\(_2\)Cl\(_2\) with 2 equivalents of \( n\)-BuLi.\(^{24}\)

Scheme 15: Co-cyclisation using Negishi’s reagent.

Examination of the reaction of ZrCp\(_2\)Cl\(_2\) with \( n\)-BuLi by \(^1\text{H} \) NMR at \(-78\) °C revealed the disappearance of a cyclopentadienyl (Cp) singlet at \( \delta_H 6.61 \) ppm corresponding to ZrCp\(_2\)Cl\(_2\) and the appearance of a Cp singlet at \( \delta_H 6.18 \) ppm, which indicated complete conversion to ZrCp\(_2\)Bu\(_2\) (Negishi’s reagent) \(^{27}\). Treatment of \(^{27}\) with 2 equivalents of I\(_2\) gave \( ^{\text{a}}\text{Bu-I} \) (ca. 2 equivalents) and ZrCp\(_2\)I\(_2\) (ca. 1 eq) providing additional evidence of the formation of ZrCp\(_2\)Bu\(_2\).\(^{24}\)

Attempts to identify the actual ‘ZrCp\(_2\)’ reactive species were carried out by treating ZrCp\(_2\)Bu\(_2\) with two equivalents of PMePh\(_2\). Negishi et al. suggested that the complex
formed was \( \text{Cp}_2\text{Zr(PMePh}_2\text{)}_2 \). Assignment was based on the presence of a triplet in the \(^1\text{H} \) NMR spectra corresponding to the two \( \text{Cp} \) groups.\(^{24} \)

However, Buchwald \textit{et al.} reported that the treatment of \( \text{ZrCp}_2\text{Bu}_2 \) with 2 equivalents of \( \text{PMe}_3 \) led to the formation of \( \text{Cp}_2\text{Zr(1-butene)(PMe}_3\text{)} \) \( \text{28a (Scheme 16)} \).\(^{25} \)

\[
\text{Scheme 16: Formation of \text{Cp}_2\text{Zr(1-butene)(PMe}_3\text{)}}.
\]

Re-examination by Negishi \textit{et al.} revealed the apparent triplet was not due to the presence of two \( \text{PMePh}_2 \) groups but had resulted from the chirality of the 1,2-butylidene moiety which caused the two \( \text{Cp} \) groups to be non-equivalent. Negish\textit{et al.} repeated the reaction of \( \text{ZrCp}_2\text{Bu}_2 \) with 2 equivalents of \( \text{PMe}_3 \) and proposed that the correct structures were \( \text{28b} \) and \( \text{28a} \) in a 90:10 mixture (Figure 1).\(^{21} \) It is proposed that the dibutylzirconocene (\( \text{ZrCp}_2\text{Bu}_2 \)) undergoes a concerted non-dissociative process to give zirconocene(1-butene) \( \text{29} \) as the ‘\( \text{ZrCp}_2 \)’ equivalent on warming (Scheme 17). Free ‘\( \text{ZrCp}_2 \)’ is believed to be too unstable to be a true intermediate.

\[
\text{Figure 1: Isomers of \text{Cp}_2\text{ZrBu(PMe}_3\text{)}}.
\]

Zirconocene(1-butene) \( \text{29} \) can either be viewed as \( \text{Cp}_2\text{Zr(II)} \) \( \text{29a} \) or a \( \text{Cp}_2\text{Zr(IV)} \) \( \text{29b} \) species. The butene ligand is weakly bound to the zirconocene and can readily be replaced by an alkyne or alkene from the co-cyclisation substrate, followed by a concerted carbometallation to afford the zirconacycle \( \text{30 (Scheme 17).} \)
Scheme 17: Zirconocene promoted intramolecular co-cyclisation using Negishi’s reagent.

The method of zirconocene promoted intramolecular co-cyclisation has proven to be very successful and can be applied to a wide variety of diynes, enynes and dienes. The method has also been extensively applied to the synthesis of complex natural products.26-30

Diyne cyclisation successfully affords 4- to 8-membered fused rings.21, 22 Enyne co-cyclisation successfully affords 5- to 8-membered fused rings (Scheme 18).3, 21, 31-33 Several successful examples with ring substitutions such as alkyl,21 protected alcohol,32, 33 amines32 and amides32 are present in the literature. Examples using substrates containing substituted alkenes are known.21 Nitrogen containing enynes with substituted alkenes are often successful, although the corresponding all carbon enynes fail to cyclise. Although terminal alkynes are incompatible with this method of zirconium promoted cyclisation, several terminally substituted alkyne derivatives, such as silicon, tin, alkyl, aryl and alkenyl, have been successfully cyclised.21

Scheme 18: Examples of zirconium promoted enyne co-cyclisation.
Diene co-cyclisation successfully affords 5- and 6-membered fused ring (Scheme 19).\textsuperscript{34} 1,6-Heptadienes co-cyclise to give the \textit{trans}-ring junction, whereas 1,7-octadienes co-cyclise to give the \textit{cis}-ring junction as the kinetic product, though heating isomerises this to give the more stable \textit{trans}-ring junction.\textsuperscript{34} Examples of substrates containing substituted alkenes are known, however tri- and tetrasubstituted alkenes are usually not successful.\textsuperscript{35-37} Instead of co-cyclisation, heavily substituted dienes may undergo a double bond migration to produce a conjugated diene-zirconocene complex when treated with ‘ZrCp\textsubscript{2}’.\textsuperscript{35} Diene co-cyclisation of substrates with ring substituents such as acetals, protected alcohols, and alkyl groups has been reported in the literature.\textsuperscript{36, 37} Dienes with nitrogen or silicon in the chain are also known.\textsuperscript{36, 37}

\begin{center}
\includegraphics[width=0.5\textwidth]{diene_cyclisation}
\end{center}

\textbf{Scheme 19:} Examples of zirconium promoted diene co-cyclisation.

1.6 \textbf{Synthesis of monocyclic zirconacycles}

The most convenient method of generating monocyclic zirconacycles is by the co-cyclisation of ethylene zirconocene 31 with either an alkyne or alkene (Scheme 20).\textsuperscript{38} Ethylene zirconocene 31 can be generated by treating ZrCp\textsubscript{2}Cl\textsubscript{2} with EtMgBr.\textsuperscript{39} Alternatively when zirconocene(1-butene) 29 is synthesised under an atmosphere of ethylene gas zirconacyclopentane is generated which reversibly eliminates ethene to give ethylene zirconocene 31.\textsuperscript{40}
1.7 Elaboration of zirconacycles

There are several ways in which zirconacycles can be elaborated. These include protonation,\(^{23}\) halogenolysis,\(^{41}\) transmetallation,\(^{42}\) metathesis to main group elements\(^{43}\) and insertion of carbon monoxide, isonitriles and carbenoids.\(^{44}\)

1.7.1 Carbonylation and isonitrile insertions into zirconacycles

The zirconium centre of a zirconacycle is electronically unsaturated (16 e\(^{-}\)) so can accept an electron pair from a donor. Carbenic species such as carbon monoxide\(^{3, 24, 34, 44}\) and isonitriles readily insert (Scheme 21).\(^{44, 45}\)

Scheme 20: Formation of monocyclic zirconacycles using ethylene zirconocene.

Scheme 21: Carbonylation and isonitriles insertion into zirconacycles
In carbonylation and isonitrile insertion, initial attack on the 16-electron zirconium centre produces an 18-electron complex \(32\) and \(33\). In the case of carbonylation, a rearrangement occurs to give the acyl complex \(34\) which rapidly rearranges to give the \(\eta^2\)-ketone complex \(36\). The \(\eta^2\)-ketone complex of zirconacyclopentanes is stable and protonation affords the alcohol \(38\). When zirconacyclopentanes and pentenes are subject to prolonged exposure to carbon monoxide, the cyclic ketone \(40\) was generated.\(^{24,34,44}\) In the case of isonitrile insertion, a rearrangement occurs to give the iminoacyl complex \(35\), which slowly rearranges to give the \(\eta^2\)-imine complex \(37\). Protonation of the \(\eta^2\)-imine complex affords the amine \(39\).\(^{44,45}\)

1.7.2 Carbenoid insertion into zirconacycles

Carbenoids have similar electronic properties to carbon monoxide and isonitriles and therefore are expected to readily insert into organozirconium species. The first publication in this field was by Negishi et al. and involved the insertion of \(\alpha\)- and \(\gamma\)-haloorganolithiums into acyclic organozirconocene derivates (Scheme 22).\(^{46}\) Carbenoid insertion into zirconacycles has been extensively investigated by Whitby et al. and these will now be detailed throughout the following section.\(^{44}\)

![Scheme 22: Carbenoid insertion into organozirconium derivatives.](image)

1.7.2.1 Insertion of allyl carbenoids

Allyl carbenoid \(42\) inserted into zirconacyclopentenes\(^{47}\) \(41\) and pentanes\(^{48}\) \(46\) (Scheme 23). Initial nucleophilic attack of the allyl carbenoid \(42\) generates an 18 electron ‘ate’ complex \(43\). A 1,2-rearrangement with loss of the leaving group affords zirconium allyl complex \(44\). Simple protonation of the complex affords the alkene products \(45a\) and \(45b\). Further elaborations of the zirconium allyl complexes by the addition of an electrophile has been reported.\(^{47-49}\) Various electrophiles such as aldehydes, ketones, acetics, ortho esters, iminium ions and thienium ions have all been successfully inserted into zirconium allyl species.\(^{49}\) A Lewis acid was needed to catalyse the insertion of...
aldehydes, acetals and ortho esters into zirconium allyl complexes. Variations of the allyl carbenoid have also been reported.\textsuperscript{50} This methodology was extended to include allyl components with carbamate and tosylate leaving groups. 2-Substituted allyl components also successfully insert. Allyl carbenoid insertion into zirconacycles has been utilised in the synthesis of several complex natural products.\textsuperscript{51-54}

\begin{center}
\textbf{Scheme 23:} Insertion of allyl carbenoids into zirconacycles.
\end{center}

1.7.2.2 Insertion of metalated epoxide carbenoids

Insertion of lithiated epoxides into zirconacycles also affords substituted alkene products (Scheme 24).\textsuperscript{55} Insertion of an electron-rich $\alpha$-silyl-$\alpha$-lithium substituted epoxide 48 into a zirconacyclopentene 47 affords 49. Epoxide 48 inserts into zirconacylopentane 50, to afford a mixture of 51 and 52. Compound 52 results from bis insertion of the carbenoid 48 into 50. Insertion of an electron-poor $\alpha$-cyano-$\alpha$-lithium substituted epoxide 53 into zirconacylopentane 50 affords 54 only. No bis-insertion was observed.
Scheme 24: Insertion of lithiated epoxides into zirconacycles.

1.7.2.3 Insertion of alkenyl carbenoids

1-Lithio-1-haloalkenes insert into zirconacyclopentenes 55 and pentanes 58 to afford substituted alkene products 57 and 59.\textsuperscript{56,57}

Scheme 25: Insertion of alkenyl carbenoids.
1.7.2.4 Insertion of propargyl and allenyl carbenoids

Propargyl 61 and allenyl 65 carbenoids have been successfully inserted into a range of zirconacyclopentanes and pentenes. An example of insertion of a propargyl carbenoid and an allenyl carbenoid are shown in Scheme 26. Propargyl carbenoid 61 was generated *in situ* by treating 1-chlorohept-2-yn with LiTMP at –78 °C. Insertion into zirconacyclopentane 60 gave the zirconacyclohexane 62 which, on protonation, afforded a mixture of 63 and 64. Allenyl carbenoid 65 was generated *in situ* by treating 3-chloroprop-1-yn with LiTMP at –78 °C. Insertion into the zirconacyclopentene 47 afforded the ring expanded products 67a and 67b via the 18 electron ‘ate’ complex 66. Protonation afforded a mixture of 68 and 69. Further elaboration by tandem insertion of propargyl or allenyl carbenoids and aldehydes has also been reported.

![Scheme 26: Insertion of propargyl and allenyl carbenoids.](image)

1.7.2.5 Insertion of substituted alkyl carbenoids

A wide range of substituted alkyl carbenoids have been inserted into a range of zirconacyclopentenes 55 and pentanes 58 to afford interesting functionalised products 70 and 71. Alkyl carbenoids with both electron-poor and electron-rich substituents have been reported and are highlighted in Scheme 27.
1.7.3 Insertion of benzyl carbenoids

Fillery demonstrated that zirconocene complexes are sufficiently reactive to trap benzyl carbenoids formed in situ.\(^1\) The carbenoids were formed by treating the corresponding benzyl chloride with LDA at \(-78\, ^\circ\text{C}\).

1.7.3.1 Benzyl carbenoid insertion into saturated zirconacycles

Fillery initially investigated the insertion of benzyl carbenoids into saturated zirconacycles \(^{50}\).\(^1\) It was demonstrated that a range of commercially available benzyl chlorides could be converted to benzyl carbenoids and subsequently inserted into zirconacycles to give \(^{72}\) on protonation (Scheme 28). The one exception was the carbenoid derived from \(p\)-nitrobenzyl chloride, which failed to insert. This was thought to be due to the strong electron-withdrawing effect of the nitro group making the carbenoid less nucleophilic.

\[
\begin{align*}
\text{Scheme 28: Benzyl carbenoid insertion into saturated zirconacycles.}
\end{align*}
\]

Fillery noted that in almost all cases a by-product was obtained, in no more than 5% yield, which was identified as the bis inserted product \(^{73}\).\(^1\) If the number of equivalents of benzyl carbenoid were increased to 5 then complete conversion to the bis inserted product \(^{73}\) was observed (Scheme 29).
Scheme 29: Benzyl carbenoid insertion into a saturated zirconacycle to give the bis inserted product.

Fillery proposed two possible mechanisms for the formation of the bis inserted product, either via a zirconium hydride intermediate or via a zirconacycloheptane (Scheme 30).

Scheme 30: Proposed mechanisms for the formation of the bis inserted product.

Fillery demonstrated that the general benzyl carbenoid methodology could be applied to a wide range of zirconacycles and carbenoids, including heteroaromatic carbenoids. Some examples are highlighted in Scheme 31.
Scheme 31: Examples of benzyl carbenoid insertion into a range of zirconacycles.

1.7.3.2 Benzyl carbenoid insertion into unsaturated zirconacycles

Fillery reported that benzyl carbenoid will insert cleanly into unsaturated zirconacycles (Scheme 32). Benzyl carbenoid insertion into a 5-membered fused zirconacycle 74 gave 76 on protonation in 85% yield. Zirconacyclohexene 75 is formed as a 1:1 ratio of diastereoisomers and was shown to be stable at rt for several weeks or after prolonged heating to 60 °C.

Scheme 32: Benzyl carbenoid insertion into unsaturated zirconacycles.

Benzyl carbenoid insertion into the 6-membered fused zirconacycle 77 afforded the skipped diene products 79. Fillery proposed that the skipped dienes 79 were formed via a β-hydride elimination to afford a zirconium hydride intermediate 80 (Scheme 33).
1.7.3.3 Benzyl carbenoid insertion into monocyclic zirconacycles

Fillery reported the benzyl carbenoid insertion into both saturated and unsaturated monocyclic zirconacycles (Scheme 34). Insertion of 1-(chloromethyl)naphthalene carbenoid, generated in situ, into monocyycle 81 gave 82 in 92% yield. Insertion of benzyl carbenoids into unsaturated monocyclic zirconacycle 83 gave E,E−1,4-dienes 84 in excellent yield.

A mixture of products 86a, 86b and 86c were produced from benzyl carbenoid insertion into zirconacycle 85. The results indicate the aryl group does not control the β-hydride elimination as both 86b and 86c are observed.

Fillery proposed that the alkene products were arising from a β-hydride elimination, which accounts for the complete stereoselectivity observed in the final products. However, the final step of the reaction could be occurring via two different
mechanisms; α-hydride elimination or protonation. Fillery investigated this by carrying out an experiment with a deuterium labelled zirconacycle 87 (Scheme 35).

Scheme 35: β-Hydrde elimination followed by α-hydrde elimination.

Fillery only observed 88, suggesting that the alkene product is formed by a β-hydride elimination followed by an α-hydride elimination.
2 Insertion of benzyl carbenoids into unsaturated zirconacycles -
discovery of a novel endocyclic cyclometallation

Dr S. Fillery showed that benzyl carbenoids could be successfully inserted into unsaturated zirconacycles (Chapter 1, Scheme 32). The methodology has been extended to include a wide range of unsaturated zirconacycles and a detailed investigation of the mechanism was carried out, the results of which are reported within this chapter.

2.1 Insertion of benzyl carbenoids into zirconacyclopentenes

Intramolecular co-cyclisation of 1-phenylhept-1-yn-6-ene 1 using zirconocene(1-butene), generated in situ from dibutylzirconocene (Negishi’s reagent), afforded zirconacyclopentene 2. Insertion of the benzyl carbenoid, generated in situ by treating benzyl chloride with LDA at –78 °C, afforded 4 on quenching with HCl, presumably generated via zirconacyclohexene 3 (Scheme 36).

Scheme 36: Reagents and Conditions: i. ZrCp₂Cl₂, n-BuLi, THF, –78 °C, 30 min then warm to rt, 2 h. ii. BnCl, LDA, –78 °C, 30 min. iii. 2 M HCl in Et₂O, –78 °C - rt, 18 h, 62% iv. MeOD followed by D₂O, –78 °C - rt, 18 h.

A deuterium quench supported this assumption and produced the bis deuterated compound 5 as a 1:1 ratio of epimers at the deuterated benzyl carbon. The chemical shifts of the diastereotopic benzyl hydrogen’s were identified by C-H correlation.
spectroscopy in d₆ benzene, at δH 2.76 and 2.63 ppm, respectively, in the ¹H NMR. Relative deuteration of each epimer was also determined by ²D NMR, which had signals at δD –4.64 and –4.75 ppm, which corresponded to the benzyl deuteriums (referenced to C₆H₆) and a signal at δD –0.92 ppm, which corresponded to the deuterated alkene. The 1,2-metallate rearrangement should occur stereospecifically with inversion so insertion of the chiral but racemic carbenoid into 2 gave rise to a 1:1 ratio of 3a and 3b.

When the reaction mixture was allowed to warm to –20 °C for 1 h before a sample was quenched with HCl, producing a 1:1 mixture of the (E)-alkene 6a and 4. A sample was also quenched with MeOD followed by D₂O, which gave a 1:1 mixture of 5b and 6a. Epimer 5b was characterised by the benzylic hydrogen signal at 2.63 ppm in the ¹H NMR and the benzylic deuterium at δD –4.64 ppm in the ²H NMR. There was complete loss of signals corresponding to the other epimer 5a. No deuterium incorporation into alkene 6a was observed. If the reaction mixture was allowed to warm to reflux for 3 h (or rt for 24 h) before quenching, a 1:1 mixture of the (E)- and (Z)-alkenes 6a and 6b was isolated in good yield. Again no deuterium incorporation was observed in either alkene when the reaction was quenched with MeOD. This indicated one diastereoisomer produced the (E)-alkene 6a where as the other diastereoisomer produced the (Z)-alkene 6b (Scheme 37).

Scheme 37: Reagents and conditions: i. –20 °C, 1 h, 2 M HCl (aq) or MeOD/D₂O, 18 h. ii. Reflux, 3 h, 2 M HCl (aq), 52% or MeOD/D₂O, 18 h.
2.2 Discussion of the possible mechanisms for the formation of the alkene products

The first mechanism considered was an endocyclic $\beta$-hydride elimination to generate a zirconocene-hydride intermediate followed by an $\alpha$-hydride elimination (Scheme 38).

Scheme 38: $\beta$-Hydride elimination.

On first inspection this appeared to be a very attractive way to describe the transformation. This mechanism has been previously proposed by our group\textsuperscript{44} and recently by Xi \textit{et al.}\textsuperscript{60} Xi \textit{et al.} proposed the observed decomposition of zirconacyclohexene 8 occurred \textit{via} $\beta$-hydride abstraction followed by reductive elimination (Scheme 39).

Scheme 39: Documented decomposition of zirconacyclohexenes.\textsuperscript{60}

An essential element of our proposed mechanism is the $\alpha$-hydride elimination, however this is known to be a slow process.\textsuperscript{61} The zirconocene-hydride intermediate 7 would also be expected to undergo a fast re-addition to the alkene to afford a zirconacyclopentene 9 (Scheme 40).
Work carried out within our group has previously reported the rapid isomerisation of the zirconacyclopentene 10a, derived from the cis-alkene, to the zirconacyclopentene 10b, derived from the trans-alkene via an exocyclic β-hydride elimination – re-addition process (Scheme 41).

If the mechanism of alkene formation is via an endocyclic β-hydride elimination one would expect to only produce the (E)-alkene 6a, due to rapid isomerisation via the zirconacyclopentene 9 formed from re-addition of the zirconocene-hydride to the alkene. However, a 1:1 ratio of (E):(Z) alkenes 6a and 6b is always observed for this system.

Hence an alternative mechanism was sought. It was proposed that the formation of the alkene products could be occurring via a novel endocyclic cyclometallation process to afford the zirconocene η²-alkene complex (Scheme 42). The mechanism supports the observed 1:1 ratio of (E):(Z) alkenes 6a and 6b. It is also suggested that the decomposition of zirconacycle 8, observed by Xi et al., may have occurred via a endocyclic cyclometallation rather β-hydride elimination. Modelling of the cyclometallation process predicted that diastereoisomer 3a gives the (E)-alkene 6a and
diastereoisomer $3b$ gives the (Z)-alkene. A more detailed discussion of this is given in section 2.3.

Such cyclometallation processes to afford zirconocene $\eta^2$-alkene complexes are well known.$^{31}$ One such example is the formation of zirconocene(1-butene) $15$ from dibutylzirconocene (Negishi’s reagent)$^{31,14}$ however the mechanism within this programme is the first endocyclic transfer to be proposed (Scheme 43).

Protonolysis of the zirconocene $\eta^2$-alkene complexe $11$ is expected to afford the saturated compound $4$, however in this case this is not observed and instead, alkene $6$ formation is observed via decomplexation of the zirconocene presumable aided by the presence of diisopropylamine $12$, present in the reaction from the \textit{in situ} generation of the benzyl carbenoid from benzyl chloride and LDA. The diisopropylamine $12$ may trap the zirconocene, as a zirconocene-amido hydride species $13$, though we have no direct evidence for this. This is a key step of the mechanism as zirconocene is a highly reactive species and could catalyse further reactions such as isomerisation of the alkene. It is worth noting that isomerisation is observed in the monocyclic systems, which provides further evidence for formation of a zirconocene $\eta^2$-alkene complex. This is discussed in greater detail in section 2.7.
To successfully distinguish between the two possible mechanisms, attempts were made to directly trap the intermediate zirconocene $\eta^2$-alkene complexes 11. The concept of trapping a zirconocene $\eta^2$-alkene complex is well reported within literature.\textsuperscript{63-65} The first example was published by Negishi et al. in 1987.\textsuperscript{63} Negishi et al. showed that a zirconocene stilbene complex 16 could be successfully trapped with acetone to give alcohol 18 on protonolysis, which was presumably formed via 17 (Scheme 44).

\begin{center}
\textbf{Scheme 44: Reagents and conditions:} i. 2 eq n-BuLi, –78 °C. ii. 0 °C, iii. rt, 1 h, iv. 3M HCl.
\end{center}

Takahashi et al. reported the successful insertion of a range of aldehydes into a variety of zirconium alkene complexes with high ($\geq 99\%$) regioselectivity (Scheme 45).\textsuperscript{64}

\begin{center}
\textbf{Scheme 45:} Insertion of a range of aldehydes into various zirconium alkene complexes.
\end{center}

Buchwald et al. extended this methodology and demonstrated that a range of unsaturated compounds, such as ketones, nitriles, alkynes and isocyanides, could be successfully inserted into zirconocene cyclobutene complex 20 (Scheme 46).\textsuperscript{65}
Scheme 46: Insertion of a range of unsaturated compounds into a zirconium-alkene complex.

An initial attempt was made to trap the zirconocene \( \eta^2 \)-alkene complexes with 1 equivalent of acetone. Monitoring the reaction by GC and GCMS revealed small amounts of new products had been formed, presumably acetone insertion into the zirconocene \( \eta^2 \)-alkene 11. The reaction was repeated using 2, 3 and 5 equivalents of acetone. The most successful result was achieved with 5 equivalents of acetone. Column chromatography allowed successful separation of a mixture of the recovered alkene products (6a and 6b) in 30% yield, and two acetone insertion products 23 and 25 (Scheme 47). Acetone insertion into the zirconocene \( \eta^2 \)-alkene complex 11 gave intermediate 21, followed by an exocyclic \( \beta \)-hydride transfer to afford 22 which on protonolysis gave alcohol 23 in 35% yield. The second acetone insertion product was identified as alcohol 25 and was isolated in 6% yield. Alcohol 25 was presumably formed by insertion of acetone into a rearranged zirconocene \( \eta^2 \)-alkene complex 24 (Scheme 47). Attempts to improve the yield of 23 were not successful. This may be due to the fact that diisopropylamine present in the reaction mixture assisted in the decomplexation of the zirconocene \( \eta^2 \)-alkene complex 11. As a result, it would appear that acetone insertion and decomplexation are competing reactions.
Attempts to trap the η²-alkene zirconocene complex with benzophenone, benzylaldehyde and phenyl isocyanate were unsuccessful.

2.3 Theoretical investigation of the mechanism
Attempts to find a transition state for the β-hydride transfer mechanism (Scheme 38) by creating a reaction profile (using semi-empirical methods with PM3 parameters extended to cope with transition metals) by reducing the relevant hydrogen-zirconium distance gave an energy maximum. A transition state search from this point successfully converged to a structure which was characterised as a transition state through calculation of the vibrational spectrum which had a single imaginary frequency. However, inspection of the imaginary frequency (the reaction coordinate) showed it to
correspond to movement of the hydrogen between the carbon, and remote alkenyl carbon (i.e. the cyclometallation mechanism, Scheme 42), not to the zirconium. Unfortunately semi-empirical calculations have severe limitations in terms of giving realistic energies. Furthermore, they do not cope well with either metal-H bonds or strained rings (as the product η²-alkene complex may be viewed). Density function theory (DFT) calculations are far more reliable, but are several orders of magnitude slower so cannot realistically be used to create reaction profiles. However, DFT calculations can be used to examine related energies of conformers.

Scheme 48: DTF relative energy calculations.°

The calculations predicted that the lowest energy conformation of 3a is a ‘chair’ like structure and cyclometallation affords (E)-alkene 6a whereas 3b is a ‘twisted boat’ like conformer and cyclometallation affords (Z)-alkene 6b (Scheme 48). This was indeed what is observed, however minimum energy calculations showed that there are two reasonable conformers of diastereoisomer 3b. The ‘twisted boat’ like conformer which leads to the (Z)-alkene 6b is 18.2 kJ/mol more stable than the ‘chair’ like conformer which leads to the (E)-alkene 6a.

2.4 Kinetic studies

It has already been shown that there is a large difference in the rate of cyclometallation between diastereoisomer 3a and 3b (see page 34) and kinetic studies were undertaken to quantify this.
This was achieved by removing aliquots (0.1 mL) of the reaction mixture and quenching them with 2 M HCl at timed intervals. The samples were analyzed by GC for loss of product 4 and appearance of alkenes 6a and 6b. The rate of cyclometallation was monitored at 20 °C over 44 h. The data represented in Figure 2 highlights the rate difference for the cyclometallation of each diastereoisomer.

![Graph](image)

**Figure 2**: Reaction Profile: Cyclometallation of diastereoisomer 3a to give the (E)-alkene 6a and 3b to give the (Z)-alkene 6b.

First order rate plots were produced by plotting ln [4] verses time; rate constant (k) and half lives have been calculated.
Figure 3: 1st Order Rate Plot: Cyclometallation of diastereoisomer 3a to give the (E)-alkene 6a and 3b to give the (Z)-alkene 6b.

The rate constant of cyclometallation of 3a to give the (E)-alkene 6a was 0.0007 s\(^{-1}\) with a half life of 16.5 min. The rate constant of cyclometallation of 3b to give the (Z)-alkene 6b was 0.00002 s\(^{-1}\) with a half life of 578 min. This clearly shows a large difference in the rate of cyclometallation of each diastereoisomer (Figure 3).

The DFT calculations (Scheme 48) indicate that the zirconacycle 3a is 25.2 kJ/mol less stable than the (E)-\(\eta^2\)-alkene complex, whereas the zirconacycle 3b is 37.5 kJ/mol less stable than the (Z)-\(\eta^2\)-alkene complex, consistent with the observed slower reaction in the later case, although it is transition state energies which are really needed.
2.5 **Cyclometallation of a deuterium labelled compound**

Minimum energy structures predict that the same hydrogen, relative to the ring junction, is transferred during the cyclometallation process in both diastereoisomers 3a and 3b. For the cyclometallation process to occur diastereoisomer 3a must take on a chair-like confirmation whereas diastereoisomer 3b must take on a twisted-boat-like confirmation (Figure 4).

![Figure 4: Conformation of diastereoisomers 3a and 3b.](image)

To demonstrate the cyclometallation mechanism and to confirm that the same hydrogen is transferred in both diastereoisomers synthesis of the mono deuterium labelled compounds 26a and 26b was attempted (Figure 5).

![Figure 5: Deuterium labelled compounds.](image)

The initial route to the deuterium labelled compounds was via stereospecific hydrometallation of alkyne 27 with a D$_2$O workup to give the (E)-alkene 28. Initially the reaction was carried out using 2 equivalents DIBAL-H at 50 °C. This, however, produced an inseparable mixture of the desired (E)-alkene 28 and the over reduced alkane 29 (Scheme 49).

![Scheme 49: Reagents and conditions: i. 2 eq DIBAL-H, pentane, rt - 50 °C, 3 h. ii. D$_2$O, rt, 18 h.](image)
The reaction was repeated with only 1 equivalent of DIBAL-H, however, no reaction was observed even after 4.5 h at 50 °C. This is due to the fact that DIBAL-H will react with the alcohol preferentially over the alkyne unit. A second equivalent of DIBAL-H was added and the reaction was monitored by GC. Before complete disappearance of the alkyne 27, alkane product 29 was also observed. However, after 2 h complete disappearance of the alkyne 27 was observed. The total amount of hydrometallation was greater than the number of DIBAL-H equivalents used. It was suggested that elimination of one of the butyl groups had occurred to generate an additional aluminium-hydride. The rate of reduction of the alkenyl aluminium must be comparable to the rate of reduction of the alkyne. Below 40 °C no reduction is observed, however above 40 °C alkane product 29 is always observed before complete disappearance of starting alkyne 27. Attempts to separate the alkene 28 from the alkane 29 using 5% silver nitrate doped silica gel proved unsuccessful.

Attempts to hydrozirconate the alkyne 27 with Schwartz reagent also proved to be unsuccessful. No over reduction was observed, however, complete reduction to the alkene 28 was not observed even with 2.2 equivalents of Schwartz reagent. A mixture of the starting alkyne 27 and alkene 28 were produced. This was most likely due to the quality of the Schwartz reagent. Further investigations into this route were not carried out due to the high cost of the Schwartz reagent and the large quantity required due to this being the first step of the sequence.

Although there are several examples of reducing an alkyne to an alkene selectively using reducing agents such as DIBAL-H, Schwartz reagent and boranes, caution should be taken as several examples convert the alkene to the epoxide prior to separating, providing a successful method of isolating the alkene from the alkane.

The focus was changed to the synthesis of the (Z)-alkene 26a (Scheme 50) as the modelling (Scheme 48) predicted the deuterium in this isomer was positioned to be transferred during the cyclometallation process in both diastereoisomers of the intermediate zirconacyclohexene.
Swern oxidation of alcohol 31 gave 32 in 96% yield. The aldehyde 32 was successfully converted to the dibromide 33, via the Corey-Fuchs reaction, in 70% yield. The dibromide 33 was treated with 2 equivalents of n-BuLi, and quenched with D\textsubscript{2}O to give deuterated alkyne 34 in 83% yield with ≥ 99% deuterium incorporation. Alkyne 34 was then selectively hydrozirconated to give the alkene 26a in 48% yield. Previously it was shown that over hydrometallation was not observed when Schwartz reagent was used, however, complete reduction was also not observed. This was attributed to the quality of the Schwartz reagent. ZrC\textsubscript{p}HCl formed in situ, by treating ZrC\textsubscript{p}Cl\textsubscript{2} with DIBAL-H at 0 °C, was used in preference to commercially available Schwartz reagent. Several equivalents of ZrC\textsubscript{p}HCl were prepared and aliquots were added until complete disappearance of the alkyne 34 was observed by GC analysis. It was estimated that 1.5 equivalents of the ZrC\textsubscript{p}HCl mixture was required to achieve complete hydrometallation of the alkyne 34.
Intramolecular co-cyclisation of enyne 26a with zirconocene(1-butene) followed by insertion of the benzyl carbenoid (Scheme 51) occurred cleanly and the reaction mixture was warmed to rt for 72 h. Purification by column chromatography yielded an inseparable mixture of (E)-alkene 36a, (Z)-alkene 36b and (E)-alkene 36c in a ratio of 2:1:1 (Figure 6). Also observed was an impurity which may have arisen due to isomerisation of the alkene by “ZrCp₂” (Figure 6). There is a large decrease in the rate of cyclometallation when the hydrogen atom is replaced with a deuterium atom; as the reaction time was increased from 24 h to 72 h.

Scheme 51: Reagents and conditions: i. ZrCp₂Cl₂, n-BuLi, THF, –78 °C - rt, 2.5 h. ii. BuCl, LDA, –78 °C, 30 min. iii. Warm to rt for 72 h. iv. 2 M HCl (aq), 18 h, rt, 72%.
Figure 6: $^1$H NMR (300 MHz, CDCl$_3$) alkene region of 36a, 36b and 36c.

A 1:1 mixture of 36a and 36b was predicted. The observation of 36c was unexpected and implies that diastereoisomer 35b gave an equal mixture of 36b and 36c. From Scheme 52 it can be seen that there is a route to the (E)-alkene 36c via a higher energy conformation. It is proposed that migration of a deuterium rather than a hydrogen adds significantly to the activation energy of conversion of 35b to 36b, therefore migration of the hydrogen to give 36c becomes competitive.

Scheme 52: Routes to alkenes 36a, b, c.$^{66}$
The differences between the deuterated and non deuterated analogues were attributed to the kinetic isotope effect, as it takes more energy to break a C-D bond than a C-H bond. It has been observed that replacing the hydrogen atom with a deuterium atom caused a large kinetic isotope effect.

The kinetic isotope effect was calculated by carrying out a reaction containing a 1:1 mixture of enyne 1 (non deuterated analogue) and enyne 26a (deuterated analogue). As diastereoisomer 35b cyclometallates to give two alkene products 36b and 36c, the kinetic isotope effect was only calculated for the diastereoisomer 35a. The kinetic isotope effect was calculated from the ratio of 6a:36a ((E)-alkene of the non-deuterated analogue:(E)-alkene of the deuterated analogue) at the initial point of cyclometallation. This was obtained from the GCMS and the results are reported in Table 1.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>6a</th>
<th>36a</th>
<th>Kinetic Isotope Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>48.4:15.1</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>52.7:13.5</td>
<td>3.9</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>42.2:13.3</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>Standard Error</td>
<td></td>
<td>±0.25</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Kinetic isotope effect.

The kinetic isotope effect for the (E)-alkene was estimated from the GCMS, which showed that the rate of cyclometallation was 3.4 times greater (± 0.25) when a C-H bond is broken rather than the C-D bond.

In conclusion, it has been shown that the same hydrogen is transferred in both diastereoisomers (3a and 3b) to give a 1:1 ratio of (E)-alkene 6a and (Z)-alkenes 6b. When the hydrogen is replaced with a deuterium a kinetic isotope effect was observed. A 2:1:1 ratio of (E)-alkene 36a, (Z)-alkene 36b and (E)-alkene 35c is observed.
2.6 Benzyl carbenoid insertion into a range of zirconacycles

The insertions of a range of benzyl carbenoids into a range of unsaturated zirconacycles was examined in order to investigate the scope of the reaction and gain further insight into the proposed novel endocyclic cyclometallation that has been proposed.

In all cases, protonation at low temperature (−78 °C) gave the benzyl inserted product generated via the zirconacyclohexene. The cyclometallation was observed in all systems to afford the styrene product, but the ratios of (E):(Z) alkenes produced and temperature of this process varied widely. The large difference in rate of cyclometallation of each diastereoisomer was observed in all examples (Table 2).
Table 2: Benzyl carbenoid insertion into a range of unsaturated zirconacycles.

a. Half lives and rates are presented in the order of diasterisomer a then b.

The first noteworthy observation is the effect of changing the aromatic carbenoid. In all cases a 1:1 ratio of \((E):(Z)\) alkenes (6a/b, 39a/b and 42a/b) were produced as expected, however, the rate of cyclometallation varied slightly with the choice of carbenoid. An electron-withdrawing subsituent on the phenyl, i.e. chlorine, had little effect on the rate of cyclometallation whereas an electron-donating subsituent, i.e. methoxy resulted in a small increase in the rate of cyclometallation.
Figure 7: 1<sup>st</sup> Order rate plot. The effect of different carbenoids on the rate of cyclometallation of zirconacyclohexanes, 3a, 37a and 40a, to give the (E)-alkenes, 6b, 39b and 42b.

In all cases there is a large difference in the rate of cyclometallation of each diastereoisomer. The half lives varied from 6.4 - 19.0 minutes for zirconacyclohexenes 3a, 37a and 40a to 385 - 578 minutes for diastereoisomer 3b, 37b and 40b at 20 °C (Figure 7 and Figure 8).

The effect of the zirconacycle was also investigated. The first consideration was the effect of the alkene subsituent (R) on the rate of cyclometallation. The phenyl group was replaced with a butyl group. The first important observation is that a 1:1 (E):(Z) was not obtained as expected and instead a 3:1 (E):(Z) was observed. By following the
reaction at –10 °C it was concluded that 43a behaves as expected and only gave the \((E)\)-alkene. Cyclometallation of diastereoisomer 43b afforded a roughly equal mixture of the \((E)\) and \((Z)\)-alkene. Several factors were considered for why this ratio of \((E):(Z)\) olefins was observed. One suggestion was that LDA was epimerising the two zirconacyclohexenes so that there was not a 1:1 ratio of the two diastereoisomers 43a and 43b prior to cyclometallation. This was considered as it has been found that the zirconacyclohexanes undergoes isomerisation in the presence of excess LDA (Chapter 3). The reaction was carried out with an excess of LDA, however, this had no effect on the reaction and again a 3:1 \((E):(Z)\) mixture was observed. This suggested that epimerisation is not observed in the zirconacyclohexenes as the alkene substituent blocks nucleophilic addition into the vacant zirconium orbital (Figure 9) (see Chapter 3).

![Figure 9: Epimerisation via nucleophilic addition.](image)

No epimerisation is observed. Nucleophilic addition into the vacant zirconium orbital causes epimerisation.

One other possibility was that zirconocene generated in the reaction isomerised the double bond. The reaction was carried out in the presence of 4-octyne as a zirconocene trap. Again the 3:1 \((E):(Z)\) ratio was produced. It was concluded that the 3:1 \((E):(Z)\) ratio was produced by the cyclometallation of diastereoisomer 43b occurring via two pathways as observed in the deuterium labelled system (Scheme 51).

Minimum energy calculations were carried out on these systems.\(^6\) As shown previously (Scheme 48), there are too possible conformers of diastereoisomers 3b. When \(R = \text{Ph}\) the ‘twisted boat’ like conformer, which leads to the \((Z)\)-alkene is 18.2 kJ/mol more stable than the ‘chair’ like conformer, which leads to the \((E)\)-alkene; diastereoisomer 3b only cyclometallates to give the \((Z)\)-alkene. However, when the calculations were repeated with a propyl group (model for \(R = \text{Bu}\) system) the energy difference between the ‘twisted boat’ like conformer and the ‘chair’ like conformer is reduced to 8.1
kJ/mol, which is consistent with the observation that diastereoisomer 43b can cyclometallate to give both the \((E)\)- and \((Z)\)-alkenes (Scheme 53).

Scheme 53: DFT relative energy calculations.

The other noteworthy observation is that changing the alkene subsituent (R) from a phenyl group to a butyl group greatly increased the rate of cyclometallation with half lives calculated as <4 minutes for diastereoisomer 43a and 28 minutes for diastereoisomer 43b at 20 °C.

The next consideration was the size of the ring fused to the zirconacycle. Increasing the fused ring from a 5 to a 6 membered ring had a dramatic effect on the outcome of the reaction. When R was either phenyl or butyl only the \((E)\)-alkene is produced. As expected the zirconacyclohexene 46a and 49a undergoes the cyclometallation to give the \((E)\)-alkene, however, zirconacyclohexenes 46b and 49b also gave the \((E)\)-alkene. Minimum energy calculations predicted that the ‘chair’ like conformer of diastereoisomer 46b is 15.3 kJ/mol more stable than the ‘twisted boat’ like conformer. When the calculations were repeated with a methyl group (model for the R = Bu system) replacing the phenyl group, it was predicted that the ‘chair’ like conformer is 14.4 kJ/mol more stable than the ‘twisted boat’ like conformer. These calculations support the fact that both diastereoisomers cyclometallate to give the \((E)\)-alkene when the fused ring is a 6-membered ring.66
Increasing the size of the ring from a 5-membered ring to a 6-membered ring caused a
dramatic reduction in the temperature at which the zirconacyclohexenes underwent the
cyclometallation. In the example with the phenyl subsituent 46, the first diastereoisomer 46a has a half life estimated as <10 minutes at –60 °C and 12.8 minutes at –10 °C for diastereoisomer 46b. In the case with the butyl subsituent 49, the half lives of both diastereoisomers were estimated at <10 minutes at –60 °C.

In summary, only a small difference in the rate of cyclometallation is observed when varying the aromatic carbenoid used. However, very dramatic effects are observed with different zirconacycles. Changing the R substituent and size of the fused ring greatly increases the rate of cyclometallation and alters the (E):(Z) ratio of the products.
2.7 Benzyl carbenoid insertion into monocyclic zirconacycles

Formation of the monocyclic zirconacycle 52 was achieved by the co-cyclisation of 4-octyne with ethylene zirconocene, generated from zirconocene dichloride treated with 2 equivalents of EtMgBr. Temperature control was essential when forming monocycle 52. Ensuring the reaction mixture was not warmed above 0 °C prevented formation of the alkyne dimer 53. Insertion of the benzyl carbenoid was facile but the reaction needed to be quenched very rapidly at −78 °C to afford alkene 55, in 57% yield (Scheme 54).

![Scheme 54: Reagents and conditions: i. ZrCp₂Cl₂, EtMgBr, THF, −78 - 0 °C, 4 h. ii. warmed to rt, 2 M HCl (aq). iii. BnCl, LDA, −78 °C, 10 min. iv. 2 M HCl in Et₂O, −78 °C - rt, 1 h, 57% v. warm to rt, 30 min. vi. MeOH, sat NaHCO₃ (aq), rt, 1 h, 56a in 47% and 56b in 14%.](image)

When the reaction mixture was warmed to rt before quenching with 2 M HCl (aq) and MeOH, the expected diene 56a and the unexpected alkene 56b were isolated in 47% and 14% yield respectively (Scheme 54). The unexpected alkene product was identified by a characteristic double triple doublet at δ_H 5.50 ppm and double double triplet δ_H 5.25 ppm in the ¹H NMR spectrum. The benzylic protons were observed as a doublet at 3.32 ppm. In addition GCMS analysis assisted in confirming the identity of alkene 56b with the molecular ion observed at 230 m/z.

It was proposed that alkene 56b was formed by isomerisation of the initial zirconocene η²-alkene complex 57 to give zirconocene η²-alkene complex 58 (Scheme 55). On work-up insertion of water into the 16-electron complex 58 gave the 18-electron zirconium complex 59. A proton transfer of 59 generated the 16-electron complex 60.
which underwent a final proton transfer to give the alkene product 56b. Complete isomerisation was not observed as the majority of zirconocene $\eta^2$-alkene complex 57 was successfully trapped by the diisopropyamine present in the reaction mixture. A rearrangement analogous to 54 to 57 did not occur with bicyclic zirconacycles, probably because the initial hydride migration to zirconium is sterically hindered.

Scheme 55: Proposed mechanism for the formation of alkene 56b.

To obtain alkene products cleanly it appeared that it was essential to trap the zirconocene produced in the cyclometallation-decomplexation process. The reaction was first attempted with an excess of 4-octyne, which successfully trapped the zirconocene, evident by the formation of dimer 53, which was formed by 2 equivalents of 4-octyne co-ordinating to zirconocene (Scheme 56). However, diene 56a could not be separated from diene 53 by column chromatography.

Scheme 56: Effects of adding alkyne traps to prevent formation of the rearranged product.
The reaction was also repeated in the presence of 2-butyne. 2-Butyne should trap the zirconocene as successfully as 4-octyne but would be more easily separated from the reaction mixture as any dimer formed should be much more volatile. When the reaction was carried out diene 56a and diene 61 were isolated as an inseparable mixture (Scheme 56). Diene 61 was formed by 2-butyne inserting into zirconocene $\eta^2$-alkene complex 57. The structure of diene 61 was deduced by NMR and GCMS analysis. The NMR data confirmed a mixture of two compounds. The most interesting new peaks in the $^1$H NMR spectra were a triplet at $\delta_H$ 5.13 ppm and a quartet at $\delta_H$ 5.05 ppm characteristic of diene 61 (Figure 10). Two products were detected by GCMS analysis: one with a retention time of 8.6 minutes, molecular ion at 228, corresponded to diene 56a and the other at 9.0 minutes, molecular ion at 284, which corresponded to diene 61.

![Figure 10: $^1$H NMR of diene 56a and 61.](image)

Further investigations were carried out in order to find a suitable trap. Cleaner reactions were obtained when either butylamine or CH$_2$Cl$_2$ were used, and it was concluded that the cleanest reaction occurred when CH$_2$Cl$_2$ was added as a trap. Work carried out
within our group by Norton demonstrated that zirconocene reacts with CH\textsubscript{2}Cl\textsubscript{2}. When a zirconocene mediated cyclisation was carried out in the presence of CH\textsubscript{2}Cl\textsubscript{2} no cyclisation was observed, as the zirconocene(1-butene) reacted preferentially with the carbon-chlorine bond of the CH\textsubscript{2}Cl\textsubscript{2}.\textsuperscript{74}

The scope of the reaction was examined by insertion of a range of benzyl carbenoids into a range of zirconacycles (52, 62 and 63) (Scheme 57).

![Scheme 57: Reagents and conditions: i. ZrCp\textsubscript{2}Cl\textsubscript{2}, EtMgBr, THF, −78 - 0 °C, 4 h. ii. ArCl, LDA, −78 °C, 5 min. iii. CH\textsubscript{2}Cl\textsubscript{2}, −78 °C, 30 min then warmed to rt, 30 min, iv. 2 M HCl (aq), rt, 18 h.]

Zirconacycle 63 is formed in greater than 99% regioselectivity when trimethyl(prop-1-ynyl)silane was used as the precursor.\textsuperscript{40} Successful insertion of the carbenoids and subsequent cyclometallations occurred cleanly, when CH\textsubscript{2}Cl\textsubscript{2} was added to trap the zirconocene, affording skipped dienes 56a, 64, 65 and 66 in good yields (52-68%).

2.8 Conclusion

A range of benzyl carbenoids have been successfully inserted into a range of zirconacyclopentenes to afford zirconacyclohexenes. A novel endocyclic cyclometallation of zirconacyclohexenes to afford zirconocene $\eta^2$-alkene complexes has been reported. The mechanism and scope of this reaction has been thoroughly investigated.
3 **Insertion of benzyl carbenoids into saturated zirconacycles**

Fillery\(^1\) showed that benzyl carbenoids could be successfully inserted into saturated zirconacycles to give the expected benzyl carbenoid inserted product (Chapter 1, Scheme 28) together with a small amount of an alkene product (Chapter 1, Scheme 29) resulting from bis-insertion of the carbenoid.

### 3.1 Mono-insertion of benzyl carbenoids into zirconacyclopentanes

This methodology was extended by inserting a large range of benzyl carbenoids into a saturated zirconacycle. The results are highlighted in Scheme 58 and Table 3. Intramolecular co-cyclisation of 4,4-bis(methoxymethyl)hepta-1,6-diene 70 with zirconocene(1-butene) generated *in situ* from dibutylzirconocene (Negishi’s reagent)\(^24\) afforded the zirconacyclopentane 71. Benzyl carbenoid insertion was achieved by treating the corresponding benzyl chloride with LDA *in situ* followed by TMEDA. Quenching with MeOH and NaHCO\(_3\) gave 73a-g generated *via* the zirconacyclohexanes 72a-g and 72a`-g` (‘ used to differentiate between the two zirconacyclohexane diastereoisomers). Fillery\(^1\) reported that bis-insertion is observed even when only 1 equivalent of carbenoid is used. It was found that adding TMEDA limited the amount of bis-insertion product 74a-g to <5%. The effect of TMEDA on the reaction is not understood.

![Scheme 58](image)

**Scheme 58:** *Reagents and conditions:* i. ZrCp\(_2\)Cl\(_2\), n-BuLi, THF, –78 °C - rt, 2 h. ii. ArCH\(_2\)Cl, LDA, TMEDA –78 °C, 1 h. iii. MeOH, NaHCO\(_3\), –78 °C - rt, 18 h.
A range of benzyl carbenoids were successfully inserted into the saturated zirconacycle 71 (Table 3). The notable exceptions are the benzyl carbenoids with cyano- and ester-substituents. The failure could be due to the electron withdrawing nature of the $p$-cyano- and $p$-ester-substituent making the carbenoid less nucleophilic preventing formation of a zirconate complex. Alternatively the zirconate complex might form, but not rearrange. If the later was true it would prevent other carbenoids attacking the zirconium. To attempt to distinguish between the hypotheses a reaction was carried out where 2 equivalents of LDA was added to a mixture of 1 equivalent of the zirconacycle 71, 1 equivalent of benzyl chloride and 1 equivalent of $p$-cyano-benzyl chloride. GC showed complete insertion of benzyl carbenoid into the zirconacycle suggesting that the failure of the $p$-cyano-benzyl carbenoid to insert was due to poor nucleophilicity of the electron-poor carbenoid.

There was no evidence that that zirconacyclohexanes 72a and 72a` underwent a cyclometallation process to afford the alkene product, analogous to those observed in the unsaturated system (Chapter 2), even on prolonged heating. Zirconacyclohexanes 72a and 72a` are stable at 66 °C for 2 days. Slow decompostion of zirconacyclohexanes 72a and 72a` was observed when heating at 66 °C was continued for longer than 2 days.

<table>
<thead>
<tr>
<th>Product</th>
<th>Ar</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>73a</td>
<td>C$_6$H$_5$</td>
<td>75</td>
</tr>
<tr>
<td>73b</td>
<td>$p$-CH$_3$C$_6$H$_4$</td>
<td>46</td>
</tr>
<tr>
<td>73c</td>
<td>$o$-CH$_3$C$_6$H$_4$</td>
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<td>73g</td>
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</tr>
<tr>
<td>73i</td>
<td>$p$-CH$_3$OOCC$_6$H$_4$</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 3: Benzyl carbenoid insertion into zirconacyclopentane 71.
The methodology was extended to show that benzyl carbamates could be used as precursors for the carbenoids. The benzyl carbamate 75 was prepared according to a known procedure (Scheme 59). A basic work up was used in each step rather than the acid work up, as previously reported, as this was found to be essential for high yields.

Scheme 59: Reagents and conditions: i. p-TsOH, reflux, 4 days, 80%; ii. Triphosgene, Et,N, benzene, reflux, 20 h, 82%; iii. NaH, BnOH, 0 °C - rt, 18 h, 58%.

Benzyl carbamate carbenoids 76 can be generated in two ways: in situ, by treating with LDA or by pre-forming, by treating benzyl carbamate 75 with sec-BuLi and TMEDA. The in situ method gave 73a, in 40% yield, with the low yield being due to incomplete carbenoid insertion. GC analysis revealed benzyl carbamate 75 and zirconacyclopentane 71 remaining even after several hours at –78 °C. Next, the benzyl carbamate carbenoid 76 was preformed by adding an equivalent of sec-BuLi to a solution of the benzyl carbamate 75 and TMEDA in THF at –78 °C for 30 minutes. The solution was then added to the zirconacyclopentane 71, which had been formed using standard co-cyclisation conditions. After stirring for 3 h at –78 °C and quenching with MeOH and NaHCO₃ the desired product 73a was produced in 60% yield. The low yield was again due to incomplete insertion of the carbamate (Scheme 60). Again, GC analysis revealed benzyl carbamate 75 and zirconacyclopentane 71 remaining even after several hours at –78 °C. It was suggested that complete insertion was not observed as either the benzyl carbamate 75 was not completely deprotonated or benzyl carbamate carbenoid 76 decomposes before it inserts into the zirconacyclopentane 71.
3.2 Bis-insertion of benzyl carbenoids into zirconacyclopentanes.

Filery demonstrated that complete conversion to the bis-inserted products could be achieved if a large excess of benzyl carbenoid was used ([Chapter 1, Scheme 29]). To extend this methodology a range of different benzyl carbenoids were inserted (Scheme 61 and Table 3).

The benzyl carbenoids were formed in situ by treating the corresponding benzyl chloride with LDA at −78 °C. Each equivalent of carbenoid was added sequentially until there was complete loss of the mono-inserted product observed by GC.
Purification by column chromatography of the bis-inserted products from co-formed benzyl carbenoid polymers was difficult and resulted in only modest yields of the bis-inserted products (Table 4).

3.3 Discussion of the possible mechanism of bis-insertion of benzyl carbenoids into zirconacyclopentanes

Fillery proposed two mechanisms of bis-insertion of benzyl carbenoids into zirconacyclopentanes (Scheme 62); via zirconacycloheptane 77 or via zirconium hydride intermediate 78.

If the mechanism is via zirconacycloheptane 77, if Ar\textsuperscript{1} and Ar\textsuperscript{2} are different, two different products 74 and 74` would be expected. If the mechanism was via the zirconium hydride intermediate 78, then only the alkene 74 would be expected.
Scheme 62: Proposed mechanisms for bis-benzyl carbenoid insertion.

Fillery suggested that the mechanism of bis-insertion was via zirconium hydride intermediate \textit{78}.\textsuperscript{1} This was supported by the observation that zirconacyclohexane \textit{72a}\textsuperscript{a} epimerised to give zirconacyclohexane \textit{72a}. Initially, as expected, a 1:1 diastereoisomer mixture of zirconacyclohexanes \textit{72a} and \textit{72a}\textsuperscript{a} was observed. The 1:1 mixture arises as
the 1,2-metallate rearrangements occurs stereospecifically with inversion, of the chiral but racemic carbenoid. However, Fillery reported that, on warming, epimerisation of the less stable diastereoisomer \(72a^\prime\) occurred to afford zirconacyclohexane \(72a\). This process took several hours at rt or a few minutes at 60 °C. DFT calculations indicate that \(72a\) is 13 kJ/mol more stable than \(72a^\prime\). Fillery proposed that epimerisation was occurring via a zirconium hydride intermediate \(78\) (Scheme 63).

![Scheme 63: Proposed mechanism for epimerisation of the zirconacyclohexanes.](image)

Further work into the mechanism of epimerisation was required as work carried out within the group by Dixon\(^62\) (Scheme 41) suggested that the zirconocene hydride intermediate \(78\) would close to form a zirconacyclopentane.

The positions of the diastereotopic benzyl hydrogen’s of \(73a\) were identified, by C-H correlation spectroscopy in CDCl\(_3\), at \(\delta_H 2.70\) and \(2.50\) ppm respectively in the \(^1\)H NMR spectra. Relative deuteration of the diastereotopic benzyl hydrogen position was confirmed by loss of the signal in the \(^1\)H NMR. The loss of the signal in the \(^1\)H NMR was used to calculate the ratio of diastereoisomers (Scheme 64).

![Scheme 64: Quenching the zirconacyclohexane with DCl in D\(_2\)O affords the bis deuterium compound 80.](image)

Initial studies confirmed that the zirconacyclohexanes \(72a\) and \(72a^\prime\) were produced as a 1:1 diastereotopic mixture, and this ratio was maintained if the reaction mixture was not
warmed above –10 °C. However, interesting results were obtained when the reaction mixture was allowed to warm to 0 °C. Study A clearly showed epimerisation of diastereoisomer 72a` to 72a, whereas no epimerisation was observed in study B even though both reactions were carried out under seemingly the same conditions (Table 5).

<table>
<thead>
<tr>
<th>Time after benzyl carbenoid insertion (min)</th>
<th>Study A (72a (%))</th>
<th>Study A (72a` (%))</th>
<th>Study B (72a (%))</th>
<th>Study B (72a` (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>51</td>
<td>49</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>10</td>
<td>65</td>
<td>35</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>30</td>
<td>74</td>
<td>26</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>90</td>
<td>77</td>
<td>23</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

Table 5: The ratio of diastereoisomers of zirconacyclohexane 72a at 0 °C. Study A and B were carried out under the same conditions. (Reagents and conditions): i. ZrCp₂Cl₂, n-BuLi, THF, –78 °C - rt, 2 h. ii. BnCl, LDA, –78 °C, 5 min. iii. Warm to 0 °C and samples (1 mL) removed at timed intervals and quenched with 2M DCl in D₂O.

It was proposed that an excess of base could be catalysing the epimerisation. Two possible mechanisms for base epimerisation of the zirconacyclohexane 72a` were proposed. The first was that the epimerisation was catalysed by the nucleophilic addition of LDA into the vacant zirconium orbital to generate benzyl anion 81. The second mechanism proposed was that LDA deprotonated the zirconacyclohexane 72a` to generate zirconocene anion 82 (Scheme 65).

Scheme 65: Proposed mechanisms of epimerisation.
This process was investigated by carrying out an experiment where initially only 0.75 equivalents of LDA was added to ensure that there was no excess of base present. A 1:1 ratio of diastereoisomers was observed, and this was maintained even when held at 0 °C for 2 h. The addition of a further 0.5 equivalents of LDA catalysed the rapid epimerisation to give only diastereoisomer 72a in 30 minutes at 0 °C. This demonstrates that the epimerisation is being catalysed by LDA. When the reaction was repeated with LiTMP as the base, no epimerisation was observed, even with a large excess of base. This led to the conclusion that epimerisation is catalysed by nucleophilic addition of the LDA into the vacant zirconium orbital.

As it was concluded that epimerisation was occurring via a nucleophilic catalysed process, rather than via a zirconium hydride intermediate, further investigation of the mechanism of bis-insertion was required.

Taking into account the discovery of the endocyclic cyclometallation process that occurred in the unsaturated systems to give the alkene products (Chapter 2), the following bis-insertion mechanism was proposed. The second equivalent of benzyl carbenoid inserts into the zirconacyclohexane 72 and 72' to afford a zirconacycloheptane 77. A subsequent cyclometallation afford the zirconocene η²-alkene complexes 83 and 83', which on decomplexation affords alkenes 74 and 74' (Scheme 66).

![Scheme 66: Proposed mechanism of bis-insertion into a saturated zirconacycle.](image-url)
As the mechanism proceeds via a zirconacycloheptane 77, the order of addition should have no effect on the outcome of the reaction. The mechanism of bis-insertion into saturated zirconacycles was investigated by sequentially adding two different benzyl carbenoids that were electronically very similar. As a result, benzyl chloride and para-methylbenzyl chloride were selected as the carbenoid precursors. Two experiments were carried out in a deficiency of base, to ensure the second equivalent of carbenoid was added to a 1:1 diastereotopic mixture of 72 and 72' and two were carried out with an excess of base, to ensure that the second equivalent of carbenoid was added to only the most stable diastereoisomer 72. The results are highlighted in Table 6.
Structural determinations of the bis-inserted products was achieved by comparing $^1$H and $^{13}$C NMR of the two bis-insertion products with 74a and 74b. Clear correlations were observed and are highlighted in Table 7 and Table 8. One notable observation is that there is no deuterium incorporation into the bis-inserted compound on a 1 M DCl in D$_2$O quench.

<table>
<thead>
<tr>
<th>1st carbenoid precursor</th>
<th>2nd carbenoid precursor</th>
<th>Excess of base added</th>
<th>74a</th>
<th>74j</th>
<th>74k</th>
<th>74b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 BnCl</td>
<td>$p$-CH$_3$BnCl</td>
<td>No</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>2 $p$-CH$_3$BnCl</td>
<td>BnCl</td>
<td>No</td>
<td>0</td>
<td>2</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>3 BnCl</td>
<td>$p$-CH$_3$BnCl</td>
<td>Yes</td>
<td>4</td>
<td>20</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>4 $p$-CH$_3$BnCl</td>
<td>BnCl</td>
<td>Yes</td>
<td>0</td>
<td>1</td>
<td>40</td>
<td>8</td>
</tr>
</tbody>
</table>

Table 6: Ratio of products from the bis-insertion reactions.

<table>
<thead>
<tr>
<th>δ (ppm)</th>
<th>Assign</th>
<th>δ (ppm)</th>
<th>Assign</th>
<th>Δ (ppm)</th>
<th>Assign</th>
<th>δ (ppm)</th>
<th>Assign</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.35</td>
<td>Ha</td>
<td>6.35</td>
<td>Ha</td>
<td>6.32</td>
<td>Ha</td>
<td>6.31</td>
<td>Ha</td>
</tr>
<tr>
<td>6.04</td>
<td>Hb</td>
<td>6.04</td>
<td>Hb</td>
<td>5.98</td>
<td>Hb</td>
<td>5.98</td>
<td>Hb</td>
</tr>
<tr>
<td>2.67</td>
<td>He</td>
<td>2.65</td>
<td>He</td>
<td>2.68</td>
<td>He</td>
<td>2.65</td>
<td>He</td>
</tr>
<tr>
<td>2.53</td>
<td>He</td>
<td>2.49</td>
<td>He</td>
<td>2.53</td>
<td>He</td>
<td>2.49</td>
<td>He</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.33</td>
<td>He</td>
<td>2.33</td>
<td>He</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>2.31</td>
<td>Hd</td>
<td>-</td>
<td>-</td>
<td>2.31</td>
<td>Hd</td>
</tr>
</tbody>
</table>

Table 7: $^1$H NMR (300 MHz, CDCl$_3$) assignments of the bis inserted products.
As expected two different alkene products are produced during the reaction, however, the ratios of the two cross-over products are not as predicted. The most interesting result is when the zirconacyclohexane is epimerised prior to insertion of the second carbenoid. In both cases the reaction is almost entirely selective, preferring the alkene to be positioned next to the aromatic group that was inserted first (entry 3 and 4, Table 6).

When a deficiency of base was used insertion of the first carbenoid afforded the zirconacyclohexanes 72 and 72\* in a 1:1 ratio of diastereoisomers. In the same way

Table 8: \(^{13}\text{C} \) NMR (300 MHz, CDCl\(_3\)) assignments of the bis inserted products.
insertion of the second benzyl carbenoid would be expected to lead to a 1:1:1:1 mixture of 77a-d. However, it is possible that epimerisation of 72' to 72 could occur during the second insertion, either due to the LDA present, or at the ‘ate’ complex stage 84 and 84' (via 85) leading to an imbalance between 77a and 77b and between 77c and 77d. It is also possible that insertion of the second carbenoid is influenced by the stereochemistry of the zirconacyclohexane i.e. 72 and 72' might select between the two available enantiomers of the carbenoid either at the initial addition stage, or via reversible formation of the ‘ate’ complex leading to an imbalance between 77a and 77b and between 77c and 77d. If 72' is epimerised to 72 before addition of the second carbenoid then only 77a and 77b can be formed and although a 1:1 mixture might be expected, an imbalance is possible for the reasons outlined above.

Scheme 67: Proposed mechanism of bis-insertion.
If $\text{Ar}_1$ and $\text{Ar}_2$ are electronically similar then 77b and 77c must give equal amounts of 74 and 74$'$ by symmetry. 77a and 77d may produce different ratios of 74 and 74$'$ but by symmetry the ratio’s must be equal and opposite. The energies of the transition states for the cyclometallation of 77a/d ($\text{Ar}_1=\text{Ar}_2=\text{Ph}$ so they are the same) were modelled using semi empirical (PM3) calculations$^{66}$ (Scheme 67) and predict that 77a will give 74$'$ and 77d will give 74. Therefore if we start with a 1:1:1:1 mix of 77a-d we would expect, by symmetry to get a 1:1 mixture of 74 and 74$'$. If we start with a 1:1 mixture of 77a and 77b (initial empimerisation of 72$'$ to 72) we would expect to get a 3:1 mixture of 74$'$ to 74. If the second benzyl carbenoid insertion is influenced by the structure of the zirconacyclohexane we could conceivable get only 77a (giving 74$'$) or 77b (giving 1:1 74$'$ and 74). In practice we observe good selectivity for 74 in this case (alkene next to aryl group from the first benzyl carbenoid inserted – $\text{Ar}_1$). Although transition states were found using semi empirical (PM3) calculations, the energies are not reliable. A more conclusive way would be to model the reaction profile using DFT calculations. Density function theory (DFT) calculations are far more reliable, but are several orders of magnitude slower so cannot realistically be used to create reaction profiles. Never the less, these calculations do cast doubt over the mechanism of bis-insertion being via a zirconacycloheptane. However, an alternative mechanism that explains the observed results is yet to be found.

### 3.4 Conclusions

A range of benzyl carbenoids, with exception of those with strongly electron-withdrawing substituents, have been successfully inserted into saturated zirconacycles. Bis-insertion of benzyl carbenoids into saturated zirconacycles affords the mono-alkene product. It was speculated that the mechanism of bis-insertion is via a zirconacycloheptane followed by an endocyclic cyclometallation to afford a zirconocene $\eta^2$-alkene complex, which on decomplexation gave the mono-alkene product.
4 **Intramolecular trapping of zirconocene \( \eta^2 \)-alkene complexes to generate bicyclic compounds**

4.1 **Introduction to the concept**

It has been shown that zirconium \( \eta^2 \)-alkene complexes, generated by a novel endocyclic cyclometallation, can be successfully trapped with species such as acetone and alkynes (Chapter 2). This led to the concept of intramolecular trapping of the zirconocene \( \eta^2 \)-alkene complex being proposed (Scheme 68). Trapping of the \( \eta^2 \)-alkene complex with a pendant alkene or alkyne species would lead to interesting bicyclic compounds in a one pot tandem reaction sequence.

![Scheme 68: Intramolecular trapping of zirconium \( \eta^2 \)-alkene complexes with alkenes or alkynes.](image)

4.2 **\( \beta \)-Branched systems**

Enyne 95 was selected as a suitable substrate to investigate the concept of intramolecular trapping of zirconocene \( \eta^2 \)-alkene complexes. The synthesis of enyne 95 is highlighted in Scheme 69. Alkylation of lactone 90 with allyl bromide yielded the lactone 91 in 41% yield.\(^{75}\) Lactone 91 was reduced with DIBAL-H to afford lactol 92 which was used crude in the subsequent reaction.\(^{75}\) Wittig olefination of 92 afforded alcohol 93, in 41% yield over the two steps.\(^{76}\) Conversion of alcohol 93 to the corresponding triflate 94 was carried out using standard conditions.\(^{77}\) Triflate 94 was used crude in the subsequent alkylation reaction to give the desired substrate 95 in 41%
yield. Parallel alkylation reactions were carried either in the presence or absence of HMPA. No improvement of yield was observed with the presence of HMPA and the low yield is believed to be due to the instability of triflate 94. The corresponding alkylation reaction with the more stable mesylate was unsuccessful.

Scheme 69: Reagent and condition: i. LDA, HMPA, allyl bromide, THF, –78 °C, 2 h, 41%. ii. DIBAL-H, toluene, –78 °C, 30 min. iii. CH$_3$PPh$_3$, KHMDS, THF, 0 °C, 15 min then rt 1 h, 41% over the two steps. iv. Triflic anhydride, pyridine, CH$_2$Cl$_2$, 0 °C, 15 min, 97%. v. Phenylacetylene, n-BuLi, THF, –78 °C – rt, 18 h, 41%.

Attempted co-cyclisation of 95 using zirconocene(1-butene), generated in situ from dibutylzirconocene (Negishi’s reagent)$^{24}$ afforded a 1:1 mixture of the dienes 98 and 99, presumably generated via zirconacyclopentenes 96 and 97 (Scheme 70). Formation of 96 and 97 was determined by removing a small amount of the reaction mixture and quenching with HCl. Analysis of the crude NMR revealed a triplet of double doublets at $\delta_H$ 5.78 ppm, a characteristic signal of the terminal alkene of 98, overlapping with a double double doublet at 5.69 ppm, a characteristic signal of the terminal alkene of 99. Both products were produced in a 9:1 mixture of diastereoisomers, determined by GC analysis. No further work was carried out on this system due to the conclusions drawn from the DFT calculation given below (Scheme 71 and Scheme 72).
DFT relative energy calculations predicted that the zirconacyclopentene 97a should be the most stable from the possible isomers shown (Scheme 71).\textsuperscript{66} It is speculated that isomerisation of zirconacyclopentene 96a to only give 97a would have been observed if the reaction mixture had been left for longer. The calculations also predicted that the initial cyclisation should be stereospecific, if under thermodynamic control, supporting the 9:1 diastereotopic ratio observed.

At this point DFT relative energy calculations were also carried out on the desired final co-cyclisation to form 100. For simplicity the co-cyclisation of diene 101 with zirconocene(1-butene) was modelled (Scheme 72). The calculations predicted that cyclisation of diene 101a to afford 100a was an unfavourable, endothermic, process, whereas cyclisation of diene 101b to afford 100b was a favourable process. Co-cyclisation of 101a is unfavourable as it involved the formation of a trans-fused 5,5 ring system. Therefore the final co-cyclisation was unlikely to be successful as the major diastereoisomer of the desired zirconacyclopentene 96a of the first co-cyclisation would have afforded 100a in the second co-cyclisation.
4.3 α-Branched systems

By moving the alkene pendant to the α-position, several problems highlighted in the system above were overcome. It was speculated that only the desired co-cyclisation should occur as a 5-membered enyne co-cyclisation should be more favourable than an 8-membered co-cyclisation. The final product would be a spirocyclic product rather than a fused cyclic product and therefore the issue of forming unfavoured 5,5 trans ring junctions would be overcome.

4.3.1 Nitrogen system

A nitrogen containing substrate was chosen for ease of synthesis. Substrate 108 was synthesised under the following conditions (Scheme 73).

Scheme 72: DFT calculations of the zirconocene mediated co-cyclisation of diene 101a.

Note in each case cyclisation is shown to the most stable of the 4 possible isomeric products.

Scheme 73: Reagents and Conditions: i. TMEDA, n-BuLi, Et₂O, –78 °C - rt, 20 h, followed by allyl bromide, –78 °C, 2 h, then warmed rt, 2 h, 57%. ii. MsCl, Et₃N, CH₂Cl₂, –10 - 0 °C, 30 min, 98%. iii. PPh₃, Br₂, CH₂Cl₂, 0 °C, 1 h, 71%. iv. BnNH₂, Et₂O, rt, 18 h, 53%. v. THF, 10% LiI, rt, 18 h, 57%.

Treatment of 2-methyl-2-propen-1-ol 102 with a preformed mixture of TMEDA and n-BuLi afforded the dianion. Alkylation with allyl bromide gave 103, in 57% yield. Amine 107 was produced by treating benzylamine with bromide in Et₂O. The
mesylate 104 was used crude in the subsequent alkylation of 107 catalysed by 10% LiI to produce the desired substrate 108 in 57% yield.

Intramolecular co-cyclisation of 108 using zirconocene(1-butene) afforded the zirconacyclopentene 109, which on quenching with HCl gave 110 in 72% yield. Insertion of the benzyl carbenoid, generated in situ by treating benzyl chloride with LDA at –78 °C, into zirconacyclopentene 109 afforded 112 on quenching with HCl in Et₂O, generated via zirconacyclohexene 111 (Scheme 74).

Initial attempts to effect the synthesis of spirocyclic compound 115 were carried out by warming the zirconacyclohexene 111 to rt for 18 h. The mixture was quenched with MeOH/NaHCO₃ for 66 h and produced an inseparable 1:1 mixture of 112 and the triene 114. When the reaction was repeated but was only allowed to quench for 18 h an interesting result was observed. The ¹H NMR spectrum revealed signals at δH 6.27 and 5.77 ppm, characteristic of the cyclopentadienes of the zirconocene. That suggested that the reaction mixture had not been completely quenched.

It was apparent that the reaction mixture required harsh quenching conditions. A range of different quenches were investigated. It was found that KOH/MeOH effectively quenched the reaction mixture in 6 h, 2 M HCl (aq) in 18 h and MeOH/NaHCO₃ required 66 h. It was concluded that the most practical quench was 2M HCl (aq) for 18 h. With all intermediates quenched the crude ¹H NMR suggested a 1:1 mixture of 112 and triene 114 had been produced. The mixture was not purified.
Scheme 74: Reagents and conditions: i. ZrCp₂Cl₂, n-BuLi, THF, –78 °C - rt, 2 h. ii. 2 M HCl (aq), rt 18 h, 72%. iii. BnCl, LDA, –78 °C, 30 min. iv. 2 M HCl in Et₂O, –78 °C - rt, 18 h, 79%. v. Warm to rt, 18 h. vi. 2 M HCl (aq), rt 18 h.

Initial reactions indicated that the cyclometallation of 111 to afford zirconocene $\eta^2$-alkene complex 113 is very slow, after 18 h a 1:1 mixture of 112 and (E)-alkene 114 is afforded. This indicated that only one diastereoisomer had undergone the cyclometallation. As the cyclometallation process has never been studied on systems containing nitrogen or systems with a substituent in the α position, model studies were conducted.
Alkylation of benzylamine with 3-chloro-2-methylprop-1-ene in H$_2$O gave N-benzyl-2-methylprop-2-en-1-amine 117 in 62% yield.$^{80}$ Enyne 118 was synthesised in 93% yield via the Mannich reaction of 117 and phenyl acetylene (Scheme 75).$^{81}$ Enyne 119 was synthesised in 51% yield by alkylation of 117 with 1-bromohex-2-yne.

![Scheme 75: Reagents and conditions: i. 3-chloro-methylprop-1-ene, NaHCO$_3$, H$_2$O, 90 °C, 18 h, 62%. ii. Phenylacetylene, formaldehyde, DMSO, rt, 20 h, 93%. iii. 1-bromohex-2-yne, K$_2$CO$_3$, MeCN, rt, 18 h, 51%.](image)

In both cases intramolecular co-cyclisation with zirconocene(1-butene) yielded the expected zirconacyclopentenes 120 and 121, which on quenching yielded 122 and 123 in 85% and 70% yields respectively. Benzyl carbenoid insertion occurred cleanly and a low temperature quench gave 126 and 127 in 72% and 75% yield respectively, generated via zirconacyclohexenes 124 and 125. On warming the zirconacyclohexenes 124 or 125 to reflux for 12 h, (E)-alkenes 128 and 129 were afforded in 55% and 53% yield respectively.
Scheme 76: Reagents and conditions. i. ZrCp₂Cl₂, n-BuLi, THF, –78 °C - rt, 2 h. ii. 2 M HCl (aq), rt 18 h, R=Ph 85%, R=Pr 70%. iii. BnCl, LDA, –78 °C, 10 min. iv. 2 M HCl in Et₂O, –78 °C – rt, 20 h, R=Ph 72%, R=Pr 75%. v. Warm to reflux, 12 h. vi. 2 M HCl (aq), rt 18 h, R=Ph 55%, R=Pr 53%.

Kinetic studies were carried out by removing aliquots of the reaction mixture and quenching them with 2 M HCl at timed intervals. The samples were analyzed by GC for loss of 126/127 and appearance of the alkene 128/129 to produce first order rate plots. The outcomes of these reactions are highlighted in Table 9.
Table 9: Summary of kinetic studies.

<table>
<thead>
<tr>
<th>Zirconacyclohexene</th>
<th>Temp of Cyclometallation (°C)</th>
<th>Half Life (min)</th>
<th>K (s⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>124a</td>
<td>20</td>
<td>11.6</td>
<td>0.0019</td>
</tr>
<tr>
<td>124b</td>
<td>66</td>
<td>115.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>125a</td>
<td>0</td>
<td>11.6</td>
<td>0.0019</td>
</tr>
<tr>
<td>125b</td>
<td>66</td>
<td>57.8</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

As observed in similar systems (Chapter 2) diastereoisomer 124b/125b cyclometallates at a much slower rate than the alternative diastereoisomer 124a/125a. Diastereoisomers 124b/125b cyclometallate at a much slower rate than the systems studies in Chapter 2. No cyclometallation of diastereoisomers 124b/125b was observed when the reaction mixture was monitored for 24 h at 20 °C. The slow rate of cyclometallation was attributed to the α-branch.

It was concluded that a 1:1 mixture of 112 and (E)-alkene 114 was observed due to the fact that the cyclometallation of diastereoisomer 111b was much slower than predicted. However, why was the (E)-alkene 114 observed and not the desired spirocycle 116? One possible explanation is the final co-cyclisation may be hindered; therefore the rate of decomplexation may be greater than the rate of co-cyclisation. Another possible explanation is the zirconocene η²-alkene complex 113 may have been stabilised by the nitrogen.

One way to determine whether the final cyclisation is feasible or not, would be to carry out a co-cyclisation of alkene 114 using Negishi’s reagent, which should yield the desired spirocycle 116. Attempted synthesis of the alkene 114 was carried out as before but with the presence of CH₂Cl₂ to aid decomplexation and the reaction mixture was warmed to reflux to increase the rate of cyclometallation. After 48 h the cyclometallation was incomplete and the mixture had started to decompose.

DFT relative energy calculations predict that the final co-cyclisation should be a favourable process (Scheme 77).
Several points can be concluded, the first noteworthy observation was that the rate of cyclometallation was very slow and therefore did not go to completion. There could be several reasons why the zirconocene $\eta^2$-alkene complex formed failed to undergo the final cyclisation. The zirconocene $\eta^2$-alkene complex may have existed as the nitrogen complex, preventing co-ordination of the alkene. The rate of decomplexation of the zirconocene $\eta^2$-alkene complex, aided by diisopropylamine may have been greater than the rate of cyclisation.

4.3.2 6-Membered system

The studies on the nitrogen system showed that an $\alpha$-substituent drastically decreases the rate of cyclometallation. Previous work carried out showed that the rate of cyclometallation was greater in a system with a 6-membered fused ring than a 5-
membered fused ring. The rate of cyclometallation was also greater in a system with an alkyl substituent rather than a phenyl substituent. Therefore, substrate 133 was synthesised (Scheme 78).

Scheme 78: Reagents and conditions: i. Diethyl malonate, Na, 10% NaI, EtOH, 0°C - rt, 18 h, 20%. ii. 2-methylenehex-5-enyl methanesulfonate 104, 10% NaH, NaI, THF, 0°C - rt, 24 h, 58%. iii. LiAlH₄, Et₂O, 0°C - rt, 4 h, 99%, iv. NaH, MeI, THF, 0°C - rt, 5 h, 85%.

Alkylation of diethyl malonate with hept-3-ynyl methanesulfonate 130 gave the desired mono-alkylated product 131 in only 20% yield. This was due to the fact that the hept-3-ynyl methanesulfonate 130 readily eliminates mesylic acid. A subsequent alkylation of 131 gave 132 in 58% yield. Reduction of 132 and methylation of the resulting diol using standard conditions gave the desired substrate 133 in 85% yield.

Scheme 79: Reagents and conditions: i. ZrCp₂Cl₂, n-BuLi, THF, –78°C – rt, 2 h. ii. 2 M HCl (aq), 2 h.
The co-cyclisation of 133 using zirconocene(1-butene) was attempted, but protonation gave no product which could be characterised as the alkene 134 expected therefore, benzyl carbenoid insertion was not pursued.

DFT relative energy calculations\(^6\) show that the co-cyclisation is thermodynamically allowed. However, the alkene is hindered and therefore the intramolecular co-cyclisation may be kinetically unfavoured (Scheme 80).

\[
\text{Heat of reaction} = -74.7 \text{ kJ/mol}
\]

**Scheme 80:** DFT calculations.

The literature reveals two methods for the co-cyclisation of unfavorable enyne systems. The first method involves the co-cyclisation of the hindered enyne 135 with zirconocene(ethylene)\(^3\) (Scheme 81). The first step of the reaction involves the zirconocene(ethylene) undergoing a co-cyclisation with the alkyne to form a zirconacyclopentene complex 136. This first step occurs at low temperature (–78 °C - rt) and it is only on warming to reflux that the alkene displaces the ethylene to give the desired zirconacyclopentene 137.\(^2\)

\[
\begin{array}{cccc}
\ & \ & \ & \\
\ & \ & \ & \\
\ & \ & \ & \\
\ & \ & \ & \\
\end{array}
\]

**Scheme 81:** Co-cyclisation of a hindered enyne with zirconocene(ethylene).

The second method illustrated in (Scheme 82) involved the co-cyclisation of the hindered enyne 138 with a preformed solution of Cp\(_2\)Zr(DMAP)\(_2\). Cp\(_2\)Zr(DMAP)\(_2\) is a
thermally more stable zirconocene(II) equivalent.\textsuperscript{82} The hindered enyne is added dropwise to a solution of Cp\textsubscript{2}Zr(DMAP)\textsubscript{2} at rt. As the concentration of enyne \textbf{138} remains low at all times intramolecular co-cyclisation is favoured over intermolecular dimerisation to afford the desired zirconacyclopentene \textbf{139}.\textsuperscript{27}

\textbf{Scheme 82}: Co-cyclisation of a hindered enyne with zirconocene-DMAP complex.

To ensure cyclisation and benzyl carbenoid insertion would be successful under the alternative conditions, the following model system was investigated. This system was chosen as the enyne has an \(\alpha\)-substituent and was conveniently available.

Initial reactions carried out showed that the intramolecular co-cyclisation of enyne \textbf{140} with Cp\textsubscript{2}Zr(DMAP)\textsubscript{2} afforded the expected zirconacyclopentane \textbf{141}. Benzyl carbenoid insertion occurred cleanly to give \textbf{143}, in 73\% yield, on quenching with HCl, \emph{via} the zirconacyclohexene \textbf{142}. On warming to room temperature, cyclometallation took place to afford the (\(E\))-alkene \textbf{144} in 53\% yield (\textbf{Scheme 83}).

\textbf{Scheme 83}: \textit{Reagents and conditions:} i. ZrCp\textsubscript{2}Cl\textsubscript{2}, \(n\)-BuLi, DMAP, THF, \(-78\) \(^\circ\text{C}\) - rt, ii. BnCl, LDA, \(-78\) \(^\circ\text{C}\), 10 min. iii. 2 M HCl in Et\textsubscript{2}O, \(-78\) \(^\circ\text{C}\) - rt, 18 h, 73\%, vi. Warm to rt, 5 h. v. 2 M HCl (aq), rt, 18 h, 53\%.
One notable observation was that the initial co-cyclisation was variable. Sometimes it occurred cleanly to give the desired zirconacyclopentene 141 whilst at other times significant amounts of the intermolecular dimerisation products 145 were observed.

![Scheme 84: Intramolecular co-cyclisation and intermolecular dimerisation.](image)

**Table 10:** Optimisation of intramolecular co-cyclisation with Cp₂Zr₂(DMAP)₂. In reaction (A) an excess of enyne 140 was added where as in reaction (B) a deficiency of enyne 140 was used.

In all cases no excess of enyne 140 had been added which led to the hypothesis that the enyne co-cyclisation is a reversible process. **Table 10** shows the outcome of the co-cyclisation under a range of different conditions.

<table>
<thead>
<tr>
<th>Time of Sampling</th>
<th>Enyne added at 0 °C</th>
<th>Enyne added at 20 °C (A)</th>
<th>Enyne added at 20 °C (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Enyne</td>
<td>0.07 : 1 : 0</td>
<td>0 : 1 : 0</td>
<td>0 : 1 : 0</td>
</tr>
<tr>
<td>added</td>
<td>0.80 : 1 : 0.04</td>
<td>0.11 : 1 : 0.10</td>
<td>0 : 1 : 0.02</td>
</tr>
<tr>
<td>1 h</td>
<td>0.28 : 1 : 0.27</td>
<td>0 : 1 : 0.27</td>
<td>0 : 1 : 0.02</td>
</tr>
<tr>
<td>21 h</td>
<td>0 : 1 : 0.97</td>
<td>0 : 1 : 0.34</td>
<td>0 : 1 : 0.17</td>
</tr>
</tbody>
</table>

In all cases no dimerisation took place when only ⅓ the enyne had been added. Results showed that the reaction should not be carried out 0 °C as the rate of co-cyclisation is significantly reduced, resulting in a build up of the enyne 140 which leads to
dimerisation. The most interesting observation is that the amount of dimerisation observed increases with time. This is even observed in the reaction which had a deficiency of enyne 140. This shows that the enyne co-cyclisation must be a reversible process.

These observations led to the conclusion that the optimum co-cyclisation conditions were at 20 °C (rt) with a slight deficiency of enyne. The resulting zirconacyclopentene should be used immediately.

Intramolecular co-cyclisation of enyne 133 with Cp₂Zr(DMAP)₂ proved to be unsuccessful even under the optimal conditions described above. Even with very slow addition (1.5 h), significant amounts of the products of dimerisation were observed in the NMR spectra. Due to time constraints no other methods of co-cyclisation were attempted.

**4.3.3 5-Membered system**

Although several interesting mechanistic observations have been observed, attempts to develop a system capable of intramolecular trapping of zirconium η²-alkene complexes to give interesting bicyclic compounds have proved unsuccessful. Based on the conclusion drawn from those experiments a 5-membered all carbon system was proposed.

In an attempt to identify potential issues with the system as early as possible the following model system was studied. Synthesis of 148 was achieved by alkylating diethyl malonate with methylallyl chloride to afford 146. Alkylation of 146 with 1-bromohex-2-yne afforded 147. Enyne 147 was reduced to give the corresponding diol. Methylation of this diol gave the desired enyne 148 in 73% yield (Scheme 85).

![Scheme 85: Reagents and conditions: i. Methylallyl chloride, NaH, THF, 0 °C - rt, 72 h, 27% yield. ii. 1-bromohex-2-yne, Na, EtOH, 0 °C - rt, 18 h, 87%. iii. LiAlH₄, Et₂O, 0 °C - rt, 18 h, 89%. iv. NaH, MeI, THF, 0 °C - rt, 18 h, 73%.

```
```

```
Intramolecular co-cyclisation of enyne 148 with zirconocene(1-butene) gave zirconacyclopentene 149, which on quenching with HCl (aq) afforded 150 in 70% yield. Benzyl carbenoid insertion afforded zirconacyclohexene 151, which on quenching with HCl in Et₂O at –78 °C afforded 152 in 65% yield. Warming of zirconacyclohexene 151 to rt afforded the (E)-alkene 153 in 86% yield (Scheme 86).

Scheme 86: Reagents and conditions: i. ZrCp₂Cl₂, n-BuLi, THF, –78 °C - rt, 2 h. ii. 2 M HCl (aq), rt 18 h, 70% iii. BnCl, LDA, –78 °C, 5 min. iv. 2 M HCl in Et₂O, –78 °C - rt, 18 h, 65%. v. Warm to rt, 24 h. vi. 2 M HCl (aq), rt, 18 h, 86%.

Kinetic studies were carried out to gain greater insight into the cyclometallation process in systems with α-substituents. The results are highlighted Table 11.

<table>
<thead>
<tr>
<th>Zirconacyclohexene</th>
<th>Temp of cyclometallation (°C)</th>
<th>Half Life (min)</th>
<th>K (s⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>151a</td>
<td>–5</td>
<td>14.4</td>
<td>0.0008</td>
</tr>
<tr>
<td>151b</td>
<td>20</td>
<td>577</td>
<td>0.00002</td>
</tr>
</tbody>
</table>

Table 11: Summary of kinetic study.
As observed in the nitrogen system, diastereoisomer 151b cyclometallates at a much slower rate than diastereoisomer 151a. The rate of cyclometallation in the all carbon system 151 is comparable to the rate of cyclometallation in the nitrogen system 125.

These results show that both diastereoisomers undergo the cyclometallation process to give the (E)-alkene. As observed in the nitrogen series, having an α-substituent dramatically decreases the rate of cyclometallation of diastereoisomer 151b.

The results from this model system provided good evidence that the initial cyclisation and cyclometallation process should be successful. DFT relative energy calculations also predicted that the final co-cyclisation is a favourable process (Scheme 87).

![Scheme 87: DFT calculations.](image)

The proposed substrate was synthesised by the following route (Scheme 88). Alkylation of diethyl malonate with 2-methylenehex-5-enyl methanesulfonate 104 yielded 154 in 37% yield. Subsequent alkylation of 154 gave 155 in 72% yield. Reduction to the diol followed by methylation occurred cleanly to give 156 in 88% overall yield.
**Scheme 88: Reagents and condition:** i. Diethyl malonate, EtOH, Na, 20% NaI, EtOH, 0 °C - rt, 3 h, 37%. ii. hex-2-ynyl methanesulfonate, NaH, 20% NaI, THF, 0 °C - rt, 24 h, 72%. iii. LiAlH₄, Et₂O, 0 °C - rt, 3 h, 94%, iv. NaH, MeI, THF, 0 °C - rt, 4 h, 88%.

Intramolecular co-cyclisation of enyne 156 with zirconocene(1-butene) gave zirconacyclopentane 157, which afforded 158 on quenching with HCl (aq). Benzyl carbenoid insertion gave 160 on quenching, generated via zirconacyclohexene 159. Warming to rt for 24 h before quenching yielded an inseparable mixture of 160 and 162. To discover whether the final cyclisation was viable, it was decided to try and isolate the (E)-alkene 162 and then co-cyclise with zirconocene(1-butene) in a stepwise process. The (E)-alkene 162 was synthesised by adding 2-butyne to the reaction mixture to ensure rapid decomplexation of the zirconocene η²-alkene complex. The isolated (E)-alkene 162 was successfully co-cyclised with zirconocene(1-butene) to give the desired spirocyclic compound 164, in 68% yield as a 1:1 mixture of diastereoisomers. The two diastereoisomers were successfully separated by preparative HPLC.
Following the successful stepwise synthesis of the spirocyclic compound 164 it was speculated that the reason the final cyclisation failed in the tandem reaction sequence was due the diisopropylamine rapidly decomplexing the zirconocene $\eta^2$-alkene complex before the final cyclisation could occur. Closer inspection of GC traces taken during initial reactions showed that a small amount of the spirocyclic compound 164 was present in the reaction mixture, supporting the speculation. 2,2,6,6-Tetramethyl
piperidine is a bulky amine, unlike diisopropylamine, and therefore should not decomplex the zirconocene $\eta^2$-alkene complex 161 as rapidly. Therefore the benzyl carbenoid was generated with LiTMP rather than LDA.

After 3 h at rt a 1:2 mixture of (E)-alkene 162 and spirocyclic compound 164 was observed. The spirocyclic compound was initially formed as a 1:1 mixture of two diastereoisomers. After 24 h, epimerisation of the spirocyclic compound had occurred to only give one diastereoisomer. Separation of (E)-alkene 162 and spirocyclic compound 164 by column chromatography and preparative HPLC proved to be unsuccessful. NMR and GC confirmed a 2:1 mixture of 164 and 162.

4.4 Further work

Changing the base from LDA to LiTMP had a dramatic effect on the outcome of the reaction. It demonstrates that the amines are greatly aiding decomplexation of the zirconocene $\eta^2$-alkene complex. This leads us to consider other bases to form the carbenoids. Nucleophilic bases, such as BuLi, cannot be used as these will react with the zirconacycle. One way that these problems maybe overcome would be to use a benzyl carbamate instead of benzyl chloride to form the benzyl carbenoid. It was shown in Chapter 2 that benzyl carbamate carbenoids can be successfully inserted into zirconacycles. The literature reveals the benzyl carbamate carbenoids are much more stable than the carbenoid derived from benzyl chloride. In fact the benzyl carbamate carbenoids can be preformed by treating with secBuLi and are stable at –78 °C. The preformed carbenoid could then be added to the zirconacycle. As a non amine base will be used, hopefully the rate of the final cyclisation will be greater than the rate of decomplexation.

4.5 Conclusions

Several attempted intramolecular trappings of zirconocene $\eta^2$-alkene complexes have been reported. The most successful system was the all carbon system 156. It was shown that the concept of intramolecular trapping of zirconocene $\eta^2$-alkene complexes is feasible, however further work is needed to optimise this process. Further investigations of the endocyclic cyclometallation process to afford zirconocene $\eta^2$-alkene complexes
were carried out. It was concluded that α-substituents decrease the rate of cyclometallation.
5 Experimental

5.1 General experimental

All reactions involving air or moisture sensitive compounds were carried out under an argon atmosphere using standard Schlenk equipment and syringe techniques. All glassware was dried in a hot oven (>140 ºC, for at least 12 hours) and cooled in a sealed desiccator over silica gel.

Unless otherwise stated, reagents were obtained from commercial suppliers and if necessary dried and distilled before use. Solvents for air or moisture sensitive reactions were prepared in the following ways. THF and diethyl ether were freshly distilled from sodium benzophenone ketyl under argon. Dichloromethane was freshly distilled over CaH₂ under argon. n-Butyllithium was used as a 2.5 M solution in hexanes, stored in Schlenk stock bottles under argon. Lithium diisopropylamide was used as a 1.8 M solution, stored in stock bottles under argon. DIBAL-H was used as a 1 M solution in hexanes or a 1 M solution in toluene, stored in stock bottles under argon. Potassium bis(trimethylsilyl)amide was used as a 0.5 M solution in toluene, stored in stock bottles under argon. Lithium 2,2,6,6-tetramethylpiperidide was prepared from 2,2,6,6-tetramethylpiperidine (distilled, stored over 4Å sieves under argon) in THF by addition of 1 equivalent of n-BuLi at 0 ºC and stirring for 20 minutes.

NMR spectra were recorded on Bruker AV300, AM300 or DPX400 spectrometers. The chemical shifts, δ, were recorded as values in ppm referenced to the CHCl₃ peak at 7.27 ppm for ¹H spectra and to the CDCl₃ central peak of a 1:1:1 triplet at 77.00 ppm for ¹³C spectra or to the C₆D₅ peak at 7.16 ppm for ¹H spectra and to the C₆D₆ central peak of a 1:1:1 triplet at 128.1 ppm for ¹³C spectra. ²H spectra were referenced to the C₆H₅D peak at 0 ppm. The following abbreviations were used to denote multiplicity and may be compounded: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sxt = sextet, m = multiplet. Coupling constants, J, are measured in hertz (Hz). ¹³C spectra were proton decoupled. DEPT, COSY and ¹H-¹³C correlation experiments were used to aid assignment of spectra.
Electron impact ionisation mass spectra (EI) were recorded on a ThermoQuest TraceMS GCMS. Electrospray mass spectra (ES) were recorded using a VG platform quadrupole spectrometer. All electrospray spectra were ES$^+$ unless otherwise stated. All values of $m/z$ are reported in atomic mass units and the peak intensity relative to the base peak is reported in parenthesis. Only the most abundant isotope is reported for compounds containing chlorine. Accurate mass spectra were recorded on a VG analytical 70-250-SE double focusing mass spectrometer using electron impact ionisation (EI) at 70eV or a Bruker Apex III using electrospray ionisation.

Infra-red spectra were run as neat films on a Thermo Mattson FTIR Golden Gate spectrometer and a Thermo Nicolet 380 FT-IR spectrometer with a Smart Orbit Goldengate attachment. Absorptions are given in wavenumbers (cm$^{-1}$) and the following abbreviations used to denote peak intensities: $s$ = strong, $m$ = medium, $w$ = weak.

Thin layer chromatography was carried out on aluminium backed silica plates and spots visualized by UV (254 nm lamp), phosphomolybdic acid or permanganate stains. Flash column chromatography on silica gel was performed on Kieselgel 60 (230-400 mesh) silica gel. Columns were packed and run under light pressure. Solvent compositions are described as ratios prior to mixing.

Gas chromatography was performed on a Hewlett Packard HP 6890 series GC system, using a HP-5 (cross-linked 5% Ph Me siloxane) 30 m column, with a film thickness of 0.25 μm and 0.32 mm internal diameter. The carrier gas was helium and the flow rate was 2.7 mL min$^{-1}$. Peak areas were determined using the standard intergrator in Chem Station 6.

<table>
<thead>
<tr>
<th>GC Method A</th>
<th>GC Method B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injector temperature: 200 °C</td>
<td>Injector temperature: 200 °C</td>
</tr>
<tr>
<td>Initial temperature: 80 °C</td>
<td>Initial temperature: 80 °C</td>
</tr>
<tr>
<td>Ramp: 25 °C per min</td>
<td>Ramp: 25 °C per min</td>
</tr>
<tr>
<td>Final temperature: 250 °C held for 4 min</td>
<td>Final temperature: 300 °C held for 5 min</td>
</tr>
</tbody>
</table>
The following compounds were prepared according to literature procedures: 1-(hept-6-en-1-ynyl)benzene $^{1,21}$ undec-1-en-6-yne$^{21}$ 1-(oct-7-en-1-ynyl)benzene$^{21}$ dodec-1-en-7-yne$^{21}$ 6-phenylpent-5-yn-1-ol $^{31,85}$ 4,4-bis(methoxymethyl)hepta-1,6-diene $^{70,36}$ benzyl 3,3-dimethyl-1-oxa-4-azaspiro[4.5]decane-4-carboxylate $^{75,1}$ and 2-methyloct-1-en-6-yne $^{140,21}$
5.2 **Kinetic experiments**

**General Procedure**

To a stirred solution of zirconocene dichloride (0.292 g, 1.0 mmol) in THF (5 mL) at –78 °C was added n-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 2 min. The solution was stirred at –78 °C for a further 30 min before dropwise addition of a solution of enyne (1.0 mmol) in THF (2 mL). After stirring for a further 30 min at –78 °C the solution was warmed to rt and stirred for a further 2 h. The solution was re-cooled to –78 °C followed by dropwise addition of the benzyl chloride derivative (1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). The solution continued to stir for 15 min at –78 °C before being warmed to the required temperature. Samples (0.1 mL) were removed from the reaction mixture and quenched with 2 M HCl (aq) (1.5 mL) at timed intervals. Et₂O (1 mL) was added to the quenched sample. The Et₂O layer was separated and passed through a short plug of MgSO₄ in Pasteur pipette. The samples were analysed by GC.
### GC retention times and experimental conditions

<table>
<thead>
<tr>
<th>Zirconacycle</th>
<th>GC retention time (min)</th>
<th>Temperature of cyclometallation (°C)</th>
<th>GC method</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Quenched zirconacycle</td>
<td>(E)-alkene</td>
<td>(Z)-alkene</td>
</tr>
<tr>
<td>3</td>
<td>7.89 (4) 8.22 (6a) 7.74 (6b)</td>
<td>20</td>
<td>A</td>
</tr>
<tr>
<td>37</td>
<td>9.72 (38) 10.52 (39a) 9.50 (39b)</td>
<td>20</td>
<td>A</td>
</tr>
<tr>
<td>40</td>
<td>9.03 (41) 9.49 (42a) 8.70 (42b)</td>
<td>20</td>
<td>A</td>
</tr>
<tr>
<td>43</td>
<td>6.18 (44) 6.38 (45a) 6.07 (45b)</td>
<td>20</td>
<td>A</td>
</tr>
<tr>
<td>46</td>
<td>7.85 (47) 8.32 (48a) -</td>
<td>−60&lt;sup&gt;a&lt;/sup&gt;</td>
<td>A</td>
</tr>
<tr>
<td>49</td>
<td>6.37 (50) 6.64 (51a) -</td>
<td>−60</td>
<td>A</td>
</tr>
<tr>
<td>124</td>
<td>10.35 (126) 10.63 (128) -</td>
<td>20&lt;sup&gt;a&lt;/sup&gt;</td>
<td>B</td>
</tr>
<tr>
<td>125</td>
<td>8.34 (127) 8.50 (129) -</td>
<td>20&lt;sup&gt;a&lt;/sup&gt;</td>
<td>B</td>
</tr>
<tr>
<td>151</td>
<td>7.73 (152) 7.85 (153) -</td>
<td>−5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>A</td>
</tr>
</tbody>
</table>

<sup>a</sup> Temperature of cyclometallation of diastereoisomer a. <sup>b</sup> Temperature of cyclometallation of diastereoisomer b.
5.3 (E)-2-(2-Benzylidenecyclopentyl)ethyl)benzene 4

To a stirred solution of zirconocene dichloride (0.292 g, 1.0 mmol) in THF (5 mL) at −78 °C was added n-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 2 min. The solution was stirred at −78 °C for a further 30 min before dropwise addition of a solution of 1-(hept-6-en-1-ynyl)benzene (0.170 g, 1.0 mmol) in THF (2 mL). After stirring for a further 30 min at −78 °C the solution was warmed to rt and stirred for a further 2 h. The solution was re-cooled to −78 °C before the dropwise addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). The solution continued to stir for a further 30 min before the addition of 2 M HCl in Et₂O (5 mL). The mixture was stirred for a further 18 h while warming to rt. The mixture was diluted with Et₂O (10 mL), washed with water (3 x 50 mL) and brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: hexane) yielded the title compound (0.162 g, 0.62 mmol, 62%) as a colourless oil.

**^1H NMR (300 MHz, CDCl₃):** δ 7.28-7.08 (10H, m, Ar-H), 6.25 (1H, apparent q, J = 2.2 Hz), 2.79-2.49 (5H, m), 2.07-1.79 (3H, m), 1.71-1.54 (2H, m), 1.39 (1H, m) ppm.

**^13C NMR (75 MHz, CDCl₃):** δ 150.21 (C, Cf), 142.70 (C, Cm), 138.83 (C, Cd), 128.38 (CHx2), 128.32 (CHx2), 128.14 (CHx2), 128.13 (CHx2), 125.69 (CH), 125.67 (CH), 120.82 (CH, Ce), 45.87 (CH, Cj), 36.66 (CH₂), 34.09 (CH₂), 31.75 (CH₂), 31.53 (CH₂), 24.88 (CH₂, Ch) ppm.

**IR ν_max/cm⁻¹ (film):** 1600 (m), 1490 (m), 1450 (m), 745 (m), 693 (s).

**LRMS (EI, CH₂Cl₂):** m/z 262 ([M⁺], 15%), 158 (40%), 129 (65%), 91 (100%).

**HRMS (EI):** C₂₀H₂₂ [M⁺] calculated 262.1722, found 262.1727.
When the reaction mixture was quenched with MeOD (3 mL) followed by D$_2$O (3 mL) the following bis-deuterated compound 5 was produced. The following changes in the $^1$H and $^{13}$C NMR were observed.

1H NMR (300 MHz, C$_6$D$_6$): $\delta$ 2.76 (0.5H, m, HI), 2.63 (0.5H, m, HI) ppm.

13C NMR (75 MHz, C$_6$D$_6$): $\delta$ 120.95 (C, t, $J = 23.0$, Ce), 33.82 (CH, t, $J = 19.4$, CI) ppm.

2H NMR (61 MHz, C$_6$H$_6$): $\delta$ -0.92 (De), -4.64 (Di), -4.75 (Di) ppm.
5.4 1-((E)-2-((E)-2-Benzylidencyclopentyl)vinyl)benzene 6a and 1-((Z)-2-((E)-2-Benzylidencyclopentyl)vinyl)benzene 6b

To a stirred solution of zirconocene dichloride (0.292 g, 1.0 mmol) in THF (5 mL) at –78 °C was added n-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 2 min. The solution was stirred at –78 °C for a further 30 min before dropwise addition of a solution of 1-(hept-6-en-1-ynyl)benzene (0.170 g, 1.0 mmol) in THF (2 mL). After stirring for a further 30 min at –78 °C the solution was warmed to rt and stirred for a further 2 h. The solution was re-cooled to –78 °C followed by dropwise addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). The solution continued to stir for 15 min at –78 °C before being warmed to reflux. The solution was stirred for a further 3 h before cooling to rt and the addition of 2 M HCl (aq) (5 mL). The mixture was stirred for 18 h before being extracted with Et₂O (50 mL). The organic layer was washed with water (3 x 50 mL) and brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: hexane) yielded a 1:1 mixture of the title compounds (0.135 g, 0.52 mmol, 52%) as a colourless oil. NMR of the crude product showed a 1:1 ratio of the (E)- and (Z)-isomers.

**1H NMR (300 MHz, CDCl₃):** δ 7.38-7.09 (20H, m, Ar-H), 6.59 (1H, d, J = 11.5, Hf), 6.58 (1H, d, J = 15.9, Hi), 6.25 (1H, apparent q, J = 2.4, He), 6.21 (1H, apparent q, J = 2.4, He'), 6.11 (1H, dd, J = 15.7, 8.4, Hk), 5.53 (1H, dd, J = 11.5, 9.9, Hk'), 3.66 (1H, m, Hj), 3.27 (1H, m, Hj'), 2.73-2.25 (4H, m), 2.07-1.85 (4H, m), 1.71-1.37 (4H, m) ppm.

**13C NMR (75 MHz, CDCl₃):** δ 148.70 (C, Cf/Cf'), 148.58, (C, Cf/Cf'), 138.57 (C, Cd/Cd'), 138.50 (C, Cd/Cd'), 137.62 (C, Cm/Cm'), 137.51 (C, Cm/Cm'), 134.75 (CH, Ck'), 133.06 (CH, Ck), 130.57 (CH, Cl), 129.86 (CH, Ct), 128.50 (CHx2), 128.36 (CHx2), 128.25 (CHx2), 128.18 (CHx4), 128.10 (CHx4), 127.00 (CH), 126.78
(CH), 126.12 (CHx2), 125.91 (CHx2), 122.85 (CH, Ce/Ce''), 122.23 (CH, Ce/Ce''), 51.00 (CH, Cj), 46.26 (CH, Cj'''), 34.14 (CH₂, Cg/Cg'''), 33.64 (CH₂, Cg/Cg''), 31.58 (CH₂, Ch/Ch'''), 31.31 (CH₂, Ch/Ch''), 25.4 (CH₂, Ci/Ci'''), 25.3 (CH₂, Ci/Ci'') ppm.

IR νmax/cm⁻¹ (film): 1600 (w), 1490 (m), 1446 (m), 745 (s), 691 (s).

LRMS (EI, CH₂Cl₂): m/z 260 ([M⁺], 35%), 169 (55%), 141 (90%), 115 (90%), 91 (80%).

To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF at –78 °C was added n-BuLi (2.5 M solution in hexanes) (2.0 mmol, 0.80 mL) dropwise over 2 min. After 30 min a solution of 1-(hept-6-en-1-ynyl)benzene (0.172 g, 1.0 mmol) was added dropwise. After 30 min the reaction mixture was warmed to rt for 2 h. The solution was re-cooled to −78 °C before the addition of benzyl chloride (0.12 mL, 1.0 mmol) followed by LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). The reaction mixture was stirred for 5 min at -78 °C before the addition of acetone (0.290 g, 5.0 mmol). The reaction mixture was stirred for a further 30 min at -78 °C before warming to rt for 20 h. The reaction mixture was quenched with MeOH (5 mL) and sat NaHCO₃ (aq) (5 mL) and stirred for 2 h. The resulting mixture was diluted with Et₂O (30 mL), washed with H₂O (3 x 50 mL) and brine (3 x 50 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: 15% Et₂O in hexane) gave firstly the title compound (0.112 g, 0.35 mmol, 35%) as a colourless oil followed by 25 (0.019 g, 0.06 mmol, 6%) and an inseperable mixture of 6a and 6b (0.078 g, 0.3 mmol, 30%).

Data for compound 23.

**¹H NMR (300 MHz, CDCl₃):** δ 7.39-7.17 (10H, m, Ar-H), 6.88 (1H, s, He), 6.50 (1H, d, J = 10.0, Hk), 3.55 (1H, d, J = 10.0, Hl), 2.72-2.65 (2H, m), 2.49 (1H, m), 2.29 (1H, m), 1.81-1.63 (2H, m), 1.56 (1H, s, OH), 1.28 (3H, s, Hr/s), 1.22 (3H, s, Hr/s) ppm.

**¹³C NMR (75 MHz, CDCl₃):** δ 144.46 (C), 143.03 (C), 141.51 (C), 138.27 (C), 129.36 (CHx2), 128.75 (CHx2), 128.22 (CHx2), 128.19 (CHx2), 126.57 (CH, Ca/p), 126.21 (CH, Ca/p), 118.66 (CH, Ce/k), 118.40 (CH, Ce/k), 73.20 (C, Cq), 57.12 (CH, Cl),
32.66 (CH$_2$, Cg/ i), 29.69 (CH$_2$, Cg/i), 28.24 (CH$_3$, Cr/s), 27.54 (CH$_3$, Cr/s), 24.22 (CH$_2$, Ch) ppm.

IR $v_{\text{max}}$/cm$^{-1}$ (film): 3445 (br), 1595 (w), 1489 (w), 1444 (w), 907 (s), 726 (s), 692 (s).

LRMS (ES, H$_2$O): m/z 341 ([M + Na]$^+$, 100%).

HRMS (ES): C$_{23}$H$_{26}$NaO [M + Na]$^+$ calculated 341.1876, found 341.1871.

Data for compound 25.

$^1$H NMR (300 MHz, CDCl$_3$): δ 7.42-7.13 (4H, m, Ar-H), 7.29-7.13 (7H, m, Ar-H + Hn), 6.43 (1H, d, $J = 15.9$, Ho), 3.92 (1H, s, He), 2.89 (1H, m, Hj), 2.60-2.45 (3H, m, Hj, Hl), 1.84-1.65 (2H, m, Hk), 1.44 (1H, s, OH), 1.23 (3H, s, Hh/g), 1.16 (3H, s, Hh/g) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$): δ 142.84 (C), 140.85 (C), 138.17 (C), 137.37 (C), 129.72 (CHx2), 129.28 (CH, Co), 128.60 (CHx2), 128.23 (CHx2), 127.15 (CH), 126.44 (CH), 126.30 (CHx2), 123.23 (CH, Cn), 73.97 (C, Cf), 55.66 (CH, Ce), 36.59 (CH$_2$, Cj), 32.85 (CH$_2$, Cl), 29.85 (CH$_3$, Ch/g), 29.56 (CH$_3$, Ch/g), 22.17 (CH$_2$, Ck) ppm.

IR $v_{\text{max}}$/cm$^{-1}$ (film): 3489 (br), 1622 (w), 1486 (m), 1448 (m), 952 (s), 756 (s), 688 (s).

LRMS (ES, H$_2$O): m/z 341 ([M + Na]$^+$, 100%).

HRMS (ES): C$_{23}$H$_{26}$NaO [M + Na]$^+$ calculated 341.1876, found 341.1872.
5.6 1-(7,7-Dibromohept-6-en-1-ynyl)benzene 33

**Synthesis of 6-Phenylhex-5-ynal 32:** Synthesis was carried out using a procedure published by Tanaka *et al.*\(^{70}\) A solution of DMSO (3.3 mL, 46.5 mmol) in CH\(_2\)Cl\(_2\) (20 mL) was added to a solution of oxalyl chloride (2.93 g, 23.1 mmol) at –78 °C. The resulting mixture was stirred at –78 °C for 15 min before the addition of 6-phenylhex-5-yn-1-ol (3.06 g, 17.6 mmol). The reaction mixture was stirred for a further 1 h at –78 °C before the addition of Et\(_3\)N (18.3 mL, 132 mmol). The solution was warmed to rt for 1 h before being quenched by the addition of H\(_2\)O (50 mL) and extracted with CH\(_2\)Cl\(_2\) (3 x 50 mL). The combined organic extracts were washed sat NH\(_4\)Cl (aq) (50 mL), dried (MgSO\(_4\)) and the solvent removed *in vacuo*. Purification by column chromatography (eluent: 20% Et\(_3\)O in hexane) yielded the title compound (2.92 g, 16.9 mmol, 96%) as a colourless oil. The compound was immediately used in the next reaction. \(^1\)H NMR data was consistent with published data.\(^{70}\)

\(^1\)H NMR (300 MHz, CDCl\(_3\)): δ 9.82 (1H, t, \(J = 1.3\), Hj), 7.37 (2H, m, Ar-H), 7.29-7.24 (3H, m, Ar-H), 2.64 (2H, td, \(J = 7.2\), 1.3, Hi), 2.49 (2H, t, \(J = 6.9\), Hg), 1.92 (2H, quin, \(J = 7.0\), Hh) ppm.

**Synthesis of 1-(7,7-Dibromohept-6-en-1-ynyl)benzene 33:** Synthesis was carried out using a procedure published by Uenishi *et al.*\(^{71}\) To a stirred solution of CBr\(_4\) (4.64 g, 14 mmol) in CH\(_2\)Cl\(_2\) (20 mL) at 0 °C was added PPh\(_3\) (7.34 g, 28 mmol) in CH\(_2\)Cl\(_2\) (20 mL). The resulting solution was warmed to rt for 1 h before the addition of 6-phenylhex-5-ynal (1.32 g, 7 mmol) in CH\(_2\)Cl\(_2\) (20 mL). The resulting solution was stirred for 30 min and the solvent removed *in vacuo*. Purification by column chromatography (eluent: hexane) yielded the title compound (1.605 g, 4.9 mmol, 70%) as a colourless oil.

\(^1\)H NMR (300 MHz, CDCl\(_3\)): δ 7.39 (2H, m, Ar-H), 7.28-7.24 (3H, m, Ar-H), 6.44 (1H, t, \(J = 7.3\), Hj), 2.44 (2H, t, \(J = 7.0\), Hg), 2.28 (2H, q, \(J = 7.5\), Hi), 1.73 (2H, quin, \(J = 7.2\), Hh) ppm.
$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 137.74 (CH, Cj), 131.54 (CHx2, Cc), 128.19 (CHx2, Cb), 127.65 (CH, Ca), 123.73 (C, Cd), 89.54 (C, Ck), 89.04 (C, Cf), 81.39 (C, Ce), 32.24 (CH$_2$, Ci), 26.50 (CH$_2$, Ch), 18.80 (CH$_2$, Cg) ppm.

IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 1597 (w), 755 (s), 692 (s).

LRMS (EI, CH$_2$Cl$_2$): m/z 328 ([M$^+$], 2% (C$_{13}$H$_{12}$Br$_{79}$/Br$^{81}$Br)), 168 (72%), 168 (100%), 115 (80%).
5.7 (6Z)-(7-2H1)Hept-6-en-1-yn-1-ylbenzene 26a

Synthesis of (7-2H)hepta-1,6-diyln-1-ylbenzene 34: To a stirred solution of 1-(7,7-dibromohept-6-en-1-ynyl)benzene (0.984 g, 3 mmol) in THF (5 mL) at –78 °C was added n-BuLi (2.5 M solution in hexanes) (2.4 mL, 6 mmol). The solution was stirred for 30 min at –78 °C before the dropwise addition of D2O (1 mL). The solution was warmed to rt for 1 h before being extracted with Et2O (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried (MgSO4) and the solvent removed in vacuo to yield the compound (0.420 g, 2.5 mmol, 83%) as a colourless oil. The compound was used without any further purification.

1H NMR (400 MHz, CDCl3): δ 7.36-7.34 (3H, m, Ar-H), 7.24 (2H, m, Ar-H), 2.51 (2H, t, J = 7.0, Hg), 2.34 (2H, t, J = 7.0, Hi), 1.80 (2H, quin, J = 7.0, Hh) ppm.

Synthesis of (6Z)-(7-2H1)hept-6-en-1-yn-1-ylbenzene 26a: Synthesis was carried out following a procedure by Negishi et al. A solution of ZrCp2HCl was prepared by treating ZrCp2Cl2 (1.46 g, 5 mmol) in THF (5 mL) with DIBAL-H (1 M in hexanes) (5 mL, 5 mmol), at 0 °C for 30 min. The resulting mixture was added portionwise to a solution of diyne 34 (0.419 g, 2.5 mmol) in THF (5 mL) at rt and monitored by GC until hydrozirconation was complete. The mixture was poured onto saturated sodium potassium tartrate solution (50 mL), stirred for 18 h at rt then extracted with Et2O (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried (MgSO4) and the solvent removed in vacuo. Purification by column chromatography (eluent: hexane) yielded the title compound (0.197 g, 1.2 mmol, 48%) as a colourless oil.

Data was consistent with known un-deuterated compound.

1H NMR (300 MHz, CDCl3): δ 7.39-7.36 (2H, m, Ar-H), 7.26-7.23 (3H, m, Ar-H), 5.81 (1H, m, Hj), 4.99 (1H, d, J = 10.3, Hk), 2.42 (2H, t, J = 7.1, Hg), 2.23 (2H, q, J = 7.1, Hi), 1.71 (2H, quin, J = 7.1, Hh) ppm.
\(^{13}\)C NMR \((75 \text{ MHz, CDCl}_3)\): \(\delta\) 137.79 (CH, Cj), 131.52 (CHx2, Cc), 128.16 (CHx2, Cb), 127.49 (CH, Ca), 123.98 (C, Cd), 114.90 (CH, t, \(J = 23.8\), Ck), 89.93 (C, Cf), 80.85 (C, Ce), 32.79 (CH\(_2\), Ci), 27.91 (CH\(_2\), Ch), 18.80 (CH\(_2\), Cg) ppm.

IR \(\nu_{\text{max}}/\text{cm}^{-1}\) \((\text{film})\): 1617 (w), 1598 (w), 1489 (m), 799 (s), 753 (s), 690 (s).

LRMS (EI, CH\(_2\)Cl\(_2\)): m/z 171 ([M\(^+\)], 12%), 143 (60%), 115 (100%).

HRMS (EI): C\(_{13}\)H\(_{13}\)D [M\(^+\)] calculated 171.1158, found 171.1159.

GC (Method A): 34 – 4.36 min and 26a – 4.22 min
5.8 \(((E)-2-((E)-2\text{-Phenylethenyl})\text{cyclopentylidene})(^{2}\text{H})\text{methyl})\text{ benzene} \ 36a, \ ((E)-2-((Z)-2\text{-Phenylethenyl})\text{cyclopentylidene})\n
\((^{2}\text{H})\text{methyl})\text{ benzene} \ 36b\text{ and } ((E)-2-((2E)-2-\text{Benzylidenecyclopentyl})(2\text{-^{2}\text{H})ethenyl})\text{ benzene} \ 36c\n
To a stirred solution of zirconocene dichloride (0.292 g, 1.0 mmol) in THF (5 mL) at –78 °C was added \(n\)-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 2 min. The solution was stirred at –78 °C for a further 30 min before dropwise addition of a solution of enyne \(26a\) (0.171 g, 1.0 mmol) in THF (2 mL). After stirring for a further 30 min at –78 °C the solution was warmed to rt and stirred for a further 2 h. The solution was re-cooled to –78 °C followed by dropwise addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). After 30 min at –78 °C the reaction mixture was warmed to rt. The reaction mixture was stirred for 72 h at rt before being quenched with 2 M HCl (aq) (5 mL). The reaction mixture was stirred for 18 h at rt before being extracted with Et\(_2\)O (50 mL). The organic layer was washed with water (3 x 50 mL) and brine (50 mL), dried (MgSO\(_4\)) and the solvent removed \textit{in vacuo}. Purification by column chromatography on silica gel (eluent: hexane) yielded the title compounds (0.188 g, 0.72 mmol, 72\%) as a colourless oil. The compounds were isolated as an inseparable 2:1:1 mixture of isomers determined from the NMR of the crude compounds.

The following differences were observed in the \(^1\text{H} \text{NMR}\) when compared with compounds \(6a\) and \(6b\) data.

\(^1\text{H} \text{NMR (300 MHz, CDCl}_3): \delta 6.65 (1H, d, J = 11.5, \text{H}^\prime), 6.51-6.44 (3H, m, \text{H}l + \text{H}l^\prime), 6.25 (1H, \text{apparent q, } J = 2.4, \text{H}e^\prime), 6.17 (2H, dd, J = 15.8, 8.4, \text{H}k), 5.60 (1H, dd, J = 11.5, 9.9, \text{H}k^\prime) \text{ ppm}.\n
\[\text{C}_{20}\text{H}_{19}\text{D} \quad \text{Mol. Wt.: 261.38} \]
GCMS (EI, CH\textsubscript{2}Cl\textsubscript{2}): (Z)-alkene - 9.85 min: 261 (40%), 91 (100%) and (E)-alkene 10.07 min: 261 (20%), 91 (100%).

5.9 Kinetic isotope experiment

To a stirred solution of zirconocene dichloride (0.292 g, 1.0 mmol) in THF (5 mL) at –78 °C was added n-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 2 min. The solution was stirred at –78 °C for a further 30 min before dropwise addition of a solution of 1-(hept-6-en-ynyl)benzene (0.085 g, 0.5 mmol) and enyne 26a (0.0.86 g, 0.5 mmol) in THF (2 mL). After stirring for a further 30 min at –78 °C the solution was warmed to rt and stirred for a further 2 h. The solution was re-cooled to –78 °C followed by dropwise addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). After 10 min at –78 °C the reaction mixture was warmed to 20 °C by placing in a water bath. Samples (0.2 mL) were removed from the reaction mixture and quenched with 2 M HCl (aq) (1.5 mL) and timed intervals. Et\textsubscript{2}O (1 mL) was added to the quenched sample. The Et\textsubscript{2}O layer was separated and passed through a short plug of MgSO\textsubscript{4} in Pasteur pipette. The samples were analysed by GCMS.

GCMS conditions:
Gas chromatography was performed on a ThermoQuest trace MS, using a Zebron 30 m column, with a film thickness of 0.25 μm and 0.25 mm internal diameter. The carrier gas was helium and the flow rate was 1 mL min\textsuperscript{-1}.
Injector Temperature: 220 °C
Initial Temperature: 60 °C
Ramp: 40 °C per min
Final Temperature: 320 °C held for 6 min
The following compound was prepared using the same method as for compound 4 but using \( p \)-methoxybenzyl chloride (0.156 g, 1 mmol) in place of benzyl chloride. Purification by column chromatography on silica gel (eluent: 5% EtOAc in hexane) yielded the title compound (0.184 g, 0.63 mmol, 63%) as a colourless oil.

\(^1\)H NMR (300 MHz, \( \text{CDCl}_3 \)): \( \delta \) 7.33-7.32 (4H, m, Ar-H), 7.23-7.15 (3H, s, Ar-H), 6.88-6.84 (2H, m, Ar-H), 6.29 (1H, apparent q, \( J = 2.3 \), He), 3.81 (3H, s, Hq), 2.78-2.55 (5H, m), 2.19-2.07 (3H, m), 1.70-1.58 (2H, m), 1.41 (1H, m) ppm.

\(^{13}\)C NMR (75 MHz, \( \text{CDCl}_3 \)): \( \delta \) 157.66 (C, Cp), 150.32 (C, Cf), 138.82 (C, Cd), 134.76 (C, Cm), 129.23 (CHx2), 128.12 (CHx4), 125.66 (CH, Ca), 120.71 (CH, Ce), 113.74 (CHx2, Co), 55.25 (CH\(_3\), Hq), 45.81 (CH, Cj), 36.90 (CH\(_2\)), 33.15 (CH\(_2\)), 31.75 (CH\(_2\)), 31.56 (CH\(_2\)), 24.89 (CH\(_2\), Ch) ppm.

IR \( \nu_{\text{max}}/\text{cm}^{-1} \) (film): 1610 (w), 1580 (w), 1510 (m), 1490 (m), 1440 (m).

LRMS (EI, \( \text{CH}_2\text{Cl}_2 \)): \( m/z \) 292 ([M\(^+\)], 5%), 207 (20%), 134 (90%), 121 (100%).

HRMS (EI): \( \text{C}_{21}\text{H}_{25}\text{O} [\text{M}\(^+\)] \) calculated 292.1827, found 292.1833.
5.11 1-((E)-2-((E)-2-Benzylidenecyclopentyl)vinyl)-4-methoxybenzene 39a and 1-((Z)-2-((E)-2-Benzylidenecyclopentyl)vinyl)-4-methoxybenzene 39b

To a stirred solution of zirconocene dichloride (0.292 g, 1.0 mmol) in THF (5 mL) at –78 °C was added n-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 2 min. The solution was stirred at –78 °C for a further 5 min before dropwise addition of a solution of 1-(hept-6-en-1-ynyl)benzene (0.170 g, 1.0 mmol) in THF (2 mL). After stirring for a further 30 min at –78 °C the solution was warmed to rt and stirred for a further 2 h. The solution was re-cooled to –78 °C followed by the dropwise addition of p-methoxybenzyl chloride (0.156 g, 0.14 mL, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). The solution was stirred for 3 min before the addition of CH₂Cl₂ (0.2 mL, 3 mmol). The solution continued to stir for 15 min at –78 °C before being warmed to rt. The solution was stirred for a further 24 h before the addition of 2 M HCl (aq) (5 mL). The mixture was stirred for 18 h before being extracted with Et₂O (50 mL). The organic layer was washed with water (3 x 50 mL) and brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: hexane - 5% Et₂O in hexane) yielded a 1:1 mixture of the title compounds (0.140 g, 0.48 mmol, 48%) as a colourless oil. NMR of the crude product showed a 1:1 ratio of the (E)- and (Z)-isomers

¹H NMR (400 MHz, CDCl₃): δ 7.38-7.26 (12H, m, Ar-H), 7.20-7.17 (2H, m, Ar-H), 6.90-6.86 (4H, m, Ar-H), 6.60 (1H, d, J = 11.3, Hl'), 6.43 (1H, d, J = 15.6, Hl), 6.30 (1H, q, J = 2.3 He), 6.26 (1H, q, J = 2.3, He'), 6.02 (1H, dd, J = 15.8, 8.3, Hk), 5.51 (1H, dd, J = 11.3, 9.8, Hk'), 3.82 (6H, s, Hq, q'), 3.71 (1H, m), 3.32 (1H, m), 2.82-2.73 (2H, m), 2.69-2.59 (2H, m), 2.06-1.93 (4H, m), 1.76-1.66 (2H, m), 1.59-1.40 (2H, m) ppm.
$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 158.81 (C, Cp/p$^\prime$), 158.50 (C, Cp/p$^\prime$), 148.87 (C, Cf/f$^\prime$), 148.78 (C, Cf/f$^\prime$), 138.63 (C, Cd/d$^\prime$), 138.56 (C, Cd/d$^\prime$), 133.32 (CH), 130.94 (C, Cm/m$^\prime$), 129.94 (C, Cm/m$^\prime$), 129.53 (CH), 129.33 (CH), 128.18 (CHx5), 128.08 (CHx4), 127.21 (CHx4), 125.88 (CHx2), 122.68 (CH, Ce/e$^\prime$), 122.08 (CH, Ce/e$^\prime$), 113.95 (CHx2, Co/o$^\prime$), 113.70 (CHx2, Co/o$^\prime$), 55.32 (CH$_3$, Cq/q$^\prime$), 55.26 (CH$_3$, Cq/q$^\prime$), 51.05 (CH, Cj/j$^\prime$), 46.35 (CH, Cj/j$^\prime$), 34.19 (CH$_2$), 33.74 (CH$_2$), 31.56 (CH$_2$), 31.31 (CH$_2$), 25.41 (CH$_2$), 25.30 (CH$_2$) ppm.

IR $\nu_{max}$/cm$^{-1}$ (film): 1606 (m), 1509 (s), 1301 (s), 1248 (s).

LRMS (EIMS, CH$_2$Cl$_2$): m/z 290 ([M$^+$], 80%), 121 (100%).

HRMS (EI): C$_{21}$H$_{24}$O [M$^+$] calculated 290.1671, found 290.1670.
The following compound was prepared using the same method as for compound 4 but using p-chlorobenzyl chloride (0.160 g, 1 mmol) in place of benzyl chloride. Purification by column chromatography on silica gel (eluent: hexane) yielded the title compound (0.233 g, 0.88 mmol, 88%) as a colourless oil.

\[ \text{C}_{20}\text{H}_{21}\text{Cl} \]

Mol. Wt.: 296.83

**\(^1\text{H NMR (400 MHz, CDCl}_3\):** δ 7.32-7.31 (4H, m Ar-H), 7.28-7.26 (2H, m, Ar-H), 7.19-7.15 (3H, m, Ar-H), 6.26 (1H, apparent q, J = 2.4, He), 2.80-2.54 (5H, m), 2.05-1.85 (3H, m), 1.70-1.60 (2H, m), 1.40 (1H, m) ppm.

**\(^{13}\text{C NMR (100 MHz, CDCl}_3\):** δ 150.01 (C, Cf), 141.10 (C, Cm), 138.71 (C, Cd), 131.37 (C, Cp), 129.72 (CHx2), 128.41 (CHx2), 128.16 (CHx4), 125.77 (CH), 120.91 (CH, Ce), 45.75 (CH, Cj), 36.56 (CH\(_2\)), 33.42 (CH\(_2\)), 31.72 (CH\(_2\)), 31.52 (CH\(_2\)), 24.89 (CH\(_2\), Ch) ppm.

**IR \(v_{\text{max}}/\text{cm}^{-1} (\text{film})\):** 1713 (m), 1588 (w) 1491 (s), 1447 (m), 1081 (s), 1014 (s), 695 (s).

**LRMS (EI, CH\(_2\)Cl\(_2\)):** m/z 296 ([M\(^+\)], 20%), 158 (30%), 158 (70%), 129 (80%), 91 (100%).

**HRMS (EI):** C\(_{20}\)H\(_{21}\)\(^{35}\)Cl [M\(^+\)] calculated 296.1332, found 296.1331.
5.13 1-((E)-2-((E)-2-Benzylidenecyclopentyl)vinyl)-4-chlorobenzene \(42a\) and 1-((Z)-2-((E)-2-Benzylidenecyclopentyl)vinyl)-4-chlorobenzene \(42b\)

The following compound was prepared using the same method as for compound \(39\) but using \(p\)-methoxybenzyl chloride (0.160 g, 1 mmol) in place of \(p\)-chlorobenzyl chloride. Purification by column chromatography on silica gel (eluent: hexane) yielded a 1:1 mixture of the title compounds (0.148 g, 0.50 mmol, 50%) as a colourless oil. NMR of the crude product showed a 1:1 ratio of the (E)- and (Z)-isomers

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.32-7.12 (18H, m, Ar-H), 6.56 (1H, d, \(J = 11.4, \text{H}^\text{I}\)), 6.41 (1H, d, \(J = 15.7, \text{H}^\text{I}\)), 6.25-6.21 (2H, m, He, e\(^{\prime}\)), 6.11 (1H, dd, \(J = 15.7, 8.4, \text{H}^\text{k}\)), 5.59 (1H, dd, \(J = 11.4, 9.8, \text{H}^\text{k}\)), 3.62 (1H, m, H\(_j\)), 3.52 (1H, m, H\(_j\)), 2.80-2.54 (4H, m), 2.03-1.89 (4H, m), 1.72-1.38 (4H, m) ppm.

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 148.42 (C, Cf/ f\(^{\prime}\)), 148.39 (C, Cf/ f\(^{\prime}\)), 138.46 (C, Cd/ d\(^{\prime}\)), 138.37 (C, Cd/d\(^{\prime}\)), 136.08 (C, Cm/m\(^{\prime}\)), 135.58 (C, Cm/m\(^{\prime}\)), 135.41 (CH), 133.81 (CH), 132.54 (Cx2, C\(_p\), p\(^{\prime}\)), 129.64 (CH), 129.33 (CH), 128.70 (CHx2), 128.61 (CHx4), 128.41 (CHx4), 128.17 (CHx4), 128.08 (CHx2), 127.31 (CH), 126.02 (CH), 122.94 (CH, Ce/e\(^{\prime}\)), 122.27 (CH, Ce/e\(^{\prime}\)), 50.91 (CH, C\(_j\)), 46.24 (CH, C\(_j\)), 34.06 (CH\(_2\), Cg\(^{\prime}\)), 33.58 (CH\(_2\), Cg), 31.56 (CH\(_2\), Ch\(_{2}\)), 31.26 (CH\(_2\), Ch\(_{2}\)), 25.45 (CH\(_2\), Ci), 25.32 (CH\(_2\), Ci\(^{\prime}\)) ppm.

IR \(v_{\text{max/cm}^{-1}}\) (film): 1602 (w), 1459 (m), 1378 (m), 722 (m).

LRMS (EI, CH\(_2\)Cl\(_2\)): m/z 294 ([M\(^+\)], 50%), 196 (100%), 141 (90%), 115 (80%), 91 (70%).

HRMS (EI): \(C_{20}H_{19}\text{Cl} [M^+\] calculated 294.1175, found 294.1166.
5.14 \((E)-(2-(2-Pentylidenecyclopentyl)ethyl)benzene\) 44

The following compound was prepared using the same method as for compound 4 but using undec-1-en-6-yne (0.150 g, 1 mmol) in place of 1-(hept-6-en-1-ynyl)benzene. Purification by column chromatography on silica gel (eluent: hexane) yielded the title compound (0.144 g, 0.59 mmol, 59%) as a colourless oil.

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.32-7.27 (2H, m, Ar-H), 7.23-7.16 (3H, m, Ar-H), 5.19 (1H, tq, \(J = 7.4, 2.3\), He), 2.72 (1H, ddd, \(J = 13.7, 10.6, 5.3\), Hi), 2.60 (1H, ddd, \(J = 13.7, 10.3, 6.4\), Hi), 2.33-2.16 (3H, m), 2.03-1.86 (4H, m), 1.77 (1H, m), 1.62-1.45 (2H, m), 1.39-1.25 (5H, m), 0.91 (3H, t, \(J = 6.8\), Ha) ppm.

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 146.08 (C, Cf), 143.05 (C, Cm), 128.36 (CHx2), 128.25 (CHx2), 125.54 (CH), 120.21 (CH, Ce), 43.85 (CH, Cj), 36.57 (CH\(_2\)), 34.16 (CH\(_2\)), 32.77 (CH\(_2\)), 31.97 (CH\(_2\)), 29.12 (CH\(_2\)x2), 24.14 (CH\(_2\)), 22.39 (CH\(_2\)), 14.05 (CH\(_3\), Ca) ppm.

IR \(\nu_{\text{max}}/\text{cm}^{-1}\) (film): 1597 (w), 1491 (m), 1450 (m), 690 (s).

LRMS (EI, CH\(_2\)Cl\(_2\)): \(m/z\) 242 ([M\(^+\)], 20\%), 138 (90\%), 91 ([C\(_6\)H\(_7\)+], 100\%).

HRMS (EI): C\(_{19}\)H\(_{26}\) [M\(^+\)] calculated 242.2035, found 242.2030.
To a stirred solution of zirconocene dichloride (0.292 g, 1.0 mmol) in THF (5 mL) at –78 °C was added n-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 2 min. The solution was stirred at –78 °C for a further 10 min before dropwise addition of a solution of undec-1-en-6-yne (0.150 g, 1.0 mmol) in THF (2 mL). After stirring for a further 10 min at –78 °C the solution was warmed to rt and stirred for a further 2 h. The solution was re-cooled to –78 °C followed by the dropwise addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). The solution continued to stir for 15 min at –78 °C before being warmed to rt. The solution was stirred for a further 3 h before the addition of 2 M HCl (aq) (5 mL). The mixture was stirred for 18 h before being extracting with Et₂O (50 mL). The organic layer was washed with water (3 x 50 mL) and brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: hexane) yielded a 3:1 mixture of the title compounds (0.128 g, 0.53 mmol, 53%) as a colourless oil. 

**1H NMR of the crude product** showed a 3:1 ratio of the (E)- and (Z)-isomers. HPLC purification (eluent: hexane) isolated the (E)-isomer.

**1H NMR (300 MHz, CDCl₃):** δ 7.40-7.28 (4H, m, Ar-H), 7.21 (1H, m, Ar-H), 6.38 (1H, d, J = 15.7, Hl), 6.10 (1H, dd, J = 15.8, 8.3, Hk), 5.17 (1H, tq, J = 7.2, 2.4, He), 3.09 (1H, q, J = 8.1), 2.41-2.23 (2H, m), 2.01-1.92 (3H, m), 1.84 (1H, m), 1.69-1.44 (2H, m), 1.37-1.27 (4H, m), 0.90 (3H, t, J = 6.8, Ha) ppm.

**13C NMR (75 MHz, CDCl₃):** δ 144.84 (C, Cf), 137.83 (C, Cm), 133.81 (CH, Ck), 129.72 (CH, Cl), 128.45 (CHx₂, Co), 126.78 (CH, Cp), 126.01 (CHx₂, Cn), 122.63 (CH, Ce), 48.98 (CH, Cj), 34.39 (CH₂), 31.79 (CH₂), 29.32 (CH₂), 28.91 (CH₂), 24.66 (CH₂), 22.44 (CH₂), 14.04 (CH₃, Ca) ppm.
**IR** \( \nu_{\text{max}}/\text{cm}^{-1} \) (film): 1600 (w), 1448 (m), 962 (s), 743 (s), 692 (s).

**LRMS (EI, CH\(_2\)Cl\(_2\))**: \( m/z \) 240 ([M\(^+\)], 50%), 91 ([C\(_6\)H\(_7\)]\(^+\), 100%).

**HRMS (EI)**: C\(_{18}\)H\(_{24}\) [M\(^+\)] calculated 240.1878, Found 240.1880.

The \(^1\)H NMR of the 3:1 mixture of the (E)- and (Z)-alkenes revealed the following peaks which are characteristic of the (Z)- isomer.

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta \) 6.53 (1H, d, \( J = 11.5 \), H\(_{I'}\)), 5.46 (1H, dd, \( J = 11.4, 9.8 \), H\(_{k'}\)), 5.17 (1H, m, H\(_e'\)) ppm.
To a stirred solution of zirconocene dichloride (0.292 g, 1.0 mmol) in THF (5 mL) at −78 °C was added n-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 2 min. The solution was stirred at −78 °C for a further 10 min before dropwise addition of a solution of 1-(oct-7-en-1-ynyl)benzene (0.184 g, 1.0 mmol) in THF (2 mL). After stirring for a further 10 min at −78 °C the solution was warmed to rt and stirred for a further 2 h. The solution was re-cooled to −78 °C followed by the dropwise addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). The solution continued to stir for a further 5 min before the addition of 2 M HCl in Et₂O (5 mL). The mixture was stir for a further 14 h while warming to rt. The mixture was diluted with Et₂O (50 mL) and washed with water (3 x 50 mL) and brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: hexane) yielded the title compound (0.147 g, 0.53 mmol, 53%) as a colourless oil.

\[ \text{C}_{21}\text{H}_{24} \]  
\text{Mol. Wt.: 276.42} 

\(^1\text{H NMR (300 MHz, CDCl}_3\) \text{: } \delta 7.34\text{-}7.18 (10H, m, Ar-H), 6.28 (1H, s, He), 2.67 (2H, t, J = 8.1, Hm), 2.45\text{-}2.24 (3H, m), 2.07 (1H, ddd, J = 8.0, 7.7, 13.5, Hg), 1.90\text{-}1.46 (7H, m) ppm.

\(^{13}\text{C NMR (75 MHz, CDCl}_3\) \text{: } \delta 145.55 (C, Cf), 142.89 (C, Cn), 138.49 (C, Cd), 128.98 (CHx2), 128.42 (CHx2), 128.30 (CHx2), 127.99 (CHx2), 125.81 (CH), 125.62 (CH), 121.85 (CH, Ce), 44.57 (CH, Hk), 34.12 (CH₂), 34.01 (CH₂), 33.72 (CH₂), 28.30 (CH₂), 27.12 (CH₂), 23.27 (CH₂) ppm.

\text{IR } \nu_{\text{max/cm}^{-1}} \text{ (film): } 1648 \text{ (w), 1599 (m), 1444 (m), 692 (s).}

\text{LRMS (EI, CH}_2\text{Cl}_2\) \text{: } m/z 276 ([M⁺], 40%), 185 (50%), 171 (90%), 117 (100%), 91 (100%).

\text{HRMS (EI): } \text{C}_{21}\text{H}_{24} [M⁺] \text{ calculated 276.1878, found 276.1886.}

5.16 (E)-(2-(2-Benzylidenecyclohexyl)ethyl)benzene 47
To a stirred solution of zirconocene dichloride (0.292 g, 1.0 mmol) in THF (5 mL) at –78 °C was added n-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 2 min. The solution was stirred at –78 °C for a further 5 min before dropwise addition of a solution of 1-(oct-7-en-1-ynyl)benzene (0.184 g, 1.0 mmol) in THF (2 mL). After stirring for a further 10 min at –78 °C the solution was warmed to rt and stirred for a further 18 h. The solution was re-cooled to –78 °C followed by dropwise addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). The solution continued to stir for 30 min at –78 °C before being warmed to rt. The solution was stirred for a further 4 h before addition of 2 M HCl (aq) (5 mL). The mixture was stirred for 18 h before being extracted with Et₂O (50 mL). The organic layer was washed with water (3 x 50 mL) and brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: hexane) yielded the title compound 48a (0.177 g, 0.65 mmol, 65%) as a colourless oil.

**¹H NMR (400 MHz, CDCl₃):** δ 7.42 (2H, d, J = 7.5, Ar-H), 7.35-7.24 (5H, m, Ar-H), 7.22-7.19 (3H, m, Ar-H), 6.47 (1H, d, J = 16.0, Hm), 6.41 (1H, dd, J = 15.8, 6.8, Hl), 6.29 (1H, s, He), 3.06 (1H, m), 2.72 (1H, m), 2.16 (1H, m), 1.95 (1H, m), 1.84 (1H, m), 1.72-1.57 (4H, m) ppm.

**¹³C NMR (100 MHz, CDCl₃):** 145.10 (C, Cf), 138.38 (C, Cd), 137.78 (C, Cn), 133.06 (CH, Cl), 130.13 (CH, Cm), 128.98 (CHx2), 128.52 (CHx2), 127.98 (CHx2), 127.01 (CH, Ca/q), 126.11 (CHx2), 125.91 (CH, Ca/q), 122.52 (CH, Ce), 48.15 (CH, Ck), 34.43 (CH₂), 28.61 (CH₂), 27.81 (CH₂), 24.87 (CH₂) ppm.

**IR νmax/cm⁻¹ (film):** 1492 (m), 1106 (s), 812 (m).

**LRMS (EI, CH₂Cl₂):** m/z 274 ([M⁺], 50%), 183 (60%), 141 (100%), 115 (70%), 91 (100%).

**HRMS (EI):** C₂₁H₂₂ [M⁺] calculated 274.1722, found 274.1721.
5.18 (E)-(2-(2-Pentylidenecyclohexyl)ethyl)benzene 50

To a stirred solution of zirconocene dichloride (0.292 g, 1.0 mmol) in THF (5 mL) at −78 °C was added n-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 2 min. The solution was stirred at −78 °C for a further 10 min before dropwise addition of a solution of dodec-1-en-7-yne (0.164 g, 1.0 mmol) in THF (2 mL). After stirring for a further 10 min at −78 °C the solution was warmed to rt and stirred for a further 2 h.

The reaction mixture was re-cooled to −78 °C followed by the dropwise addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) in THF (2 mL) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). The solution continued to stir for a further 5 min before the addition of 2 M HCl in Et₂O (5 mL). The mixture was stir for a further 18 h while warming to rt. The mixture was diluted with Et₂O (50 mL) and washed with water (3 x 50 mL) and brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: hexane) yielded a mixture of the title compound 50 and (0.157 g, 0.55 mmol, 55%) and 1-((E)-2-((E)-2-pentylidenecyclohexyl)vinyl)benzene 51a (0.015 g, 0.06 mmol, 6%) as a colourless oil.

¹H NMR (300 MHz, CDCl₃): δ 7.31-7.26 (2H, m, Ar-H), 7.23-7.15 (3H, m, Ar-H), 5.12 (1H, t, J = 7.2, He), 2.56 (2H, t, J = 8.4, Hm), 2.16-1.90 (6H, m), 1.71-1.41 (7H, m), 1.36-1.28 (4H, m), 0.94-0.89 (3H, m) ppm.

¹³C NMR (75 MHz, CDCl₃): δ 143.20 (C, Cf), 141.36 (C, Cn), 128.38 (CHx2), 128.21 (CHx2), 125.48 (CH), 121.35 (CH, Ce), 44.25 (CH, Ck), 34.06 (CH₂x2), 33.91 (CH₂), 32.51 (CH₂), 28.24 (CH₂), 26.79 (CH₂), 26.41 (CH₂), 23.63 (CH₂), 22.32 (CH₂), 14.03 (CH₃, Ca) ppm.

IR νmax/cm⁻¹ (film): 1498 (m), 1453 (m), 746 (s), 696 (s).

LRMS (EI, CH₂Cl₂): m/z 256 ([M⁺], 10%), 152 (805), 95 (100%).

HRMS (EI): C₁₉H₂₈ [M⁺] calculated 256.2191, found 256.2193.
To a stirred solution of zirconocene dichloride (0.292 g, 1.0 mmol) in THF (5 mL) at −78 °C was added n-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 2 min. The solution was stirred at −78 °C for a further 10 min before dropwise addition of a solution of dodec-1-en-7-yne (0.164 g, 1.0 mmol) in THF (2 mL). After stirring for a further 10 min at −78 °C the solution was warmed to rt and stirred for a further 2 h. The reaction mixture was re-cooled to −78 °C followed by the dropwise addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). The solution continued to stir for 20 min at −78 °C before being warmed to rt. The solution was stirred for a further 30 min before the addition of 2 M HCl (aq) (5 mL). The mixture was stirred for 18 h at rt before being extracted with Et₂O (50 mL). The organic layer was washed with water (3 x 50 mL) and brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: hexane) yielded the title compound 51a (0.183 g, 0.72 mmol, 72%) as a colourless oil.

**1H NMR (300 MHz, CDCl₃):** δ 7.41-7.18 (5H, m, Ar-H), 6.33 (1H, dd, J = 16.7, 6.0, Hl), 6.28 (1H, d, J = 16.7, Hm), 5.13 (1H, t, J = 7.3, He), 2.84 (1H, m, Hk), 2.44 (1H, m), 2.05-1.19 (3H, m), 1.84-1.71 (2H, m), 1.65-1.41 (4H, m), 2.34-1.26 (4H, m), 0.89 (3H, t, J = 7.0, Ha) ppm.

**13C NMR (75 MHz, CDCl₃):** δ 141.08, (C, Cf), 137.95 (C, Cn), 133.72 (CH, Cl), 129.42 (CH, Cm), 128.41 (CHx2), 126.77 (CH, Cq), 126.00 (CHx2), 122.22 (CH, Ce), 47.77 (CH, Ck), 34.39 (CH₂), 32.37 (CH₂), 27.68 (CH₂x2), 26.91 (CH₂), 24.96 (CH₂), 22.63 (CH₂), 14.01 (CH₃, Ca) ppm.

**IR νmax/cm⁻¹ (film):** 1600 (w), 1448 (m), 746 (s), 693 (s).

**LRMS (EI, CH₂Cl₂):** m/z 254 ([M⁺], 20%), 197 (100%), 149 (30%), 91 (40%).

**HRMS (EI):** C₁₉H₂₆ [M⁺] calculated 254.2035, found 254.2037.
5.20 \((E)-(4-\text{Propyloct-4-enyl})\text{benzene} 55\)

To a stirred solution of zirconocene dichloride (0.292 g, 1.0 mmol) in THF (5 mL) at –78 °C was added EtMgBr (1 M solution in THF) (2 mL, 2.0 mmol) dropwise over 2 min. The solution was stirred at –78 °C for a further 1 h before dropwise addition of 4-octyne (0.110 g, 0.15 mL, 1.0 mmol). After stirring for a further 10 min at –78 °C the solution was warmed to slowly to 0 °C over 4 h. The reaction mixture was re-cooled to –78 °C before the dropwise addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). The reaction mixture continued to stir for a further 10 min before the addition of 2 M HCl in Et₂O (5 mL). The reaction mixture was stirred for a further 1 h while warming to rt before being poured onto NaHCO₃ (aq) (10 mL). The mixture was extracted with Et₂O (50 mL) and washed with water (3 x 50 mL) and brine (50 mL), dried (MgSO₄) and the solvent removed \textit{in vacuo}. Purification by column chromatography on silica gel (eluent: hexane) yielded the title compound (0.130 g, 0.57 mmol, 57%) as a colourless oil.

\(^{1}\text{H} \text{NMR} \ (300 \text{ MHz, CDCl}_3): \delta 7.32-7.27 \ (2\text{H, m, Ar-H}), \ 7.21-7.17 \ (3\text{H, m, Ar-H}), \ 5.17 \ (1\text{H, t, } J = 7.0, \text{ Hf}), \ 2.61 \ (2\text{H, t, } J = 7.7, \text{ Hg}), \ 2.07-1.97 \ (6\text{H, m}, \ 1.79-1.69 \ (2\text{H, m, Hf}), \ 1.46-1.32 \ (4\text{H, m}), \ 0.92 \ (3\text{H, t, } J = 7.3, \text{ Hl/o }), \ 0.89 \ (3\text{H, t, } J = 7.3, \text{ Hl/o}) \text{ ppm.}\)

\(^{13}\text{C} \text{NMR} \ (75 \text{ MHz, CDCl}_3): \delta 142.82 \ (\text{C, Cd}), \ 138.88 \ (\text{C, Ch}), \ 128.41 \ (\text{CHx2}), \ 128.21 \ (\text{CHx2}), \ 125.57 \ (\text{CH}), \ 125.26 \ (\text{CH, Ci}), \ 36.54 \ (\text{CH}_2), \ 35.68 \ (\text{CH}_2), \ 32.12 \ (\text{CH}_2), \ 30.08 \ (\text{CH}_2), \ 29.84 \ (\text{CH}_2), \ 23.26 \ (\text{CH}_2), \ 21.61 \ (\text{CH}_2), \ 14.20 \ (\text{CH}_3, \text{ Cl/o}), \ 13.88 \ (\text{CH}_3, \text{ Cl/o}) \text{ ppm.}\)

\text{IR} v_{\text{max}/\text{cm}^{-1}} \text{ (film): } 1454 \ (m), \ 744 \ (m), \ 697 \ (s).\)

\text{LRMS (EI, CH}_2\text{Cl}_2): \text{m/z} \ 230 \ ([\text{M}^+], \ 25\%), \ 156 \ (35\%), \ 135 \ (40\%), \ 115 \ (30\%), \ 73 \ (100\%).\)

\text{HRMS (EI): } \text{C}_{17}\text{H}_{26} [\text{M}^+] \text{ calculated 230.2035, found 230.2033.}\)
5.21 ((1E,4E)-4-Propylocta-1,4-dien-1-yl)benzene 56a and (E)-(4-
Propyloct-2-enyl)benzene 56b

To a stirred solution of zirconocene dichloride (0.292 g, 1.0
mmol) in THF (5 mL) at −78 °C was added EtMgBr (1 M
solution in THF) (2 mL, 2.0 mmol) dropwise over 2 min.
The solution was stirred at −78 °C for a further 1 h before
dropwise addition of 4-octyne (0.110 g, 0.15 mL, 1.0 mmol).
After stirring for a further 10 min at −78 °C the solution was
warmed to slowly to 0 °C over 4 h. The solution was re-cooled to −78 °C before the
dropwise addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M
solution in THF) (0.6 mL, 1.0 mmol). The reaction mixture was stirred for a further 10
min at −78 °C before being warmed to rt. The reaction mixture continued to stir for a
further 30 min before the addition of MeOH (5 mL) and sat NaHCO₃ (aq) (5 mL). The
mixture was stirred for a further 1 h before being extracted with Et₂O (50 mL). The
organic layer was washed with water (3 x 50 mL) and brine (50 mL), dried (MgSO₄)
and the solvent removed in vacuo. Purification by column chromatography on silica gel
(eluent: hexane) yielded 56b (0.03 g, 0.14 mmol, 14%) followed by 56a (0.108 g, 47
mmol, 47%) as a colourless oils.

Data for compound 56a

¹H NMR (300 MHz, CDCl₃): δ 7.39-7.19 (5H, m, Ar-H), 6.40 (1H, d, J = 15.8, He),
6.21 (1H, dt, J = 15.8, 6.8, Hf), 5.25 (1H, t, J = 7.1, Hi), 2.90 (2H, d, J = 6.8, Hg),
2.08-1.99 (4H, m, Hj, m), 1.51-1.33 (4H, m, Hk, n), 0.93 (3H, t, J = 7.1, Hl/o), 0.90
(3H, t, J = 7.1, Hl/o) ppm.

¹³C NMR (75 MHz, CDCl₃): δ 137.80 (Cx2, Ch, Cd), 130.68 (CH, Ce), 129.53 (CH,
Cf), 128.43 (CHx2), 126.82 (CH), 126.47 (CH), 126.00 (CHx2), 40.62 (CH₂, Cg),
32.30 (CH₂), 29.98 (CH₂), 23.16 (CH₂), 21.47 (CH₂), 14.13 (CH₃, Cl/o), 13.93 (CH₃,
Cl/o) ppm.

IR v_max/cm⁻¹ (film): 1598 (w), 1445 (m), 964 (s), 746 (s), 691 (s).

LRMS (EI, CH₂Cl₂): m/z 228 ([M⁺], 30%), 185 (60%), 143 (60%), 129 (50%), 115
(50%), 91 ([Bn⁺], 100%).
HRMS (EI): C_{17}H_{24} [M^+] calculated 228.1878, found 228.1873.

(E)-(4-Propyloct-2-enyl)benzene 56b

^{1}H NMR (300 MHz, CDCl$_3$): $\delta$ 7.19-7.13 (5H, m, Ar-H), 5.50 (1H, ddd, $J = 15.2, 6.8, 0.7$, Hf), 5.25 (1H, ddt, $J = 15.2, 8.8, 1.2$, Hg), 3.32 (2H, br d, $J = 6.8$, He), 1.95 (1H, m, Hh), 1.36-1.20 (10H, m, Hi, j, k, m, n), 0.91-0.87 (6H, m, Hl, o) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 141.31 (C, Cd), 136.93 (CH), 128.47 (CHx2), 128.27 (CHx2), 128.22 (CH), 125.78 (CH), 42.46 (CH, Ch), 39.10 (CH$_2$, Ce), 37.74 (CH$_2$), 35.14 (CH$_2$), 29.55 (CH$_2$), 22.80 (CH$_2$), 20.39 (CH$_2$), 14.19 (CH$_3$, Cl/o), 14.12 (CH$_3$, Cl/o) ppm.

IR $\nu_{\text{max}}$/cm$^{-1}$ (film): 1604 (w), 1453 (m), 733 (s), 697 (s).

LRMS (EI, CH$_2$Cl$_2$): m/z 230 ([M$^+$], 20%), 131 (60%), 117 (100%), 91 ([Bn$^+$], 90%).

HRMS (EI): C$_{17}$H$_{26}$ [M$^+$] calculated 230.2035, found 230.2030.
5.22 ((1E,4E)-4-Propylocta-1,4-dien-1-yl)benzene 56a and 1-((4E)-2-((E)-But-2-en-2-yl)-4-propyloct-4-enyl)benzene 61

To a stirred solution of zirconocene dichloride (0.292 g, 1.0 mmol) in THF (5 mL) at −78 °C was added EtMgBr (1 M solution in THF) (2 mL, 2.0 mmol) dropwise over 2 min. The solution was stirred at −78 °C for a further 1 h before dropwise addition of 4-octyne (0.110 g, 0.15 mL, 1.0 mmol). After stirring for a further 10 min at −78 °C the solution was warmed to slowly to 0 °C over 4 h. The solution was re-cooled to −78 °C before the dropwise addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). After 5 min at −78 °C 2-butyne (0.24 mL, 3.0 mmol) was added. The reaction mixture was stirred for a further 30 min at −78 °C before being warmed to rt. The solution continued to stir for a further 30 min before the addition of 2 M HCl (aq) (5 mL) The mixture was stirred for a further 18 h before being extracted with Et₂O (50 mL). The organic layer was washed with water (3 x 50 mL) and brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: hexane) yielded the title compounds as an inseparable 1:1 mixture (0.142 g, 0.56 mmol, 56%).

**¹H NMR (300 MHz, CDCl₃):** 7.39-7.09 (10H, m, Ar-H), 6.39 (1H, d, J = 15.8, He), 6.20 (1H, dt, J = 15.8, 6.8, Hf), 5.25 (1H, t, J = 7.1, Hi), 5.13 (1H, t, J = 7.3, Hi`), 5.05 (1H, q, J = 6.6, Hq`), 2.90 (2H, d, J = 6.6, Hg), 2.70 - 2.53 (2H, m), 2.44 (1H, quin, J = 7.3, Hf`), 2.08-1.93 (11H, m), 1.49-1.29 (14H, m), 0.96-0.85 (12H, m) ppm.

**¹³C NMR (75 MHz, CDCl₃):** 141.64 (C, Cp`), 137.80 (C2x2, Cd, h), 137.61 (C, Cd'h`), 136.79 (C, Cd'h`) 130.71 (CH, Ce), 129.51 (CH, Cf), 128.97 (CHx4), 128.44 (CHx2), 127.86 (CHx2), 126.84 (CH), 126.49 (CH), 125.99 (CHx2), 125.41 (CH), 120.13 (CH, Ci`), 49.06 (CH, Cf`), 40.86 (CH2, Cg`), 40.62 (CH2, Cg), 39.60 (CH2, Ce`), 32.30 (CH2), 31.46 (CH2), 29.98 (CH2), 29.78 (CH2), 23.22 (CH2), 23.17 (CH2),
21.47 (CH₂), 21.35 (CH₂), 14.13 (CH₃x2), 13.91 (CH₃), 13.71 (CH₃), 13.08 (CH₃),
12.14 (CH₃) ppm.

**GCMS (EI, CH₂Cl₂):** 8.63 min: 228 ([M⁺], 50%), 185 (100%), 143 (90%), 115 (70%),
91 (70%). 9.01 min: 284 ([M⁺], 5%), 241 (30%), 193 (95%), 150 (80%), 117 (100%),
91 (70%).

5.23 (\(1E,4E\)-4-Propylocta-1,4-dien-1-yl)benzene 56a

To a stirred solution of zirconocene dichloride (0.292 g, 1.0 mmol) in THF (5 mL) at –78 °C was added EtMgBr (1 M solution in THF) (2 mL, 2.0 mmol) dropwise over 2 min. The solution was stirred at –78 °C for a further 1 h before dropwise addition of 4-octyne (0.110 g, 0.15 mL, 1.0 mmol). After stirring for a further 10 min at –78 °C the solution was warmed to slowly to 0 °C over 4 h. The solution was re-cooled to −78 °C before the dropwise addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). After 5 min at −78 °C CH₂Cl₂ (0.3 mL, 2.0 mmol) was added. The reaction mixture was stirred for a further 30 min at −78 °C before being warmed to rt. The solution continued to stir for a further 30 min before the addition of 2 M HCl (aq) (5 mL). The mixture was stirred for a further 18 h before being extracted with Et₂O (50 mL). The organic layer was washed with water (3 x 50 mL) and brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: hexane) yielded the title compound (0.1517 g, 0.67 mmol, 67%) as a colourless oil.

See experiment 5.21 for data for 56a
5.24 1-((1E,4E)-4-Propylocta-1,4-dien-1-yl)naphthalene 64

The following compound was prepared using the same method as for compound 56a as described in experiment 5.23 but using 1-(chloromethyl)naphthalene (0.176g, 1 mmol) in place of benzyl chloride. Purification by column chromatography on silica gel (eluent: hexane) yielded the title compound (0.178 g, 0.65 mmol, 65%) as a colourless oil.

$^1$H NMR (300 MHz, CDCl$_3$): δ 8.15 (1H, d, $J = 9.5$, Ar-H), 7.86 (1H, m, Ar-H), 7.76 (1H, d, $J = 8.2$, Ar-H), 7.59-7.42 (4H, m, Ar-H), 7.14 (1H, d, $J = 15.6$, Hk), 6.23 (1H, dt, $J = 15.5$, 7.0, Hl), 5.31 (1H, t, $J = 7.2$, Ho), 3.02 (2H, d, $J = 7.0$, Hm), 2.15-2.02 (4H, m, Hp, s), 1.56-1.35 (4H, m, Hq, t), 0.95 (3H, t, $J = 7.3$, Hr/v), 0.94 (3H, t, $J = 7.32$, Hr/r) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$): δ 137.82 (C, Cn), 135.65 (C, Cj), 133.59 (C, Cf), 132.81 (CH), 131.13 (C, Ca), 128.42 (CH), 127.91 (CH), 127.25 (CH), 126.66 (CH), 125.78 (CH), 125.65 (CH), 125.60 (CH), 123.94 (CH), 123.56 (CH, Co), 41.04 (CH$_2$, Cm), 32.40 (CH$_2$), 30.01 (CH$_2$), 23.18 (CH$_2$), 21.53 (CH$_2$), 14.18 (CH$_3$, Cr/v), 13.93 (CH$_3$, Cr/v) ppm.

IR $\nu_{\text{max}}$/cm$^{-1}$ (film): 1591 (w), 1456 (m), 968 (m), 775 (s).

LRMS (EI, CH$_2$Cl$_2$): m/z: 278 ([M$^+$], 80%), 235 (80%), 193 (60%), 165 (100%), 141 (80%).

HRMS (EI): C$_{21}$H$_{26}$ [M$^+$] calculated 278.2035, found 278.2032.
To a stirred solution of zirconocene dichloride (0.292 g, 1.0 mmol) in THF (5 mL) at −78 °C was added EtMgBr (1 M solution in THF) (2 mL, 2.0 mmol) dropwise over 2 min. The solution was stirred at −78 °C for a further 1 h before dropwise addition of diphenylacetylene (0.178 g, 1.0 mmol) in THF (3 mL). After stirring for a further 10 min at −78 °C the solution was warmed slowly to 0 °C over 4 h. The solution was re-cooled to −78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). After 5 min at −78 °C CHCl₂ (0.3 mL, 2.0 mmol) was added. The solution was stirred for a further 30 min at −78 °C before being warmed to rt. The solution continued to stir for a further 30 min before the addition of 2 M HCl (aq) (5 mL). The solution was stirred for a further 18 h before being extracted with Et₂O (50 mL). The organic layer was washed with water (3 x 50 mL) and brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by recrystallisation (hexane) yielded the title compound (0.201 g, 0.68 mmol, 68%) as a white crystalline solid.

**¹H NMR (300 MHz, CDCl₃):** δ 7.39-7.22 (10H, m, Ar-H), 7.12-7.10 (3H, m, Ar-H), 6.99-6.96 (2H, m, Ar-H), 6.53 (1H, s, Hi), 6.49 (1H, d, J = 15.8, He), 6.32 (1H, dt, J = 15.8, 6.8, Hf), 3.41 (2H, d, J = 6.8, Hg) ppm.

**¹³C NMR (75 MHz, CDCl₃):** δ 141.33 (C, Ch/n), 141.28 (C, Ch/n), 137.55 (C, Cd/j), 137.24 (C, Cd/j), 131.85 (CH, Ce), 129.02 (CHx2), 128.52 (CHx6), 127.82 (CHx2), 127.59 (CH), 127.23 (CH), 127.09 (CH), 127.00 (CH), 126.29 (CH, Ci), 126.12 (CHx2), 43.83 (CH₂, Cg) ppm.

Tentative assignments based on ¹³C NMR intergration.

**IR vmax/cm⁻¹ (film):** 1597 (w), 1491 (m), 1443 (m), 700 (s), 690 (s).

**LRMS (EI, CHCl₃):** m/z 296 ([M⁺], 80%), 205 (100%), 178 (55%), 115 (30%).

**HRMS (EI):** C₂₃H₂₀ [M⁺] calculated 296.1565, found 296.1557.

**M.p:** 67-70 °C.
To a stirred solution of zirconocene dichloride (0.292 g, 1.0 mmol) in THF (5 mL) at –78 °C was added EtMgBr (1 M solution in THF) (2 mL, 2.0 mmol) dropwise over 2 min. The solution was stirred at –78 °C for a further 1 h before dropwise addition of (trimethylsilyl)propyne (0.15 mL, 0.112 g, 1.0 mmol) in THF (3 mL). After stirring for a further 10 min at –78 °C the solution was warmed to slowly to 0 °C over 4 h. The solution was re-cooled to –78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). After 5 min at –78 °C CH₂Cl₂ (0.3 mL, 2.0 mmol) was added. The solution was stirred for a further 30 min at –78 °C before being warmed to rt. The solution continued to stir for a further 30 min before the addition of 2 M HCl (aq) (5 mL). The mixture was stirred for a further 18 h before being extracted with Et₂O (50 mL). The organic layer was washed with water (3 x 50 mL) and brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: hexane) yielded the title compound (0.092 g, 0.52 mmol, 52%) as a colourless oil.

**¹H NMR (300 MHz, CDCl₃):** δ 7.41-7.20 (5H, m, Ar-H), 6.42 (1H, d, J = 15.7, He), 6.24 (1H, dt, J = 15.7, 7.0, Hf), 5.31 (1H, s, Hi), 2.97 (2H, d, J = 7.1, Hg), 1.84 (3H, s, Hk), 0.13 (9H, s, Hj) ppm.

**¹³C NMR (75 MHz, CDCl₃):** δ 153.30 (C, Ch), 137.66 (C, Cd), 131.38 (CH, Ce), 128.48 (CHx2), 128.38 (CH, Cf), 126.99 (CH), 126.07 (CHx2), 124.52 (CH, Ci), 46.07 (CH₂, Cg), 21.76 (CH₃, Ck), 0.07 (CH₃x3, Cj) ppm.

**IR νmax/cm⁻¹ (film):** 1617 (m), 836 (s), 747 (s), 690 (s).

**LRMS (EI, CH₂Cl₂):** m/z 230 ([M⁺], 30%), 156 (30%), 135 (30%), 73 (100%).

**HRMS (EI):** C₁₅H₂₂Si [M⁺] calculated 230.1491, found 230.1485.
5.27 *rac-(2-((1R,2R)-4,4-Bis(methoxymethyl)-2-methylcyclopentyl)ethyl)benzene* 73a

**Method A**

To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF at −78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of 4,4-bis(methoxymethyl)-1,6-heptadiene (0.184 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. The reaction mixture was cooled to −78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) followed by TMEDA (0.15 mL, 0.116 g, 1 mmol) dropwise. The reaction mixture was quenched after 1 h at −78 °C with MeOH (5 mL) and sat NaHCO₃ (aq) (5 mL) then allowed to warm to rt with stirring for 18 h. The resulting mixture was diluted with Et₂O (100 mL), washed with H₂O (3 x 50 mL) and brine (50 mL), dried (MgSO₄) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 5% EtOAc in hexane) gave the title compound (0.206 g, 0.75 mmol, 75%) as a colourless oil.

**1H NMR** (300 MHz, CDCl₃): δ 7.31-7.22 (2H, m, Hn), 7.16-7.14 (3H, m, Ho, p), 3.36 (6H, s, Hf, g), 3.25 (2H, dd, J = 9.0, 4.0, He/h), 3.20 (2H, dd, J = 9.2, 4.4, He/h), 2.70 (1H, ddd, J = 13.9, 11.0, 4.8, Hi), 2.50 (1H, ddd, J = 13.7, 10.2, 6.4, Hi), 1.95-1.86 (2H, m, Hc/i, j), 1.75 (1H, dd, J = 12.8, 7.0, Hc/i), 1.51 (1H, m, Hb/k), 1.40-1.26 (2H, m, Hb/k), 1.10 (1H, dd, J = 13.0, 10.2, Hc/i), 1.01 (1H, dd, J = 13.0, 11.0, Hc/i), 0.95 (3H, d, J = 6.4, Ha) ppm.

**13C NMR** (75 MHz, CDCl₃): δ 143.04 (C, Cm), 128.23 (CHx4, Cn, o), 125.54 (CH, Cp), 88.0 (CH₂, Ce/h), 77.87 (CH₂, Ce/h), 59.22 (CH₃x2, Cf, g), 46.45 (CH, Cj), 45.28 (C, Cd), 41.85 (CH₂), 39.82 (CH, Cb), 39.45 (CH₂), 35.97 (CH₂), 34.76 (CH₂), 18.05 (CH₃, Ca) ppm.

**IR ν max/cm⁻¹ (film):** 1500 (m), 1450 (m), 1105 (s), 698 (s).

**LRMS (EI, CH₂Cl₂):** m/z 276 ([M⁺], 30%), 212 (60%), 143 (60%), 91 ([C₇H₇⁺], 100%).
HRMS (EI): C₁₈H₂₈O₂ [M⁺] calculated 276.2089, found 276.2086.

When a sample of the reaction mixture was quenched with 2 M DCl in D₂O the bis-deuterated compound 80 was produced. The following changes in the ¹H and ¹³C NMR were observed.

$$\text{C}_{18}\text{H}_{26}\text{D}_2\text{O}_2 \quad \text{Mol. Wt.: 278.43}$$

\[\text{¹H NMR (300 MHz, CDCl}_3\text{): } \delta 2.66 (0.5 \text{ H, m, CHD}), 2.48 (0.5H, m, CHD), 0.91 (2H, d, J = 6.4, CH}_2\text{D}) \text{ ppm.} \]

\[\text{¹³C NMR (75 MHz, CDCl}_3\text{): } \delta 34.8 (\text{CH}_2, \text{ t, } J = 58.0, \text{ CHD}), 18.0 (\text{CH}_3, \text{ t, } J = 58.0, \text{ CH}_2\text{D}) \text{ ppm.} \]

Epimerisation experiment

Following the above procedure for the preparation of the benzyl carbenoid inserted zirconacycle. The reaction mixture was warmed to 0 °C and samples of the reaction mixture (1 mL) were removed at timed intervals and quenched with 2 M DCl in D₂O (2 mL). The samples were stirred for 2 h before being diluted with Et₂O (5 mL), washed with H₂O (3 x 5 mL) and brine (5 mL), dried (MgSO₄) and the solvent removed in vacuo. The ratio of diastereoisomers was determined from the ¹H NMR spectra.

Synthesis of 73a using benzyl carbamate carbenoid:

**Method B**

In situ formation of benzyl carbenoid carbamate.

To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF at −78 °C was added n-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of 4,4-bis(methoxymethyl)-1,6-heptadiene (0.184 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. The reaction mixture was cooled to −78 °C before the addition of carbamate 75 (0.303 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) dropwise. The reaction mixture was quenched after 3 h at −78 °C with MeOH (5 mL) and sat NaHCO₃ (aq) (5 mL) then allowed to warm to rt with stirring for 18 h. The resulting mixture was diluted with Et₂O (100 mL), washed with H₂O (3 x 50 mL) and brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: 5% EtOAc in hexane) gave the title compound (0.111 g, 0.40 mmol, 40%) as a colourless oil.
Method C

Preforming benzyl carbamate carbenoid method.

To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF at −78 °C was added $n$-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of 4,4-bis(methoxymethyl)-1,6-heptadiene (0.184 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. The reaction mixture was cooled to −78 °C before the addition of benzyl carbamate carbenoid 76, preformed by treating a solution of benzyl carbamate 75 (0.303 g, 1.0 mmol) and TMEDA (0.15 mL, 0.116 g, 1 mmol) in THF (5 mL) at -78 °C with $sec$-BuLi (0.80 M in cyclohexane) (1.25 mL, 1 mmol) for 30 min. The reaction mixture was quenched after 3 h at −78 °C with MeOH (5 mL) and sat NaHCO$_3$ (aq) (5 mL) then allowed to warm to rt with stirring for 18 h. The resulting mixture was diluted with Et$_2$O (100 mL), washed with H$_2$O (3 x 50 mL) and brine (50 mL), dried (MgSO$_4$) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: 5% EtOAc in hexane) gave the title compound (0.166 g, 0.60 mmol, 60%) as a colourless oil.

GC (Method A): 71 – 2.72 min, 73a – 6.26 min and 75 – 5.01 min.
Synthesis of 3,3-dimethyl-1-oxa-4-aza-[4.5]-spirodecane: Cyclohexanone (52 mL, 49 g, 0.50 mol) and 2-amino-2-methyl-1-propanol (47.0 mL, 44.60g, 0.5 mol) were refluxed neat under a Dean and Stark apparatus with para-toluene sulfonylic acid (100 mg) for 4 days. After this time the reaction mixture was diluted with pentane (500 ml), washed with NaHCO$_3$ (3 x 100ml), dried (MgSO$_4$) and the solvent removed in vacuo. The crude compound was purified by distillation (bp 105-118°C, 0.1 mmHg) to yield the 3,3-dimethyl 1-oxa-4-aza-[4.5]-spirodecane (68.0 g, 0.4 mol, 80%).

Synthesis of 3,3-dimethyl-1-oxa-4-aza-[4.5]spirodecane-4-carbonyl chloride: To a solution of triphosgene (5.0 g, 16.8 mmol) in benzene (60 mL) was added 3,3-dimethyl-1-oxa-4-aza-[4.5]-spirodecane (8.50 g, 51 mmol) in benzene (20 mL) followed by Et$_3$N (7.4 mL, 5.37 g, 53 mmol) dropwise. The mixture was refluxed for 20 h and then cooled and poured onto NaHCO$_3$ (aq) (250 mL). The reaction mixture was extracted with Et$_2$O (3 x 250 mL), dried (MgSO$_4$) and the solvent was removed in vacuo to yield 3,3-dimethyl-1-oxa-4-aza-[4.5]spirodecane-4-carbonyl chloride (9.56 g, 41 mmol, 82%). The compound was used without further purification.

Synthesis of benzyl 3,3-dimethyl-1-oxa-4-aza-[4.5]-spirodecane-4-carboxylate: To sodium hydride (60% solution in mineral oil) (2.3 g 57.5 mmol) suspended in Et$_2$O (200 mL) was added dropwise benzyl alcohol (5.70 mL, 5.96 g, 55 mmol) at 0 °C. The mixture was stirred at rt for 1 h before the dropwise addition of a solution of 3,3-dimethyl-1-oxa-4-aza-[4.5]spirodecane-4-carbonyl chloride (11.58 g, 50 mmol) in Et$_2$O (80 mL). The mixture was stirred at rt for 18 h before being poured onto water (100 mL). The water layer was then separated and extracted with Et$_2$O (3 x 100 mL). The combined organic layers were dried (MgSO$_4$) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: 5% Et$_2$O in hexane) yielded the title compound (8.81 g, 29 mmol, 58%) as a low melting solid.

Data was consistent with published data.$^1$
$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.38-7.31 (5H, m, Ar-H), 5.13 (2H, s, Hi), 3.70 (2H, s, He), 2.45-2.17 (2H, m), 1.62-1.34 (14H, m) ppm.

IR $v_{\text{max}}$/cm$^{-1}$ (film): 1694 (s), 1610 (m), 1600 (m), 1600 (w), 1520 (w), 1500 (m), 1440 (w), 950 (m), 900 (m).
The title compound was prepared using the same method as for compound 73a (Method A) but \( p \)-methylbenzyl chloride (0.140 g, 1 mmol) replaced benzyl chloride. Purification by column chromatography on silica gel (eluent: 5% EtOAc in hexane) gave the title compound (0.133 g, 0.46 mmol, 46%) as a colourless oil.

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta \) 7.11-7.05 (4H, m, Hn, o), 3.36 (6H, s, Hf, g), 3.24 (2H, dd, \( J = 8.8, 3.1, \) He/h), 3.20 (2H, dd, \( J = 4.0, 8.6, \) He/h), 2.66 (1H, ddd, \( J = 14.0, 10.8, 4.3, \) Hl), 2.47 (1H, ddd, \( J = 13.8, 10.3, 6.3, \) Hl), 2.32 (3H, s, Hq), 1.92-1.82 (2H, m, Hc/i, j), 1.74 (1H, dd, \( J = 13.1, 7.1, \) Hc/i) 1.56-1.22 (3H, m, Hb, k), 1.09 (1H, dd, \( J = 13.0, 10.4, \) Hc/i), 1.01 (1H, dd, \( J = 13.0, 11.1, \) Hc/i), 0.94 (3H, d, \( J = 6.2, \) Ha) ppm.

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta \) 139.97 (C, Cp), 134.94 (C, Cm), 128.93 (CHx2), 128.10 (CHx2), 78.98 (CH\(_2\), Ce/h), 77.85 (CH\(_2\), Ce/h), 59.24 (CH\(_3\)x2, Cf, g), 46.44 (CH, Cj), 45.23 (C, Cd), 41.85 (CH\(_2\)), 39.83 (CH, Cb), 39.47 (CH\(_2\)), 36.15 (CH\(_2\)), 34.32 (CH\(_2\)), 20.98 (CH\(_3\), Cq), 18.05 (CH\(_3\), Ca) ppm.

IR \( \text{v}_{\text{max}}/\text{cm}^{-1} \) (film): \( 1515 \) (m), \( 1448 \) (m), \( 1105 \) (s) 806 (m).

LRMS (ES, MeCN): \( m/\epsilon \) 313 ([M + Na]\(^+\), 100%).

HRMS (ES): C\(_{19}\)H\(_{30}\)NaO\(_2\) [M + Na]\(^+\) calculated 313.2138, found 313.2134.
5.30 *rac*-1-((1R,2R)-4,4-Bis(methoxymethyl)-2-methylcyclopentyl)ethyl)-2-methylbenzene 73c

The title compound was prepared using the same method as for compound 73a (Method A) but o-methylbenzyl chloride (0.140 g, 1 mmol) replaced benzyl chloride. Purification by column chromatography on silica gel (eluent: 5% EtOAc in hexane) gave the title compound (0.133 g, 0.46 mmol, 46%) as a colourless oil.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.14-7.11 (4H, m, Ar- H), 3.37 (3H, s, Hf/g), 3.36 (3H, s, Hf/g), 3.24 (4H, dd, $J = 11.5, 8.8$, He, h), 2.67 (1H, ddd, $J = 13.7, 11.9, 4.9$, Hl), 2.50 (1H, ddd, $J = 13.6, 11.2, 5.5$, Hl), 2.31 (3H, s, Hs), 1.93 (1H, dd, $J = 12.9, 6.9$, Hc/i), 1.85 (1H, m, Hj) 1.76 (1H, dd, $J = 12.9, 10.5$, Hc/i), 1.53-1.20 (3H, m, Hb, k), 1.03 (1H, dd, $J = 13.0, 10.5$, Hc/i), 0.96 (1H, dd, $J = 13.0, 11.0$, Hc/i), 0.96 (3H, d, $J = 6.2$, Ha) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 141.24 (C, Cm), 135.71 (C, Cn), 130.08 (CH), 128.57 (CH), 125.89 (CH), 125.72 (CH), 78.02 (CH$_2$, Ce/h), 77.89 (CH$_2$, Ce/h), 59.26 (CH$_3$x2, Cf/g), 46.94 (CH, Cj), 45.32 (C, Cd), 41.83 (CH$_2$), 39.78 (CH, Cb), 39.50 (CH$_2$), 34.65 (CH$_2$), 32.19 (CH$_2$), 19.26 (CH$_3$, Cs), 18.11 (CH$_3$, Ca) ppm.

IR $\nu_{max}$/cm$^{-1}$ (film): 1493 (m), 1458 (m), 1104 (s), 736 (s).

LRMS (ES, MeCN): $m/z$ 313 ([M + Na]$^+$, 100%).

HRMS (ES): C$_{19}$H$_{30}$NaO$_2$ [M + Na]$^+$ calculated 313.2138, found 313.2132.
5.31 *rac*-1-(2-((1R,2R)-4,4-Bis(methoxymethyl)-2-methylcyclopentyl)ethyl)-4-methoxybenzene 73d

The title compound was prepared using the same method as for compound 73a (Method A) but *p*-methoxybenzyl chloride (0.156 g, 1 mmol) replaced benzyl chloride. Purification by column chromatography on silica gel (eluent: 15% EtOAc in hexane) gave the title compound (0.113 g, 0.37 mmol, 37%) as a colourless oil.

$^1$H NMR (300 MHz, CDCl$_3$): δ 7.10 (2H, d, *J* = 8.6, Hn), 6.83 (2H, d, *J* = 8.6, Ho), 3.80 (3H, s, Hq), 3.36 (6H, s, Hf, g), 3.24 (2H, dd, *J* = 8.8, 3.5, He/h), 3.19 (2H, dd, *J* = 8.8, 4.6, He/h) 2.64 (1H, ddd, *J* = 14.5, 10.9, 4.3, Hl), 2.45 (1H, ddd, *J* = 16.3, 10.0, 6.3, Hl), 2.0-1.81 (2H, m, Hc/i, j), 1.74 (1H, dd, *J* = 12.2, 6.9, Hc/i), 1.51 (1H, m, Hb/k), 1.39-1.22 (2H, m, Hb/k), 1.08 (1H, dd, *J* = 13.0, 10.4, Hc/i), 1.0 (1H, dd, *J* = 13.0, 11.0, Hc/i), 0.94 (3H, d, *J* = 6.4, Ha) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$): δ 157.58 (C, Cp), 135.15 (C, Cm), 129.07 (CHx2, Co), 113.68 (CHx2, Cn), 78.97 (CH$_2$, Ce/h), 77.84 (CH$_2$, Ce/h), 59.24 (CH$_3$x2, Cf, g), 55.24 (CH$_3$, Cq), 46.36 (CH, Cj), 45.23 (C, Cd), 41.84 (CH$_2$, Cb), 39.82 (CH, Cb), 39.45 (CH$_2$), 36.22 (CH$_2$), 33.82 (CH$_2$), 18.06 (CH$_3$, Ca) ppm.

IR $\nu_{\text{max}}$/cm$^{-1}$ (film): 1511 (s), 1457 (m) 1233 (s), 1104 (s).

LRMS (EI, CH$_2$Cl$_2$): *m/z* 306 ([M$^+$], 80%), 185 (15%), 121 (100%).

HRMS (EI): C$_{19}$H$_{30}$O$_3$ [M$^+$] calculated 306.2195, found 306.2198.
5.32 *rac-1-(2-((1R,2R)-4,4-Bis(methoxymethyl)-2-methylcyclopentyl)ethyl)-4-fluorobenzene* 73e

The title compound was prepared using the same method as for compound 74a (Method A) but p-fluorobenzyl chloride (0.144 g, 1 mmol) replaced benzyl chloride. Purification by column chromatography on silica gel (eluent: 10% EtOAc in hexane) gave the title compound (0.140 g, 0.47 mmol, 47%) as a colourless oil.

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.13 (2H, dd, $J = 8.7, 5.6$, Hn), 6.96 (2H, t, $J = 8.8$, Ho), 3.36 (3H, s, Hf/g), 3.35 (3H, s, Hf/g), 3.26-3.17 (4H, m, He, h), 2.67 (1H, ddd, $J = 14.4, 10.6, 4.5$, Cl), 2.49 (1H, ddd, $J = 14.0, 10.0, 6.6$, Cl), 1.87 (2H, dd, $J = 16.3, 6.7$, Hc/i, j), 1.75 (1H, dd, $J = 13.0, 7.1$, Hc/i), 1.51 (1H, m, Hb/k), 1.38-1.20 (2H, m, Hb/k), 1.10 (1H, dd, $J = 13.0, 10.4$, Hc/i), 1.02 (1H, dd, $J = 13.0, 11.0$, Hc/i), 0.94 (3H, d, $J = 6.2$, Ha) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 161.09 (C, d, $J = 242$, Cp), 138.53 (C, d, $J = 2.8$, Cm), 129.45 (CHx2, d, $J = 7.7$, Cn), 114.87 (CHx2, d, $J = 20.9$, Co), 77.96 (CH$_2$, Ce/h), 77.84 (CH$_2$, Ce/Ch), 59.17 (CH$_3$x2, Cf, g) 46.26 (CH, Cj), 45.26 (C, Cd), 41.8 (CH$_2$), 38.78 (CH, Cb), 39.38 (CH$_2$), 36.01 (CH$_2$), 33.88 (CH$_2$), 18.00 (CH$_3$, Ca) ppm.

IR $v_{max}$/cm$^{-1}$ (film): 1600 (m), 1510 (s), 1460 (m), 1160 (s).

LRMS (ES, MeCN): $m/z$ 317 ([M + Na]$^+$, 100%).

HRMS (ES): C$_{18}$H$_{27}$FNaO$_2$ [M + Na]$^+$ calculated 317.1887, found 317.1883.
5.33 rac-1-(2-((1R,2R)-4,4-Bis(methoxymethyl)-2-methylcyclopentyl)ethyl)-4-chlorobenzene 73f

The title compound was prepared using the same method as for compound 74a (Method A) but p-chlorobenzyl chloride (0.160 g, 1 mmol) replaced benzyl chloride. Purification by column chromatography on silica gel (eluent: 5% EtOAc in hexane) gave the title compound (0.094 g, 0.30 mmol, 30%) as a colourless oil.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.24 (2H, d, $J = 8.4$, Ho), 7.10 (2H, d, $J = 8.4$, Hn), 3.36 (3H, s, Hf/g), 3.35 (3H, s, Hf/g), 3.23 (2H, dd, $J = 8.8$, 4.9, He/h), 3.20 (2H, dd, $J = 8.8$, 4.6, He/h), 2.66 (1H, ddd, $J = 14.0$, 10.9, 4.5, Hi), 2.48 (1H, ddd, $J = 13.8$, 10.2, 6.7, Hl), 1.90-1.82 (2H, m, Hc/i, j), 1.74 (1H, dd, $J = 13.0$, 7.0, Hc/i), 1.52 (1H, m, Hb/k), 1.37-1.24 (2H, m, Hb/k), 1.09 (1H, dd, $J = 13.0$, 10.4, Hc/i), 1.02 (1H, dd, $J = 13.0$, 11.0, Hc/i), 0.94 (3H, d, $J = 7.4$, Ha) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 141.42 (C, Cp), 131.26 (C, Cm), 129.58 (CHx2), 128.32 (CHx2), 78.00 (CH$_2$, Ce/h), 77.89 (CH$_2$, Ce/h), 59.24 (CH$_3$x2, Cf, g), 46.29 (CH, Cb), 45.28 (C, Cd), 41.82 (CH$_2$), 39.83 (CH, Cj), 39.41 (CH$_2$), 35.81 (CH$_2$), 34.09 (CH$_2$), 18.04 (CH$_3$, Ca) ppm.

IR $\nu_{max}$/cm$^{-1}$ (film): 1492 (m), 1458 (m), 1106 (s) 812 (m).

LRMS (ES, MeCN): $m/z$ 333 ([M + Na]$^+$, 100%).

HRMS (ES): C$_{18}$H$_{27}$ClNaO$_2$ [M + Na]$^+$ calculated 333.1592, found 333.1586.
5.34 rac-1-(2-((1R,2R)-4,4-Bis(methoxymethyl)-2-methylcyclopentyl)ethyl)-3-chlorobenzene 73g

The title compound was prepared using the same method as for compound 73a (Method A) but m-chlorobenzyl chloride (0.160 g, 1 mmol) replaced benzyl chloride. Purification by column chromatography on silica gel (eluent: 5% EtOAc in hexane) gave the title compound (0.189 g, 0.61 mmol, 61%) as a colourless oil.

$^1$H NMR (300 MHz, CDCl$_3$): δ 7.23-7.13 (4H, m, Ar-H), 6.29 (6H, s, Hf, g), 3.24 (2H, dd, $J = 8.8, 4.2$ Hz, He/h), 3.19 (2H, dd, $J = 8.8, 3.3$, He/h), 2.67 (1H, ddd, $J = 14.1, 11.3, 4.8$, Hl), 2.49 (1H, ddd, $J = 13.7, 10.1, 6.4$, Hl), 1.91-1.83 (2H, m, Hc/i, j), 1.75 (1H, dd, $J = 7.1, 13.0$, Hc/i), 1.62-1.55 (3H, m, Hb, k), 1.09 (1H, dd, $J = 13.0, 10.4$, Hc/i), 1.09 (1H, dd, $J = 13.0, 11.0$, Hc/i), 1.02 (3H, d, $J = 6.4$, Ha) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$): δ 145.06 (C, Cm), 140.0 (C, Co), 129.48 (CH), 128.38 (CH), 126.44 (CH), 125.76 (CH), 78.0 (CH$_2$, Ce/h), 77.89 (CH$_2$, Ce/h), 59.24 (CH$_3$x2, Cg, f), 46.34 (CH, Ch), 45.28 (C, Cd), 41.80 (CH$_2$), 39.83 (CH, Cj), 39.93 (CH$_2$), 35.46 (CH$_2$), 34.45 (CH$_2$), 18.04 (CH$_3$, Ca) ppm.

IR $\nu_{\text{max}}$/cm$^{-1}$ (film): 1515 (w), 1475 (m), 1448 (m), 1106 (s).

LRMS (ES, MeCN): $m/z$ 333 ([M + Na]$^+$, 100%).

HRMS (ES): C$_{18}$H$_{27}$ClNaO$_2$ [M + Na]$^+$ calculated 333.1592, found 333.1591.
To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF at –78 °C was added n-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of 4,4-(bis(methoxymethyl)-1,6-heptadiene (0.184 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. The reaction mixture was cooled to –78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) dropwise. The reaction mixture was stirred at –78 °C for 40 min before the addition of a further equivalent of benzyl carbenoid (benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol)). Addition of further equivalents of carbenoid was repeated until a total of 5 equivalents had been added. The reaction mixture was quenched with MeOH (5 mL) and sat NaHCO₃ (aq) (5 mL) then allowed to warm to rt with stirring for 18 h. The resulting mixture was diluted with Et₂O (100 mL), washed with H₂O (3 x 50 mL) and brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: 5% EtOAc in hexane) gave the title compound (0.181 g, 0.50 mmol, 50%) as a colourless oil.

¹H NMR (400 MHz, CDCl₃): δ 7.30-7.09 (10H, m, Ar-H), 6.35 (1H, d, J = 15.8, Hq), 6.04 (1H, dd, J = 15.8, 8.4, Hp), 3.38 (6H, s, Hk, l), 3.30-3.23 (4H, m, Hj, m), 2.67 (1H, ddd, J = 13.6, 11.3, 5.3, He), 2.53 (1H, ddd, J = 13.6, 10.5, 6.3, He), 2.28 (1H, m, Ho), 1.98-1.87 (2H, m), 1.77 (1H, dd, J = 13.2, 7.3), 1.71 (1H, m), 1.45-1.34 (2H, m), 1.20 (1H, t, J = 12.0, CH₂) ppm.

¹³C NMR (300 MHz, CDCl₃): δ 142.82 (C, Cd), 137.77 (C, Cr), 133.79 (CH, Cp), 129.81 (CH, Cq), 128.44 (CHx2), 128.29 (CHx2), 128.24 (CHx2), 126.84 (CH, Cv), 126.0 (CHx2), 125.88 (CH, Ca), 77.92 (CH₂, Cj/m), 77.89 (CH₂, Cj/m), 59.28 (CH₃x2, Ck, l), 49.85 (CH, Co), 45.84 (C, Ci), 45.26 (CH, Cg), 40.02 (CH₂), 39.15 (CH₂), 35.94 (CH₂), 34.72 (CH₂) ppm.
**IR \( v_{max}/\text{cm}^{-1} \) (film):** 1600 (w), 1495 (m), 1475 (m), 1448 (m), 1104 (s), 963 (s), 745 (s), 693 (s).

**LRMS (ES, MeCN):** \( m/z \) 387 ([M+Na]\(^+\), 100\%).

**HRMS (ES):** \( \text{C}_{25}\text{H}_{32}\text{NaO}_2 \) [M+Na]\(^+\) calculated 387.2295, found 387.2288.

**GC (Method B):** 9.06 min (73a – 6.26 min).
5.36 rac-1-((1R,2R)-4,4-Bis(methoxymethyl)-2-((E)-4-methylstyril)cyclopentyl)ethyl)-4-methylbenzene 74b

To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF at –78 °C was added n-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of 4,4-(bismethoxymethyl)-1,6-heptadiene (0.184 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. The reaction mixture was cooled to –78 °C before the addition of p-methylbenzyl chloride (0.13 mL, 0.140 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) dropwise. After 20 min at –78 °C a further 2 eq of p-methylbenzyl chloride (0.26 mL, 0.280 g, 2.0 mmol) and LDA (1.8 M solution in THF) (1.2 mL, 2.0 mmol) was added dropwise. After a further 20 min the reaction mixture was quenched with 2 M HCl (aq) (5 mL) then allowed to warm to rt with stirring for 18 h. The resulting mixture was diluted with Et₂O (100 mL), washed with H₂O (3 x 50 mL) and brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo.

Purification by column chromatography on silica gel (eluent: 5% Et₂O in hexane) gave the title compound (0.188 g, 0.48 mmol, 48%) as a colourless oil.

¹H NMR (400 MHz, CDCl₃): δ 7.23 (2H, d, J = 8.2, Ar-H), 7.11-7.02 (6H, m, Ar-H), 6.31 (1H, d, J = 15.9, Hr), 5.98 (1H, dd, J = 15.7, 8.4, Hq), 3.38 (6H, s, Hl, m), 3.31-3.22 (4H, m, Hk, n), 2.65 (1H, ddd, J = 13.5, 11.2, 4.9, Hf), 2.49 (1H, ddd, J = 13.7, 10.6, 6.4, Hf), 2.33 (3H, s, Ha/w), 2.31 (3H, s, Ha/w), 2.18 (1H, m, Ho), 1.95 (1H, dd, J = 13.2, 7.5, CH₂), 1.86 (1H, m), 1.81 (1H, dd, J = 13.3, 7.3), 1.70 (1H, m), 1.43-1.32 (2H, m), 1.18 (1H, dd, J = 12.9, 11.1) ppm.

¹³C NMR (100 MHz, CDCl₃): δ 139.75 (C, Cb), 136.52 (C, Cs), 134.93 (Cx2, Cc, u), 132.70 (CH), 129.58 (CH), 129.12 (CHx2), 128.91 (CHx2), 128.14 (CHx2), 125.86 (CHx2), 77.88 (CH₂, Ck/m), 77.84 (CH₂, Ck/m), 59.27 (CH₃x2, Cl, m), 49.85 (CH, Cp), 47.72 (C, Cj), 45.24 (CH, Ch), 40.00 (CH₂), 39.12 (CH₂), 36.12 (CH₂), 34.26 (CH₂), 21.11 (CH₃), 20.96 (CH₃) ppm.

IR v_max/cm⁻¹ (film): 1514 (m), 1475 (m), 1447 (m), 1104 (s), 964 (s) 849(m).
LRMS (ES, MeCN): $m/z$ 415 ([M+Na]$^+$, 100%).

HRMS (ES): $C_{27}H_{36}NaO_2$ [M+Na]$^+$ calculated 415.2608, found 415.2598.

GC (Method B): 9.76 min (73b – 6.64 min).
5.37 *rac*-1-Chloro-4-((E)-2-((1R,2R)-2-(4-chlorophenethyl)-4,4-bis(methoxymethyl)cyclopentyl)vinyl)benzene 74f

The title compound was prepared using the same method as for compound 74a but *p*-chlorobenzyl chloride (0.800 g, 5 mmol) replaced benzyl chloride. Purification by column chromatography on silica gel (eluent: 5% EtOAc in hexane) gave the title compound (0.184 g, 0.43 mmol, 43%) as a colourless oil.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.29-7.23 (6H, m, Ar-H), 7.10-7.08 (2H, d, J = 8.3, Ar-H), 6.31 (1H, d, J = 15.8, Hq), 6.01 (1H, dd, J = 15.8, 8.5, Hp), 3.39 (6H, s, Hk, l), 3.31-3.22 (4H, m, Hm, j), 2.67 (1H, ddd, J = 14.1, 10.8, 4.8, He), 2.51 (1H, ddd, J = 13.6, 10.2, 6.5, He), 2.28 (1H, m, Ho), 1.95 (1H, dd, J = 13.1, 7.5, CH$_2$), 1.91-1.80 (2H, m, CH$_2$/CH), 1.69 (1H, m, CH$_2$), 1.44-1.36 (2H, m, CH$_2$), 1.21 (1H, dd, J = 12.8, 11.3, CH$_2$) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 141.10 (C, Cd), 136.08 (C, Cr), 134.33 (CH, Cp), 132.45 (C, Cv), 131.32 (C, Ca), 129.61 (CHx2), 128.58 (CH, Cq), 128.57 (CHx2), 128.33 (CHx2), 127.17 (CHx2), 77.88 (CH$_2$, Cj/m), 77.85 (CH$_2$, Cj/m), 59.29 (CH$_3$x2, Ck, l), 49.89 (CH, Co), 45.78 (C, Ci), 45.07 (CH, Cg), 39.91 (CH$_2$), 39.06 (CH$_2$), 35.78 (CH$_2$), 34.01 (CH$_2$) ppm.

IR $\nu_{\text{max}}$/cm$^{-1}$ (film): 1490 (s), 1104 (s), 965 (s).

LRMS (ES, MeCN): m/z 455 ([M+Na]$^+$, 100%).

HRMS (ES): C$_{25}$H$_{30}$Cl$_2$NaO$_2$[M+Na]$^+$ calculated 455.1515, found 455.1508.

GC (Method B): 10.45 min (73f – 10.45 min).
5.38 rac-1-((1R,2R)-4,4-Bis(methoxymethyl)-2-((E)-styryl)cyclopentyl)ethyl)-4-methylbenzene

To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF at −78 °C was added n-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of 4,4-(bismethoxymethyl)-1,6-heptadiene (0.184 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. The reaction mixture was cooled to −78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) dropwise. After 40 min at −78 °C the reaction mixture was warmed to rt for 40 min before being cooled to 0 °C and LDA (1.8 M solution in THF) (0.3 mL, 0.5 mmol) added dropwise. A sample was removed (0.5 mL) and quenched with 1 M DCl in D$_2$O (1 mL) to confirm the diastereotopic ratio of the mono-inserted product. The reaction mixture was cooled to −78 °C before the addition of p-methylbenzyl chloride (0.13 mL, 0.140 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). After a further 20 min the reaction mixture was quenched with 1 M DCl in D$_2$O (5 mL) then allowed to warm to rt with stirring for 18 h. The resulting mixture was diluted with Et$_2$O (100 mL), washed with H$_2$O (3 x 50 mL) and brine (50 mL), dried (MgSO$_4$) and the solvent removed in vacuo. Purification by column chromatography on silica (eluent: 5% Et$_2$O in hexane) yielded a mixture of mono-inserted (73a), bis-inserted (74a), cross over bis-inserted (74j) and cross over bis-inserted (74k) in a ratio of 8:4:20:1. The yield was not calculated as the reaction was carried out as part of a mechanistic study and several samples were removed from the reaction mixture during the course of the reaction. The crossover products were observed as a ratio of 20:1 (title compound (74j): minor (74k)). Further purification by prep HPLC (eluent: hexane) was carried out to give a pure sample of the title compound as a colourless oil.

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.35-7.17 (5H m, Ar-H), 7.09-7.03 (4H, m, Ar-H), 6.35 (1H, d, J = 15.9, Hr), 6.04 (1H, dd, J = 15.9, 8.5, Hq), 3.38 (6H, s, Hl, m), 3.31-3.23 (4H, m, Hk, n), 2.65 (1H, ddd, J = 13.5, 11.0, 5.1, Hf), 2.49 (1H, ddd, J = 13.5,
10.6, 6.3, Hf), 2.31 (3H, s, Ha), 2.27 (1H, m, Hp), 1.95 (1H, dd J = 13.0, 7.5 Hz, CH₂), 1.90 (1H, m, CH), 1.82 (1H, dd, J = 13.4, 7.3, CH₂), 1.71 (1H, m, CH₂), 1.44-1.27 (2H, m, CH₂), 1.19 (1H, dd, J = 12.9, 11.1, CH₂) ppm.

$^{13}$C NMR (100 MHz, CDCl₃): δ 139.73 (C, Cb), 137.69 (C, Cs), 134.98 (C, Ce), 133.72 (CH, Cq), 129.77 (CH, Cr), 128.92 (CHx₂), 128.44 (CHx₂, Cu), 128.14 (CHx₂), 126.82 (CH, Cv), 125.92 (CHx₂, Ct), 77.86 (CH, Ck/h), 77.82 (CH, Ck/h), 59.29 (CH₃x₂, Cl, m), 49.87 (CH, Cp), 45.72 (C, Cj), 45.24 (CH, Ch), 39.95 (CH₂), 39.12 (CH₂), 36.14 (CH₂), 34.27 (CH₂), 20.96 (CH₃, Ca) ppm.

IR ν max/cm⁻¹ (film): 1514 (w), 1494 (w), 1448 (m), 1104 (s), 963 (s), 746 (s).

LRMS (ES, MeCN): m/z 401 ([M+Na]⁺, 100%).


NMR analysis of the mono inserted product prior to insertion of the second benzyl carbenoid revealed that there was only one diastereoisomer.

$^1$H NMR (300 MHz, CDCl₃): δ 7.36-7.18 (5H, m, Ar-H), 3.36 (6H, s, Hf, g), 3.26-3.17 (4H, m, He, h), 2.67 (1H, m, Hl), 1.92-1.85 (2H, m, Hc/i, b), 1.74 (1H, dd, J = 13.0, 6.9, Hc/i), 1.52-1.27 (3H, m, Hj, k), 1.10 (1H, dd, J = 13.0, 10.4, Hc/i), 1.01 (1H, dd, J = 13.0, 11.2, Hc/i), 0.92 (2H, d, J = 6.0, Ha) ppm.
To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF at –78 °C was added n-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of 4,4-(bismethoxymethyl)-1,6-heptadiene (0.184 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. The reaction mixture was cooled to –78 °C before the addition of p-methylbenzyl chloride (0.13 mL, 0.140 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) dropwise. After 40 min at –78 °C the reaction mixture was warmed to rt for 40 min before being cooled to 0 °C and LDA (1.8 M solution in THF) (0.3 mL, 0.5 mmol) added dropwise. A sample was removed (0.5 mL) and quenched with 1 M DCl in D$_2$O (1 mL) to confirm the diastereotopic ratio of the mono-inserted product. The reaction mixture was cooled to –78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). After a further 20 min the reaction mixture was quenched with 1 M DCl in D$_2$O (5 mL) then allowed to warm to rt with stirring for 18 h. The resulting mixture was diluted with Et$_2$O (100 mL), washed with H$_2$O (3 x 50 mL) and brine (50 mL), dried (MgSO$_4$) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: 5% Et$_2$O in hexane) yielded a mixture of mono-inserted (73b), bis-inserted (74b), cross over bis-inserted (74k) and cross over bis-inserted (74j) in a ratio of 40:8:40:1. The yield was not calculated as the reaction was carried out as part of a mechanistic study and several samples were removed from the reaction mixture during the course of the reaction. The crossover products were observed as a ratio of 40:1 (title compound (74k): minor (74j)). Further purification by prep HPLC (eluent: hexane) was carried out to give a pure sample of the title compound as a colourless oil.

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.25-7.09 (9H, m, Ar-H), 6.32 (1H, d, J = 15.7, Hq), 5.98 (1H, dd, J = 15.7, 8.4, Hp), 3.38 (6H, s, Hk, l), 3.32-3.22 (4H, m, Hj, m), 2.68 (1H, ddd, J = 13.5, 11.0, 4.9, He), 2.53 (1H, ddd, J = 13.6, 10.6, 6.2, He), 2.33 (3H, s,
1.95 (1H, dd, J = 13.0, 7.3, CH₂), 1.87 (1H, m, CH₂), 1.81 (1H, dd, J = 13.4, 7.3, CH₂), 1.70 (1H, m CH₂), 1.45 (2H, m, CH₂), 1.19 (1H, dd, J = 12.9, 11.1, CH₂) ppm.

^13^C NMR (100 MHz, CDCl₃): δ 142.84 (C, Cd), 136.57 (C, Cr), 134.90 (C, Cv), 132.67 (CH, Cp), 129.62 (CH, Cq), 129.14 (CHx2, Ct), 128.29 (CHx2), 128.22 (CHx2), 125.87 (CHx2, Cs), 125.56 (CH, Ca), 77.87 (CH₂, Cj/m), 77.84 (CH₂, Cj/m), 59.29 (CH₃x2, Ck, l), 49.88 (CH, Co), 45.70 (C, Ci), 45.26 (CH, Cg), 40.00 (CH₂), 39.12 (CH₂), 35.97 (CH₂), 34.72 (CH₂), 21.12 (CH₃, Cu) ppm.

IR vₘₐₓ/cm⁻¹ (film): 1513 (m), 1496 (w), 1453 (m), 1104 (s), 964 (s), 699 (s).

LRMS (ES, MeCN): m/z 401 ([M+Na]^+, 100%).


NMR analysis of the mono-inserted product prior to insertion of the second benzyl carbenoid revealed that there was only one diastereoisomer.

^1^H NMR (300 MHz, CDCl₃): δ 7.09 (4H, s, Ar-H), 3.36 (6H, s, Hf, g), 3.26-3.18 (4H, m, He, h), 2.64 (1H, m, Hl), 2.33 (3H, s, Hq) 1.91-1.83 (2H, m, Hc/i, b), 1.74 (1H, dd, J = 13.0, 7.0, Hc/i), 1.39-1.22 (3H, m, Hj, k), 1.10 (1H, dd, J = 12.8, 10.3, Hc/i), 1.01 (1H, dd, J = 12.8, 11.6, Hc/i), 0.91 (2H, d, J = 6.0, Ha) ppm.
5.40 \textit{rac}-1-(2-((1R,2R)-4,4-Bis(methoxymethyl)-2-((E)-styryl)cyclopentyl)ethyl)-4-methylbenzene 74j and \textit{rac}-1-((E)-2-((1R,2R)-4,4-Bis(methoxymethyl)-2-phenethylcyclopentyl)vinyl)-4-methylbenzene 74k

To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF at –78 °C was added n-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of 4,4-bis(methoxymethyl)-1,6-heptadiene (0.184 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. The reaction mixture was cooled to –78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) dropwise. After 40 min as –78 °C the reaction mixture was warmed to rt for 40 min. A sample was removed (0.5 mL) and quenched with 1 M DCl in D$_2$O (1 mL) to confirm the diastereotopic ratio of the mono-inserted product. The reaction mixture was cooled to –78 °C before the addition of \textit{p}-methylbenzyl chloride (0.13 mL, 0.140 g, 1.0 mmol) and LDA (0.6 mL of 1.8 M solution in THF, 1.0 mmol). After a further 20 min the reaction mixture was quenched with 1 M DCl in D$_2$O (5 mL) then allowed to warm to rt with stirring for 18 h. The resulting mixture was diluted with Et$_2$O (100 mL), washed with H$_2$O (3 x 50 mL) and brine (50 mL), dried (MgSO$_4$) and the solvent removed \textit{in vacuo}. Purification by column chromatography on silica gel (elucent: 5% Et$_2$O in hexane) yielded a mixture of mono-inserted (73a), bis-inserted (74a), cross over bis-inserted (74j) and cross over bis-inserted (74k) in a ratio of 1:2:4:3.

$^{13}$C NMR (75 MHz, CDCl$_3$): δ 142.82 (C, Cd’), 139.72 (C, Cb), 137.68 (C, Cs), 136.54 (C, Cr’), 134.96 (C, Cu’), 134.89 (C, Ce), 133.72 (CH, Cq), 129.76 (CH, Cr), 129.12 (CH), 128.91 (CH), 128.43 (CH), 128.29 (CH), 128.22 (CH), 128.14 (CH), 126.82 (CH, Cu), 125.97 (CH, Cv), 125.86 (CH), 77.86 (CH$_2$), 77.82 (CH$_2$), 59.27 (CH$_3$), 49.87 (CH, Cp, o’), 45.72 (C, Cj, Ci’), 45.34 (CH, Ch, g’), 39.95 (CH$_2$), 39.11
(CH₂), 36.13 (CH₂), 35.97 (CH₂), 34.72 (CH₂), 34.25 (CH₂), 21.11 (CH₃, Cu⁺), 20.96 (CH₃, Ca) ppm.

NMR analysis of the mono inserted product prior to insertion of the second benzyl carbenoid revealed a 1:1 ratio of diastereoisomers

\[
\begin{align*}
\text{C}_{18}H_{26}D_2O_2 &\quad \text{Mol. Wt.: 278.43} \\
\text{C}_{18}H_{26}D_2O_2 &\quad : \quad \text{Mol. Wt.: 278.43}
\end{align*}
\]

\[^1\text{H NMR (300 MHz, CDCl}_3\text{):} \delta 7.37-7.18 (5H, m, Ar-H), 3.36 (6H, s, Hf, g), 3.26-3.17 (4H, m, He, h), 2.68 (0.5H, m, Hl'), 2.50 (0.5H, m, Hl), 1.91-1.85 (2H, m, Hc/i, b), 1.74 (1H, dd, J = 13.0, 7.0, Hc/i), 1.42-1.19 (3H, m, Hj, k), 1.01 (1H, dd, J = 12.7, 10.2, Hc/i), 0.92 (2H, d, J = 5.9, Ha) ppm.
\]

NMR analysis of the mono inserted product remaining after the insertion of the second benzyl carbenoid revealed a 1:0.75 ratio of diastereoisomers.

\[
\begin{align*}
\text{C}_{18}H_{26}D_2O_2 &\quad \text{Mol. Wt.: 278.43} \\
\text{C}_{18}H_{26}D_2O_2 &\quad : \quad \text{Mol. Wt.: 278.43}
\end{align*}
\]

\[^1\text{H NMR (300 MHz, CDCl}_3\text{):} \delta 7.31-7.15 (5H, m, Ar-H), 3.36 (6H, s, Hf, g), 3.26-3.17 (4H, m, He, h), 2.70 (0.57H, m, Hl'), 2.50 (0.43H, m, Hl), 1.90-1.85 (2H, m, Hc/i, b), 1.73 (1H, dd, J = 13.0, 7.4, Hc/i), 1.52-1.26 (3H, m, Hj, k), 1.09 (1H, dd, J = 13.1, 10.4, Hc/i), 1.01 (1H, dd, J = 12.8, 11.2, Hc/i), 0.92 (2H, d, J = 6.0, Ha) ppm.
\]
5.41 *rac*-1-((E)-2-((1R,2R)-4,4-Bis(methoxymethyl)-2-phenethylcyclopentyl)vinyl)-4-methylbenzene 74k and *rac*-1-((1R,2R)-4,4-Bis(methoxymethyl)-2-((E)-styryl)cyclopentyl)ethyl)-4-methylbenzene 74j

To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF at −78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of 4,4-bis(methoxymethyl)-1,6-heptadiene (0.184 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. The reaction mixture was cooled to −78 °C before the addition of *p*-methylbenzyl chloride (0.13 mL, 0.140 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) dropwise. After 40 min as −78 °C the reaction mixture was warmed to rt for 40 min. A sample was removed (0.5 mL) and quenched with 1 M DCl in D$_2$O (1 mL) to confirm the diastereotopic ratio of the mono-inserted product. The reaction mixture was cooled to −78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (0.6 mL of 1.8 M solution in THF, 1.0 mmol). After a further 20 min the reaction mixture was quenched with 1 M DCl in D$_2$O (5 mL) then allowed to warm to rt with stirring for 18 h. The resulting mixture was diluted with Et$_2$O (100 mL), washed with H$_2$O (3 x 50 mL) and brine (50 mL), dried (MgSO$_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 5% Et$_2$O in hexane) yielded a mixture of mono-inserted (73b), bis-inserted (74b), cross over bis-inserted (74j) and cross over bis-inserted (74k) in a ratio of 4:3:2:10.

**$^{13}$C NMR (75 MHz, CDCl$_3$):** δ 142.87 (C, Cd'), 136.59 (C, Cr'), 134.94 (C, Cu'), 133.77 (CH, Cr), 132.71 (CH, Cp'), 129.65 (CH, Cq'), 129.17 (CH), 128.95 (CH, Ce), 128.47 (CH, Ct), 128.26 (CH), 128.19 (CH, Cd), 126.86 (CH, Cu), 125.90 (CH, Cv), 125.60 (CH, Ca), 77.91 (CH$_2$), 77.88 (CH$_2$), 59.32 (CH$_3$), 49.91 (CH), 45.75 (C), 45.29
(CH), 40.03 (CH₂), 39.16 (CH₂), 39.01 (CH₂), 34.77 (CH₂), 34.31 (CH₂), 21.16 (CH₃, Cu⁺), 21.60 (CH₃, Ca) ppm.

NMR analysis of the mono inserted product prior to insertion of the second benzyl carbenoid revealed a 1:1 ratio of diastereoisomers.

\[^1\text{H NMR (300 MHz, CDCl}_3\text{): }\delta 7.09 (4\text{H, s, Ar-H}), 3.36 (6\text{H, s, Hf, g}), 3.27-3.18 (4\text{H, m, He, h}), 2.64 (0.5\text{H, m, Hl}), 2.42 (0.5\text{H, m, Hl}) 2.33 (3\text{H, s, Hq}) 1.91-1.85 (2\text{H, m, Hc/i, b}), 1.74 (1\text{H, dd, }J = 13.0, 9.4, \text{Hc/i}), 1.55-1.24 (3\text{H, m, Hj, k}), 1.09 (1\text{H, dd, }J = 13.0, 10.4, \text{Hc/i}), 1.01 (1\text{H, dd, }J = 13.1, 11.5, \text{Hc/i}), 0.92 (2\text{H, d, }J = 6.0, \text{Ha})\text{ ppm.}\]

NMR analysis of the mono inserted product remaining after the insertion of the second benzyl carbenoid revealed a 0.4:0.6 ratio of diastereoisomers.

\[^1\text{H NMR (300 MHz, CDCl}_3\text{): }\delta 7.09 (4\text{H, s, Ar-H}), 3.36 (6\text{H, s, Hf, g}), 3.26-3.17 (4\text{H, m, He, h}), 2.63 (0.6\text{H, m, Hl}), 2.42 (0.4\text{H, m, Hl}) 2.33 (3\text{H, s, Hq}) 1.90-1.84 (2\text{H, m, Hc/i, b}), 1.73 (1\text{H, dd, }J = 13.0, 7.4, \text{Hc/i}), 1.55-1.24 (3\text{H, m, Hj, k}), 1.09 (1\text{H, dd, }J = 13.0, 10.4, \text{Hc/i}), 1.01 (1\text{H, dd, }J = 13.1, 11.3, \text{Hc/i}), 0.92 (2\text{H, d, }J = 6.0, \text{Ha})\text{ ppm.}\]
5.42 3-Allyldihydrofuran-2(3H)-one 91

Synthesis was carried out using a procedure published by Walton and Fraser-Reid.75 n-BuLi (2.5 M solution in hexanes) (14.0 mL, 34.9 mmol) was added to a solution of distilled diisopropylamine (4.90 mL, 34.9 mmol) in THF (250 mL) at 0 ºC and then cooled to –78 ºC. A solution of the dihydrofuran-2(3H)-one (2.50 g, 29 mmol) in THF (25 mL) was added dropwise. After 30 min HMPA (7.6 mL, 43.6 mmol) was added followed by allyl bromide (2.8 mL, 31.9 mmol). The mixture was stirred for 2 h at –78 ºC and quenched with sat NH₄Cl (aq) (25 mL) before being warmed to rt. The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: 20 % EtOAc in hexane) to yield the title compound (1.47 g, 12 mmol, 41%) as a colourless oil.

Data was consistent with published data75.

$^1$H NMR (400 MHz, CDCl₃): 5.78 (1H, tdd, $J = 7.0, 10.0, 17.1$, Hf), 5.15-5.09 (2H, m, He), 4.32 (1H, ddd, $J = 3.3, 9.0, 12.0$, Ha), 4.19 (1H, ddd, $J = 7.0, 9.3, 16.3$, Ha), 2.68-2.57 (2H, m), 2.40-2.22 (2H, m), 1.99 (1H, tt, $J = 6.9, 9.5$, Hc) ppm.

$^{13}$C NMR (100 MHz, CDCl₃): δ 178.72 (C=O, Cg), 134.35 (CH, Ce), 117.65 (CH₂, Cf), 66.49 (CH₂, Ca), 38.79 (CH, Ce), 34.29 (CH₂), 27.76 (CH₂) ppm.

IR $v_{max}$ cm$^{-1}$ (film): 1761 (s), 1642 (w), 1440 (w), 1374 (w) 1163 (s), 916 (m).
Synthesis was carried out using a procedure published by Walton and Fraser-Reid.\textsuperscript{25} To a solution of 3-allyldihydrofuran-2(3\textit{H})-one (1.26 g, 10 mmol) in toluene (50 mL) at \(-78 \, ^\circ\text{C}\) was added DIBAL-H (1M solution in toluene) (40 mL, 40 mmol). After 30 min at \(-78 \, ^\circ\text{C}\) the mixture was quenched by dropwise addition of MeOH (20 mL). Sat potassium sodium tartrate (aq) (30 mL) and sat NH\(_4\)Cl (aq) (20 mL) was added and the reaction mixture was stirred for 3 h until the organic layer was clear. The reaction mixture was diluted with EtOAc (100 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried (MgSO\(_4\)) and the solvent removed \textit{in vacuo} to give 3-allyltetrahydrofuran-2-ol \textit{92} (0.72 g) which was used directly in the next reaction.

Wittig olefination was carried out using a procedure published by Bailey \textit{et al.}\textsuperscript{26} To a solution methyltriphenylphosphonium bromide (5.36 g, 15 mmol) in THF (50 mL) at 0 \(^\circ\text{C}\) was added KHMDS (0.5 M solution in toluene) (30 mL, 15 mmol). The resulting yellow suspension was stirred at 0 \(^\circ\text{C}\) for 15 min before warming to rt for 1 h. The mixture was then recooled to 0 \(^\circ\text{C}\) and a solution of 3-allyltetrahydrofuran-2-ol \textit{92} (0.72 g) in THF (5 mL) was added slowly over 40 min. The mixture was stirred for a further 1 h at rt, poured onto 2 M HCl (aq) (75 mL) and extracted with Et\(_2\)O (1 x 50 mL). The combined organic extracts were washed with sat NaHCO\(_3\) (aq) (50 mL) and brine (50 mL), dried (MgSO\(_4\)) and the solvent removed \textit{in vacuo}. Purification by column chromatography on silica gel (eluent: 25 \% EtOAc in hexane) yielded the title compound (0.51 g, 4.1 mmol, 41\%) as a colourless oil.

Data was consistent with published data\textsuperscript{26}.

\textsuperscript{1}H NMR (300 MHz, CDCl\(_3\)): 5.66 (1H, tdd, \(J = 6.9, 10.4, 17.4\), He), 5.52 (1H, br dd, \(J = 8.4, 17.6\), Hg), 4.96-4.90 (4H, m, Hf, h), 3.64-3.50 (2H, m), 2.18-2.00 (2H, m), 1.95 (1H, br s, OH), 1.63 (1H, m, He), 1.46-1.36 (2H, m) ppm.
\(^{13}\text{C NMR (75 MHz, CDCl}_3\):} \text{\(\delta\)} 142.12 (CH\(_2\), f/h), 136.51 (CH\(_2\), Cf/h), 116.06 (CH, Cg/e), 114.90 (CH, Cg/e), 61.08 (CH\(_2\), Ca), 40.69 (CH, Cc), 39.61 (CH\(_2\)), 36.93 (CH\(_2\)) ppm.

**IR \(v_{\text{max}/\text{cm}^{-1}}\) (film):** 3328 (br s), 1640 (m), 1440 (w), 1419 (w), 1050 (m), 992 (s), 999 (s).
5.44 1-(5-Vinyloct-7-en-1-ynyl)benzene 95

Standard procedure was published by Baum et al.77 A solution of 3-vinylhex-5-en-1-ol (0.81 g, 6.4 mmol), pyridine (0.52 mL, 6.4 mmol) and CH$_2$Cl$_2$ (2 mL) was added dropwise over 15 min to a solution of triflic anhydride (2.08 g, 7.4 mmol) in CH$_2$Cl$_2$ (5 mL) at 0 °C. After 15 min the solution was diluted with CH$_2$Cl$_2$ (50 mL), washed with water (3 x 50 mL), dried (MgSO$_4$) and the solvent removed in vacuo to give 3-vinylhex-5-enyl trifluoromethanesulfonate 94 (1.50 g, 6.2 mmol, 97%) which was used directly in the next reaction.

To a stirred solution of phenylacetylene (0.29 mL, 2.7 mmol) in THF (10 mL) at –78 ºC was added n-BuLi (2.5 M solution in THF) (1.1 mL, 2.8 mmol) dropwise. After 30 min at –78 ºC a solution of 3-vinylhex-5-enyl trifluoromethanesulfonate 94 (0.774 g, 3.2 mmol) in THF (2 mL) was added and the mixture was allowed to warm to rt for 18 h. The reaction mixture was quenched with sat NH$_4$Cl (aq) (20 mL) and extracted with Et$_2$O (10 mL). The aqueous layer was separated and re-extracted with Et$_2$O (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried (MgSO$_4$) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: 10 % EtOAc in hexane) yielded the title compound (0.268 g, 1.1 mmol, 41%) as a colourless oil.

$^1$H NMR (300 MHz, CDCl$_3$): 7.33-7.30 (2H, m, Ar-H), 7.20-7.18 (3H, m, Ar-H), 5.71 (1H, tdd, J = 17.4, 10.5, 7.1, Hk), 5.52 (1H, ddd, J = 18.0, 9.6, 8.4, Hm), 5.02-4.91 (4H, m, Hl, n), 2.41-2.18 (3H, m), 2.11-2.04 (2H, m), 1.69 (1H, m), 1.45 (1H, m) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$): 141.38 (CH, Cm/k), 136.57 (CH, Cm/k), 131.51 (CHx2), 128.16 (CHx2), 127.48 (CH), 124.02 (C, Cd), 116.01 (CH$_2$, Cn/l), 115.35 (CH$_2$, Cn/l), 90.08 (C, Ce/f), 80.90 (C, Ce/f) 42.84 (CH, Ci), 39.26 (CH$_2$), 32.98 (CH$_2$), 17.20 (CH$_2$, Cg) ppm.

IR $\nu_{max}$/cm$^{-1}$ (film): 1640 (w), 1598 (w), 1489 (m), 993 (m), 911 (s), 754 (s), 690 (s).

LRMS (EI, CH$_2$Cl$_2$): 210 ([M$^+$], 2%), 169 (100%), 141 (60%), 115 (100%).

HRMS (ES): C$_{16}$H$_{18}$ [M$^+$] calculated 210.1409, found 210.1413.
5.45 Attempted zirconocene mediated co-cyclisation of 1-(5-Vinylct-7-en-1-ynyl)benzene.

To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at –78 °C was added n-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of 1-(5-Vinylct-7-en-1-ynyl)benzene 95 (0.210 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. A sample (1 mL) was removed, quenched with 2 M HCl (aq) (1 mL) and stirred for 2 h. The reaction mixture was extracted with Et₂O (5 mL), washed with water (3 x 5 mL) and brine (5 mL), dried (MgSO₄) and the solvent removed in vacuo.

\[ \text{Ph} \quad \text{Ph} \]

\[ 98 \quad 99 \]

Analysis of the crude \(^1\)H NMR revealed the following peaks which are characteristic of a 1:1 mixture of 98 and 99.

\(^1\)H NMR (300 MHz, CDCl₃): 6.17 (1H, s, Ha/a’), 6.16 (1H, s, Ha/a’), 5.78 (1H, tdd, J = 7.0, 9.6, 17.3, Hc), 5.69 (1H, ddd, J = 7.5, 10.2, 17.5, Hc’), 5.03-4.84 (4H, m, Hd, d’), 1.13 (3H, d, J = 11.3, Hb/b’), 1.12 (3H, d, J = 11.9, Hb/b’) ppm.

GC (method B): 8.62 and 8.86 min.
5.46 2-Methylenehex-5-en-1-ol 103

Synthesis was carried out using a procedure published by Trost et al.\textsuperscript{78} To a solution of n-BuLi (2.5 M in hexanes) (320 ml, 800 mmol) at –78 °C was added TMEDA (121 mL, 800 mmol) dropwise. Et\textsubscript{2}O (160 mL) was added to the reaction mixture. 2-Methyl-2-propen-1-ol (34 mL, 400 mmol) was added and the solution was warmed to rt for 20 h. The solution was cooled to –78 °C before the dropwise addition of allyl bromide (25.4 mL, 300 mmol) in Et\textsubscript{2}O (40 mL). The solution was stirred for 2 h at –78 °C and then warmed to rt for a further 2 h. The reaction mixture was quenched with sat NH\textsubscript{4}Cl (aq) (50 mL) and extracted with Et\textsubscript{2}O (3 x 400 mL). The combined organic layers were washed with CuSO\textsubscript{4} (aq) (3 x 400 mL) and brine (2 x 400 mL), dried (MgSO\textsubscript{4}) and the solvent removed by distillation to yield the title compound (19.2 g, 170 mmol, 57%) as a pale yellow oil. The compound was used crude without any further purification.

Data was consistent with published data.\textsuperscript{78}

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \(\delta\) 5.81 (1H, ddd, \(J = 16.2, 10.2, 6.3, \text{Hf}\)), 5.06-4.87 (4H, m, \(\text{Hg, c}\)), 4.05 (2H, s, \(\text{Ha}\)), 2.27-2.14 (4H, m, \(\text{Hd, e}\)) 1.73 (1H, s, \(\text{OH}\)) ppm.

\textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): \(\delta\) 148.26 (C, \(\text{Cb}\)), 138.08 (CH, \(\text{Cf}\)), 114.71 (CH\textsubscript{2}, \(\text{Cg/Cc}\)), 109.44 (CH\textsubscript{2}, \(\text{Cg/Cc}\)), 65.67 (CH\textsubscript{2}, \(\text{Ca}\)), 32.12 (CH\textsubscript{2}), 31.82 (CH\textsubscript{2}) ppm.

IR \(v_{\text{max/cm}}^{-1}\) (film): 3336 (br), 1641 (m), 1449 (m), 1023 (m), 993 (m), 899 (s).
5.47 *N*-Benzyl-3-phenylprop-2-yn-1-amine 107

Synthesis of (3-bromoprop-1-ynyl)benzene 106 was carried out following a procedure published by Chan *et al.* To a solution of PPh₃ (9.43 g, 38 mmol) in CH₂Cl₂ (150 mL) at 0 °C was added bromine (1.95 mL, 6.07 g, 38 mmol) dropwise. The solution was stirred for 30 min before the addition of 3-phenyl-2-propyne-1-ol (5 g, 38.0 mmol). The solution was stirred for 1 h before the addition of hexane (600 mL). The resulting suspension was passed through a short silica pad. The solvent was removed *in vacuo* to yield the title compound (5.30 g, 27 mmol, 71%) as a colourless oil. Alkyne 106 was used crude without any further purification. Data was consistent with published data.

**¹H NMR (300 MHz, CDCl₃):** δ 7.45 (2H, m, Ar-H), 7.35-7.32 (3H, m, Ar-H), 4.18 (2H, s, Hg) ppm.

Synthesis of *N*-benzyl-3-phenylprop-2-yn-1-amine 107:

To a solution of benzylamine (11.5 g, 48 mmol) in Et₂O (10 mL) at 0 °C was added (3-bromoprop-1-ynyl)benzene (5.3 g, 24 mmol) and the mixture was stirred at rt for 18 h. The reaction mixture was poured onto H₂O (100 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried (MgSO₄) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 5% Et₃N, 10% Et₂O in hexane) yielded the title compound (2.82 g, 12.7 mmol, 53%) as a colourless oil.

**¹H NMR (300 MHz, CDCl₃):** δ 7.54 (2H, m, Ar-H), 7.38 (2H, d, J = 8.1, Ar-H), 7.27-7.16 (3H, m, Ar-H), 7.09-7.06 (3H, m, Ar-H). 3.80 (2H, s, He), 3.47 (2H, s, Hf), 1.05 (1H, br s, NH) ppm.

**¹³C NMR (75 MHz, CDCl₃):** δ 140.42 (C, Cd), 132.0 (CHx2, Cj), 128.67 (CHx2), 128.61 (CHx2), 128.58 (CHx2), 128.13 (CH), 127.22 (CH), 124.21 (C, Ci), 88.72 (C, Cg/h), 83.94 (C, Cg/h), 52.62 (CH₂, Ce), 38.39 (CH₂, Ch) ppm

**IR νₓ/cm⁻¹ (film):** 1599 (m), 1486 (m) 756 (s), 733 (s), 688 (s).

**LRMS (ES, MeCN):** m/z 222 ([M + H]⁺, 100%).
Synthesis of 2-methylenehex-5-en-yl methanesulfonate 104: To a stirred solution of 2-methylenehex-5-en-1-ol 103 (4.0 g, 35.7 mmol) and Et₃N (5.5 g, 54 mmol) in CH₂Cl₂ (100 mL) at –10 °C was added MsCl (3.3 mL, 42 mmol) dropwise maintaining the temperature between –10 - 0 °C. The solution was warmed to rt and stirred for 30 min before being poured onto H₂O (50 mL). The organic layer was separated. The aqueous layer was re-extracted with CH₂Cl₂ (3 x 50 mL). The combined organic extracts were washed with 2 M HCl (aq) (50 mL), H₂O (50 mL), sat NaHCO₃ (aq) (50 mL) and brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo to yield 2-methylenehex-5-en-yl methanesulfonate 104 (6.65g, 35 mmol, 98%) as a pale yellow oil. The compound was used crude without any further purification.

¹H NMR (300 MHz, CDCl₃): δ 5.89-5.75 (1H, m, Hb), 5.21-4.99 (4H, m, Ha, f), 4.67 (2H, s, Hg), 3.03 (3H, s, Hh), 2.25 (4H, m, Hd, c) ppm.

Synthesis of N-benzyl-2-methylene-N-(3-phenylprop-2-ynyl)hex-5-en-1-amine 108: To a stirred solution of amine 107 (3.32 g, 15 mmol) and LiI (0.40 g, 3 mmol) in THF (30 mL) at 0 °C was added 2-methylenehex-5-en-yl methanesulfonate 104 (2.85 g, 15 mmol) in THF (5 mL) dropwise. The solution was warmed to rt and stirred for 18 h before being poured onto H₂O (50 mL) and extracted with Et₂O (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: 5% Et₃N, 10% Et₂O in hexane) yielded the title compound (2.68 g, 8.5 mmol, 57%) as a colourless oil.

¹H NMR (300 MHz, CDCl₃): δ 7.51-7.23 (10H, m, Ar-H), 5.84 (1H, m, Hr), 5.10-4.94 (4H, m, Ho, s), 3.69 (2H, s, He), 3.60 (2H, s, Hf), 3.17 (2H, s, Hm), 2.28-2.19 (4H, m, Hp, q) ppm.

¹³C NMR (75 MHz, CDCl₃): δ 146.24 (C, Cn), 139.10 (C, Cd), 138.57 (CH, Cr), 131.72 (CHx2, Cj), 129.01 (CHx2), 138.24 (CHx4), 127.91 (CH), 127.01 (CH), 123.44
(C, Ci), 114.46 (CH₂, Cs), 112.94 (CH₂, Co), 85.56 (C, Cg/h), 84.61 (C, Cg/h), 58.85 (CH₂, Cm), 57.49 (CH₂, Ce), 42.17 (CH₂, Cf), 33.37 (CH₂, Cp), 31.86 (CH₂, Cq) ppm.

**IR** νₘₐₓ/cm⁻¹ (film): 2359 (w), 1641 (m), 1489 (m), 904 (s), 754 (s), 690 (s).

**LRMS (ES, MeCN):** m/z 316 ([M + H]⁺, 100%).

**HRMS (ES):** C₂₃H₂₆N [M + H]⁺ calculated 316.2060, found 316.2066.
5.49 (Z)-1-Benzyl-4-benzylidene-3-(but-3-en-1-yl)-3-methylpyrrolidine

To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at –78 °C was added n-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of N-benzyl-2-methylene-N-(3-phenylprop-2-ynyl)hex-5-en-1-amine 108 (0.315 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. 2 M HCl (aq) (5 mL) was added and the mixture was stirred for 18 h before neutralising with 2 M NaOH (aq) (5 mL). The reaction mixture was extracted with Et₂O (50 mL), washed with water (3 x 50 mL) and brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: 5% Et₂O in hexane) yielded the title compound (0.229 g, 0.72 mmol, 72%) as a colourless oil.

¹H NMR (300 MHz, CDCl₃): δ 7.38-7.14 (10H, m, Ar-H), 6.14 (1H, s, Hh), 5.84 (1H, tdd, J = 17.0, 10.1, 6.4, Hr), 5.02 (1H, dd, J = 17.0, 1.3, Hs), 4.93 (1H, dd, J = 10.1, 1.3, Hs), 3.69 (2H, s), 3.60 (2H, s), 2.60 (1H, d, J = 8.7, Hm), 2.42 (1H, d, J = 8.7, Hm), 2.25-1.92 (2H, m, Hq), 1.72-1.62 (2H, m, Hp), 1.24 (3H, s, Ho) ppm.

¹³C NMR (75 MHz, CDCl₃): δ 150.56 (C, Cg), 139.35 (CH, Cr), 139.31 (C), 138.09 (C), 128.37 (CHx2), 128.27 (CHx2), 128.22 (CHx2), 127.95 (CHx2), 126.82 (CH), 126.04 (CH), 119.64 (CH, Cn), 113.98 (CH₂, Cs), 65.10 (CH₂), 60.32 (CH₂), 58.91 (CH₂), 46.22 (C, Cn), 40.18 (CH₂, Cn), 29.53 (CH₂, Cq), 26.09 (CH₃, Co) ppm.

IR vₘₐₓ/cm⁻¹ (film): 1639 (w), 1539 (m), 1494 (m), 907 (s), 736 (s), 694 (s).

LRMS (ES, MeCN): m/z 318 ([M + H]⁺, 100%).

HRMS (ES): C₂₃H₂₈N [M + H]⁺ calculated 318.2216, found 318.2222.
To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at −78 °C was added n-BuLi (2.5 M solution in hexanes) (0.8 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of N-benzyl-2-methylene-N-(3-phenylprop-2-ynyl)hex-5-en-1-amine (0.315 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. The solution was re-cooled to −78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) dropwise. The solution continued to stir for a further 30 min before the addition of 2 M HCl (aq) in Et₂O (5 mL). The solution was stirred for a further 18 h while warming to rt. The mixture was neutralised with 2 M NaOH (aq) (5 mL) before being extracted with Et₂O (50 mL), washed with water (3 x 50 mL) and brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: 10% Et₂O in hexane) yielded the title compound (0.320 g, 0.79 mmol, 79%) as a colourless oil.

1H NMR (300 MHz, CDCl₃): δ 7.39-7.16 (15H, m, Ar-H), 6.17 (1H, s, Hh), 5.83 (1H, tdd, J = 16.9, 10.3, 6.6, Hw), 5.01 (1H, dd, J = 16.9, 1.8, Hx), 4.93 (1H, dd, J = 10.3, 1.8, Hx), 3.70 (2H, s, He), 3.62 (2H, m, Hf), 2.78-2.54 (4H, m), 2.27-2.03 (2H, m), 1.96 (1H, ddd, J = 14.4, 13.5, 5.1, Hp), 1.86-1.74 (2H, m), 1.66 (1H, ddd, J = 17.0, 12.2, 5.1, Hp) ppm.

13C NMR (75 MHz, CDCl₃): δ 148.46 (C, Cg), 143.12 (C, Cq), 139.33 (CH, Cw), 139.28 (C), 137.99 (C), 128.40 (CHx8), 128.27 (CHx2), 128.06 (CHx2), 126.87 (CH), 126.81 (CH), 125.62 (CH), 120.49 (CH, Ch), 114.09 (CH₂, Cx), 63.29 (CH₂), 60.44 (CH₂), 59.32 (CH₂), 49.52 (C, Cn), 41.88 (CH₂), 38.84 (CH₂), 31.40 (CH₂), 29.23 (CH₂) ppm.

IR νmax/cm⁻¹ (film): 1639 (m), 1494 (m), 907 (s), 733 (s), 695 (s).

LRMS (ES, MeCN): m/z 408 ([M + H]⁺, 100%).

HRMS (ES): C₃₀H₃₄N [M + H]⁺ calculated 408.2686, found 408.2679.
5.51 N-Benzyl-2-methylprop-2-en-1-amine

Synthesis of N-benzyl-2-methylprop-2-en-1-amine was carried out using a procedure published by Itoh et al.\textsuperscript{80} To a stirred solution of benzylamine (22.0 mL, 22.0 g, 200 mmol) and NaHCO\textsubscript{3} (5.50 g, 65 mmol) in H\textsubscript{2}O (200 mL) was added 3-chloro-2-methylprop-1-ene (4.90 mL, 4.50 g, 50 mmol) dropwise. The mixture was heated to 90 °C and stirred for 18 h. The mixture was cooled to rt and the organic layer was separated. The aqueous layer was extracted with Et\textsubscript{2}O (3 x 100 mL). The combined organic layers were washed with H\textsubscript{2}O (3 x 100 mL) and brine (100 mL), dried (MgSO\textsubscript{4}) and the solvent removed \textit{in vacuo}. Purification by column chromatography on silica gel (eluent: 50% Et\textsubscript{2}O in hexane) yielded the title compound (4.97 g, 31 mmol, 62%) as a pale yellow oil.

Data was consistent with published data.\textsuperscript{80}

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \( \delta \) 7.32-7.21 (5H, m, Ar-H), 4.89 (1H, s, Hh), 4.84 (1H, s, Hh), 3.75 (2H, s, He), 3.18 (2H, s, Hf), 1.75 (3H, s, Hi), 1.44 (1H, br, NH) ppm.

\textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): \( \delta \) 143.87 (C), 140.46 (C), 128.32 (CHx2), 128.10 (CHx2), 126.84 (CH, Ca), 110.73 (CH\textsubscript{2}, Ch), 54.97 (CH\textsubscript{2}), 53.05 (CH\textsubscript{2}), 20.76 (CH\textsubscript{3}, Ci) ppm.

IR \( \nu_{\text{max}}/\text{cm}^{-1} \) (film): 1652 (w), 1452 (m), 883 (m), 734 (s), 696 (s).

LRMS (ES, MeCN): \textit{m/z} 162 ([M + H]\textsuperscript{+}, 100%)
Synthesis of \(N\)-benzyl-2-methyl-\(N\)-(3-phenylprop-2-ynyl)prop-2-en-1-amine \textbf{118}

\begin{center}
\includegraphics[width=0.5\textwidth]{image}
\end{center}

in DMSO (25 mL) was added followed by phenyl acetylene (1.1 mL, 1.05 g, 10.3 mmol) and formaldehyde (37 % solution in H\textsubscript{2}O) (11.7 mL, 144.2 mmol). The resulting mixture was stirred at rt for 20 h. The reaction mixture was quenched with sat NH\textsubscript{4}Cl (aq) (50 mL) before being extracted with Et\textsubscript{2}O (3 x 30 mL). The combined organic layers were washed with H\textsubscript{2}O (3 x 30 mL) and brine (50 mL), dried (MgSO\textsubscript{4}) and the solvent removed \textit{in vacuo}. Purification by column chromatography on silica gel (eluent: 5% Et\textsubscript{2}O in hexane) yielded the title compound (2.64 g, 9.6 mmol, 93%) as a colourless oil.

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \(\delta\) 7.50-7.23 (10H, m, Ar-H), 5.04 (1H, s, HH), 4.92 (1H, s, HH), 3.70 (2H, s, He), 3.50 (2H, s, Hj), 3.15 (2H, s, Hf), 1.82 (3H, s, Hi) ppm.

\textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): \(\delta\) 142.11 (C, Cg), 139.13 (C, Cd), 131.73 (CHx2), 128.98 (CHx2), 128.25 (CHx4), 127.91 (CH), 126.98 (CH), 123.46 (C, Cm), 113.35 (CH\textsubscript{2}, Cn), 85.54 (C, Ck/l) 84.60 (C, Ck/l), 60.45 (CH\textsubscript{2}), 57.24 (CH\textsubscript{2}), 42.12 (CH\textsubscript{2}), 20.75 (CH\textsubscript{3}, Ci) ppm.

IR \(\nu_{\text{max}}/\text{cm}^{-1}\) (film): 1652 (w), 1489 (m), 1442 (m), 754 (s), 740 (s), 689 (s).

LRMS (ES, MeCN): \(m/z\) 276 ([M + H]\textsuperscript{+}, 100%).

HRMS (ES): C\textsubscript{20}H\textsubscript{22}N [M + H]\textsuperscript{+} calculated 276.1747, found 276.1750.
To a stirred suspension of K$_2$CO$_3$ (6.40 g, 46.5 mmol) in MeCN (45 mL) was added $N$-benzyl-2-methylprop-2-en-1-amine 117 (2.50 g, 15.5 mmol) in MeCN (5 mL) dropwise. After 30 min 1-bromohex-2-yne (3.72 g, 23.3 mmol) in MeCN (5 mL) was added dropwise. The resulting mixture was stirred at rt for 18 h. The reaction mixture was quenched with sat NaHCO$_3$ (aq) (50 mL) and extracted with Et$_2$O (3 x 30 mL). The combined organic layers were washed with H$_2$O (3 x 30 mL) and brine (50 mL), dried (MgSO$_4$) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent 5% Et$_2$O in Hexane) yielded the title compound (1.93 g, 8.0 mmol, 51%) as a colourless oil.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.39-7.22 (5H, m. Ar-H), 4.98 (1H, s, Hh), 4.89 (1H, s, Hh), 3.61 (2H, s, He), 3.26 (2H, t, J = 2.2, Hj), 3.06 (2H, s, Hf), 2.23 (2H, tt, J = 7.0, 2.2, Hm), 1.71 (3H, s, Hi), 1.59 (2H, sxt, J = 7.2, Hh), 1.05 (3H, t, J = 7.3, Ho) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 143.33 (C, Cg), 139.34 (C, Cd), 128.94 (CHx2), 128.10 (CHx2), 126.84 (CH, Ca), 113.05 (CH$_2$, Ch), 85.37 (C, Cl), 74.66 (C, Ck), 60.26 (CH$_2$, Ce/f), 56.99 (CH$_2$, Ce/f), 44.75 (CH$_2$, Cj), 22.55 (CH$_2$, Cn), 20.74 (CH$_2$, Ci), 20.74 (CH$_3$, Ci), 13.56 (CH$_3$, Co) ppm.

IR $\nu_{\max}$/cm$^{-1}$ (film): 1652 (w), 1454 (m), 1431 (m), 897 (s), 738 (s), 696 (s).

LRMS (ES, MeCN): $m/z$ 242 ([M + H]$^+$, 100%).

HRMS (ES): C$_{17}$H$_{23}$N $[M + H]^+$ calculated 242.1903, found 242.1905.
To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at -78 °C was added n-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of N-benzyl-2-methyl-N-(3-phenylprop-2-ynyl)prop-2-en-1-amine (0.275 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h before being quenched with 2 M HCl (aq) (5 mL). The reaction mixture was stirred for 18 h before being neutralised with 2 M NaOH (aq) (5 mL). The reaction mixture was extracted with Et₂O (50 mL), washed with water (3 x 50 mL) and brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: 5% Et₂O in hexane) yielded the title compound (0.236 g, 0.85 mmol, 85%) as a colourless oil.

**¹H NMR (300 MHz, CDCl₃):** δ 7.42 (10H, m, Ar-H), 6.19 (1H, t, J = 2.5, Hh), 3.72 (2H, s, He), 3.64 (2H, d, J = 2.5, Hf), 2.5 (2H, s, Hm), 1.27 (6H, s, Ho) ppm.

**¹³C NMR (75 MHz, CDCl₃):** δ 151.62 (C, Cg), 139.32 (C, Cd), 138.16 (C, Ci), 128.42 (CHx2), 128.27 (CHx2), 128.22 (CHx2), 127.89 (CHx2), 126.80 (CH), 125.97 (CH), 118.91 (CH, Ch), 67.43 (CH₂), 60.28 (CH₂), 58.78 (CH₂), 43.16 (C, Cn), 28.09 (CH₃x2, Co) ppm.

**IR νmax/cm⁻¹ (film):** 1597 (w), 1494 (m), 1447 (m), 737 (s), 693(s).

**LRMS (ES, MeCN):** m/z 278 ([M + H]⁺, 100%).

**HRMS (ES):** C₂₀H₂₅N [M + H]⁺ calculated 277.1903, found 278.1899.
5.55 (Z)-1-Benzyl-4-butyldiene-3,3-dimethylpyrrolidine 123

To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at –78 °C was added n-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of N-benzyl-N-(2-methylallyl)hex-2-yn-1-amine 119 (0.241 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h before being quenched with 2 M HCl (aq) (5 mL). The reaction mixture was stirred for 18 h before being neutralised with 2 M NaOH (aq) (5 mL). The reaction mixture was extracted with Et₂O (50 mL), washed with water (3 x 50 mL) and brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: 5% Et₂O in hexane) yielded the title compound (0.170 g, 0.70 mmol, 70%) as a colourless oil.

¹H NMR (300 MHz, CDCl₃): δ 7.38-7.21 (5H, m, Ar-H), 5.08 (1H, tt, J = 7.3, 2.6, Hh), 3.62 (2H, s, He), 3.24-3.23 (2H, m, Hf), 2.40 (2H, s, Hl), 1.86 (2H, q, J = 7.3, Hi), 1.35 (2H, sxt, J = 7.3, Hj), 1.12 (6H, s, Hn), 0.87 (3H, t, J = 7.3, Hk) ppm.

¹³C NMR (75 MHz, CDCl₃): δ 148.43 (C, Cg), 139.53 (C, Cd), 128.50 (CHx2), 128.15 (CHx2), 126.71 (CH, Ca), 118.04 (CH, Ch), 68.39 (CH₂), 60.53 (CH₂), 57.02 (CH₂, Cf), 41.35 (C, Cm), 31.32 (CH₂, Ci), 28.20 (CH₃x2, Cn), 22.71 (CH₂, Cj), 13.71 (CH₃, Ck) ppm.

IR νmax/cm⁻¹ (film): 1495 (m), 1454 (m), 738 (m), 697(s).

LRMS (ES, MeCN): m/z 244 ([M + H]⁺, 100%).

HRMS (ES): C₁₇H₂₅N [M + H]⁺ calculated 244.2060, found 244.2056.
To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at –78 °C was added n-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of N-benzyl-2-methyl-N-(3-phenylprop-2-ynyl)prop-2-en-1-amine 118 (0.275 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. The solution was re-cooled to –78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) dropwise. The solution continued to stir for a further 10 min before the addition of 2 M HCl in Et₂O (5 mL). The mixture was stirred for a further 20 h while warming to rt. The mixture was neutralised with 2 M NaOH (aq) (5 mL) before being extracted with Et₂O (50 mL). The organic layer was washed with water (3 x 50 mL) and brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: 5% Et₂O in hexane) yielded the title compound (0.264 g, 0.72 mmol, 72%) as a colourless oil.

**¹H NMR (300 MHz, CDCl₃):** δ 7.41 (15H, m, Ar-H), 6.19 (1H, t, J = 2.4, Hh), 3.72 (2H, s, He), 3.60-3.63 (2H, m, Hf), 2.79-2.67 (2H, m, Hm, q), 2.63-2.46 (2H, m, Hm, q), 1.89 (2H, dd, J = 9.7, 7.7, Hp), 1.31 (3H, s, Ho) ppm.

**¹³C NMR (75 MHz, CDCl₃):** δ 150.45 (C, Cg), 143.06 (C, Cr), 139.32 (C, Cd), 138.08 (C, Ci), 128.38 (CHx2), 128.31 (CHx8), 127.97 (CHx2), 126.85 (CH, Ca), 126.08 (CH, Cl), 125.85 (CH, Cv), 119.72 (CH, Ch), 65.02 (CH₂, Cm), 60.03 (CH₂, Ce), 58.95 (CH₂, Cf), 46.64 (C, Cn), 43.28 (CH₂), 31.70 (CH₂), 26.17 (CH₃, Co) ppm.

**IR vₘₓₓ/cm⁻¹ (film):** 1603 (w), 1495 (m), 1455 (m), 1028 (m), 694 (s).

**LRMS (ES, MeCN):** m/z 368 ([M + H]⁺, 100%).

**HRMS (ES):** C₂₇H₃₀N [M + H]⁺ calculated 368.2373, found 368.2379.
To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at –78 °C was added n-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of N-benzyl-N-(2-methylallyl)hex-2-yn-1-amine 119 (0.241 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. The solution was re-cooled to –78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) dropwise. The solution continued to stir for a further 10 min before the addition of 2 M HCl in Et₂O (5 mL). The mixture was stirred for a further 20 h while warming to rt. The mixture was neutralised with 2 M NaOH (aq) (5 mL) before being extracted with Et₂O (50 mL). The organic layer was washed with water (3 x 50 mL) and brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: 5% Et₂O in hexane) yielded the title compound (0.250 g, 0.75 mmol, 75%) as a colourless oil.

**¹H NMR (300 MHz, CDCl₃):** δ 7.40-7.17 (10H, m, Ar-H), 5.11 (1H, tt, J = 7.1, 2.4, Hh), 3.65 (2H, s, He), 3.33-3.22 (2H, m, Hf), 2.68 (1H, ddd, J = 13.4, 11, 5.6, Hp), 6.23 (1H, d, J = 8.6, Hl), 2.52 (1H, ddd, J = 13.4, 10.8, 5.6, Hp), 2.41 (1H, d, J = 8.6, Hl), 1.92 (2H, apparent q, J = 7.2, Hi), 1.80-1.73 (2H, m, Ho), 1.39 (2H, sxt, J = 7.3, Hj), 1.18 (3H, s, Hn), 0.90 (3H, t, J = 7.3, Hk) ppm.

**¹³C NMR (75 MHz, CDCl₃):** δ 147.18 (C, Cg), 143.38 (C, Cq), 139.56 (C, Cd), 128.45 (CHx2), 128.34 (CHx2), 128.27 (CHx2), 128.19 (CHx2), 126.76 (CH, Ca), 125.49 (CH, Ct), 119.13 (CH, Ch), 66.11 (CH₂, Cl), 60.53 (CH₂, Ce), 57.23 (CH₂, Cf), 44.72 (C, Cm), 43.32 (CH₂, Co), 31.72 (CH₂), 31.38 (CH₂), 26.09 (CH₂, Cj), 22.77 (CH₃, Cn), 13.78 (CH₃, Ck) ppm.

**IR vmax/cm⁻¹ (film):** 1495 (m), 1453 (m), 839 (m), 696 (s).

**LRMS (ES, MeCN):** m/z 343 ([M + H]⁺, 100%).

**HRMS (ES):** C₂₄H₃₂N [M + H]⁺ calculated 343.2529, found 343.2524.
To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at –78 °C was added n-BuLi (2.5 M solution in hexanes) (0.8 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of N-benzyl-2-methyl-N-(3-phenylprop-2-ynyl)prop-2-en-1-amine (0.275 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. The solution was re-cooled to –78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) dropwise. The solution continued to stir for a further 10 min before being warmed to reflux. The solution was stirred for 12 h at reflux before cooling to rt. The reaction mixture was quenched 2 M HCl in Et₂O (5 mL) before being stirred for a further 18 h at rt. The mixture was neutralised with 2 M NaOH (aq) (5 mL) before being extracted Et₂O (50 mL), washed with water (3 x 50 mL) and brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: 5% Et₂O in hexane) yielded the title compounds (0.201 g, 0.55 mmol, 55%) as a colourless oil.

^1H NMR (300 MHz, CDCl₃): δ 7.41 (15H, Ar-H), 6.51 (1H, d, J = 16.1, Hp), 6.37 (1H, d, J = 16.1, Hq), 6.16 (1H, s, Hh), 3.78-3.57 (4H, m, He, m), 2.70 (1H, d, J = 8.8, Hf), 2.64 (1H, d, J = 8.8, Hf), 1.48 (3H, s, Ho) ppm.

^13C NMR (75 MHz, CDCl₃): δ 149.06 (C, Cg), 139.06 (C, Cr), 137.82 (C, Cd), 137.66 (C, Ci), 136.93 (CH, Cp), 128.47 (CHx2), 128.45 (CHx2), 128.31 (CHx2), 128.27 (CHx2), 127.98 (CHx2), 127.00 (CH), 126.94 (CH), 126.91 (CH), 126.26 (CH), 126.20 (CHx2), 121.65 (CH, Ch), 66.29 (CH₂, Cm), 60.29 (CH₂, Ce), 58.39 (CH₂, Cf), 49.30 (C, Cm), 24.93 (CH₃, Co) ppm.

IR v_max/cm⁻¹ (film): 1493 (m), 1447 (m), 744 (s), 692 (s).

LRMS (ES, MeCN): m/z 366 ([M + H]^+), 100%.

HRMS (ES): C_{27}H_{28}N [M + H]^+ calculated 366.2216, found 366.2218.
5.59 (4Z)-1-Benzyl-4-butylidene-3-methyl-3-(E)-styrylpyrrolidine 129

To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at –78 °C was added n-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of N-benzyl-N-(2-methylallyl)hex-2-yn-1-amine 119 (0.241 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. The solution was re-cooled to –78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) dropwise. The solution continued to stir for a further 10 min before being warmed to reflux. The solution was stirred for 12 h at reflux before cooling to rt. The reaction mixture was quenched with 2 M HCl in Et₂O (5 mL) before being stirred for a further 18 h at rt. The mixture was neutralised with 2 M NaOH (aq) (5 mL) before being extracted with Et₂O (50 mL), washed with water (3 x 50 mL) and brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: 5% Et₂O in hexane) yielded the title compound (0.176 g, 0.53 mmol, 53%) as a colourless oil.

¹H NMR (300 MHz, CDCl₃): δ 7.38-7.16 (10H, m, Ar-H), 6.41 (1H, d, J = 16.0, Hp), 6.28 (1H, d, J = 16.0, Ho), 5.11 (1H, tt, J = 7.5, 2.4, Hh), 3.72-3.62 (2H, m, He), 3.37 (1H, d, J= 13.7, Hf), 3.24 (1H, d, J= 13.7, Hf), 2.66 (1H, d, J = 8.7, Hi), 2.56 (1H, d, J = 8.7, Hi), 1.93-1.84 (2H, m, Hi), 1.39-1.24 (5H, m, Hj, n), 0.87 (3H, t, J = 7.5, Hk) ppm.

¹³C NMR (75 MHz, CDCl₃): δ 145.95 (C, Cg), 139.18 (C, Cq), 137.89 (C, Cd), 137.69 (CH, Co), 128.56 (CHx2), 128.42 (CHx2), 128.21 (CHx2), 126.85 (CH, Ca), 126.80 (CH, Ct), 126.25 (CH, Cp), 126.12 (CHx2), 121.27 (CH, Ch), 67.09 (CH₂, Cl), 60.35 (CH₂, Ce), 56.61 (CH₂, Cf), 47.55 (C, Cm), 31.47 (CH₂, Ci), 25.09 (CH₂, Cj), 22.59 (CH₃, Cn), 13.76 (CH₃, Ck) ppm.

IR ν_max/cm⁻¹ (film): 1495 (m), 1455 (m), 1028 (m), 694 (s).

LRMS (ES, MeCN): m/z 332 ([M + H]⁺, 100%).

5.60 Diethyl 2-(hept-3-ynyl)malonate 131

Synthesis of hept-3-ynyl methanesulfonate 130: To a stirred solution of hept-3-yn-1-ol (5.60 g, 50 mmol) and triethylamine (10.4 mL, 7.6 g, 75 mmol) in CH₂Cl₂ (120 mL) at −10 °C was added methanesulfonyl chloride (6.84 g, 4.60 mL, 60 mmol) dropwise. After 30 min at −10 °C the reaction mixture was poured onto H₂O (50 mL). The aqueous layer was separated and re-extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were washed with 2M HCl (aq) (50 mL), H₂O (50 mL), NaHCO₃ (50 mL) and brine (50 mL). The organic layer was dried (MgSO₄) and solvent removed in vacuo to yield hept-3-ynyl methanesulfonate 130 (9.14 g, 48.0 mmol, 96%) No further purification was required.

¹H NMR (300 MHz, CDCl₃): δ 4.26 (2H, t, J = 6.6, Hg), 3.04 (3H, s, Hh), 2.64-2.60 (2H, m, Hf), 2.14 -2.08 (2H, m, Hc), 1.54-1.44 (2H, m, Hb), 0.96 (3H, t, J = 7.2, Ha) ppm.

Synthesis of diethyl 2-(hept-3-ynyl)malonate 131: Sodium (1.4 g, 60 g-atom) was added portion wise to ethanol (100 mL) at 0 °C. Once complete dissolution was observed a solution of diethyl malonate (12 g, 75 mmol) in ethanol (10 ml) was added dropwise and the solution was stirred for 15 min at 0 °C. A solution of mesylate 130 (9.5 g, 50 mmol) in ethanol (50 mL) and 10% NaI (0.75 g, 5 mmol) in ethanol (5 mL) was added dropwise and the solution was stirred for a further 18 h. The reaction mixture was poured onto H₂O (500 mL) and extracted with Et₂O (3 x 200 mL). The combined organic extracts were washed with H₂O (3 x 100 mL) and brine (100 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: 10% Et₂O in hexane) yielded the title compound 131 (2.57 g, 10 mmol, 20%) as a colourless oil.

¹H NMR (300 MHz, CDCl₃): δ 4.21 (2H, q, J = 7.2, Hb/ m), 4.20 (2H, q, J = 7.2, Hb/ m), 3.57 (1H, t, J = 7.3, Hd), 2.28-2.26 (2H, m, He), 2.13-2.05 (4H, m, Hf, i), 1.50 (2H, sxt, J = 7.3, Hj), 1.28 (6H, t, J = 7.2, Ha, n), 0.97 (3H, t, J = 7.3, Hk) ppm.
$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 169.21 (Cx2, Cc, l) 81.64 (C, Cg/h), 78.09 (C, Cg/h), 61.36 (CH$_2$x2, Cb, m), 50.74 (CH, Cd), 28.08 (CH$_2$, Ce), 22.39 (CH$_2$), 20.72 (CH$_2$), 16.77 (CH$_2$), 14.05 (CH$_3$x2, Ca, n), 13.43 (CH$_3$, Ck) ppm.

IR $v_{\text{max/cm}^{-1}}$ (film): 1748 (s), 1730 (s), 1151(s), 1022 (m).

LRMS (ES, MeCN): $m/z$ 277 ([M + Na]$^+$, 100%).
To a stirred suspension of NaH (60% suspension in mineral oil) (4.80 g, 12.5 mmol) in THF (20 mL) at 0 °C was added malonate 131 (2.57 g, 10 mmol) in THF (10 mL) dropwise. The solution was stirred for a further 15 min before the addition of mesylate 104 (2.28 g, 12 mmol) in THF (10 mL) and NaI (0.37 g, 2.4 mmol) in THF (10 mL). The solution was warmed to rt and stirred for 24 h. The reaction mixture was quenched by the dropwise addition of sat NH₄Cl (aq) (50 mL) before being extracted with Et₂O (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent gradient: 0 - 10% Et₂O in hexane) yielded the title compound (2.0 g, 5.8 mmol, 58%) as a colourless oil.

**¹H NMR (300 MHz, CDCl₃):** δ 5.87 (1H, ddt, J = 16.8, 10.4, 6.8, Hm), 5.03-4.94 (4H, m, Hl, q), 4.17 (4H, q, J = 6.8, Cb, t), 2.71 (2H, s, Hr), 2.18-2.23 (8H, m, CH₂), 2.03-1.99 (2H, m, CH₂), 1.49 (2H, sxt, J = 7.2, Hj), 1.25 (6H, t, J = 7.2, Ha, n), 0.96 (3H, t, J = 7.2, Hk) ppm.

**¹³C NMR (75 MHz, CDCl₃):** δ 171.15 (Cx2, Cc, s), 143.70 (C, Cp), 138.0 (CH, Cm), 115.04 (CH₂, Cq/l), 114.61 (CH₂, Cq/l), 80.53 (C, Cg/h), 78.88 (C, Cg/h), 61.28 (CH₂x2, Cb, t), 56.62 (C, Cd), 38.22 (CH₂), 35.77 (CH₂), 32.10 (CH₂x2), 22.37 (CH₂, Ci), 20.67 (CH₂, Cj), 14.29 (CH₂, Cf), 13.97 (CH₃x2, Ca, v), 13.46 (CH₃, Ck) ppm.

**IR v_max/cm⁻¹ (film):** 1729 (s), 1238 (s), 1178 (s), 1082 (m).

**LRMS (ES, MeCN):** m/z 371 ([M + Na]⁺, 100%).
Synthesis of 2-(hept-3-yn-1-yl)-2-(2-methylenehex-5-en-1-yl)propane-1,3-diol: To a stirred suspension of LiAlH₄ (0.66 g, 17.4 mmol) in Et₂O (40 mL) at 0 °C was added malonate 132 (2.0 g, 5.8 mmol) in Et₂O (10 mL). The solution was warmed to rt and stirred for 4 h before the dropwise addition of 2 M NaOH (aq) (5 mL) followed by water (20 mL). The mixture was poured onto 2 M HCl (aq) (20 mL) and extracted with Et₂O (3 x 50 mL). The combined organic extracts were washed with H₂O (3 x 50 mL), dried (MgSO₄) and the solvent removed in vacuo to yield the title compound (1.56, 5.8 mmol, 99%) as a colourless oil. No further purification was required.

¹H NMR (300 MHz, CDCl₃): δ 5.82 (1H, ddt, J = 16.4, 10.4, 6.0, Hp), 5.06-4.79 (4H, m, Hq/m), 3.62 (2H, s, Ci/j), 3.61 (2H, s, Ci/j), 2.42 (2H, br s, OH), 2.27-2.19 (4H, m), 2.16-2.11 (4H, m), 2.03 (2H, s, Ck), 1.65 (2H, t, J = 6.8), 1.51 (2H, sxt, J = 7.2, Hb), 0.97 (3H, t, J = 7.2, Ha) ppm

Synthesis of 7,7-bis(methoxymethyl)-5-methylenetetradec-1-en-10-yne 133: To a stirred suspension of NaH (60% suspension in mineral oil) (0.67 g, 17.4 mmol) in THF (40 mL) at 0 °C was added the 2-(hept-3-ynyl)-2-(2-methylenehex-5-enyl)propane-1,3-diol (1.56 g, 5.8 mmol) in THF (10 mL) dropwise. After 30 min MeI (1.25 g, 8.7 mmol) in THF (5 mL) was added and the solution was stirred at 0 °C for 30 min. The remaining MeI (1.25 g, 8.7 mmol) in THF (5 mL) was added and the solution was warmed to rt and stirred for 5 h. The reaction mixture was quenched with the dropwise addition on MeOH (10 mL) poured onto H₂O (50 mL) and extracted with Et₂O (3 x 30 mL). The combined organic extracts were washed with brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography on silica gel (elucent gradient: 5% Et₂O in hexane) yielded the title compound (2.15 g, 7.4 mmol, 85%) as a colourless oil.
\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta 5.81 (1\text{H}, \text{ddt}, J = 16.5, 10.2, 6.3, \text{Hi})\), 5.06-4.77 (4H, m, Hk, p), 3.29 (6H, s, Ha, s), 3.15 (4H, s, Hb, r), 2.25-2.09 (8H, m), 2.05 (2H, s, Hq), 1.60-1.55 (2H, m), 1.50 (2H, sxt, \(J = 7.2, \text{Hi}\)), 0.97 (3H, t, \(J = 7.2 \text{Hj}\)) ppm.

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta 145.53 (\text{C, Co})\), 138.60 (CH, Cl), 114.37 (CH\(_2\), Cp/k), 113.93 (CH\(_2\), Cp/k), 80.63 (C, Cl/g), 79.79 (C, Cl/g), 75.07 (CH\(_2\), Cb/r), 74.95 (CH\(_2\), Cb/r), 58.83 (CH\(_3\)x2, Ca, s), 41.88 (C, Cc), 37.87 (CH\(_2\)), 37.20 (CH\(_2\)), 32.82 (CH\(_2\)), 32.58 (CH\(_2\)), 22.50 (CH\(_2\)), 20.82 (CH\(_2\)), 13.50 (CH\(_2\), Ci), 13.35 (CH\(_3\), Cj) ppm.

IR \(\nu_{\text{max}}/\text{cm}^{-1}\) (film): 1639 (m), 1449 (m), 1104 (s).

LRMS (ES, MeCN): \(m/z 315 ([M + Na]^+, 100%)\).

HRMS (ES): C\(_{19}\)H\(_{32}\)NaO\(_2\) [M + Na]^+ calculated 315.2295, found 315.2290.
To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at −78 °C was added n-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of DMAP (0.268 g, 2.2 mmol) in THF (5 mL) was added. The solution was warmed to rt and stirred for a further 1 h before a solution of 2-methylhept-1-en-5-yne (0.116 g, 0.95 mmol) in THF (2 mL) was added dropwise over 1 h. The solution was recooled to −78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) dropwise. The solution continued to stir for a further 10 min at −78 °C before the addition of 2 M HCl in Et₂O (5 mL). The solution was stirred for a further 18 h while warming to rt before being diluted with Et₂O (50 mL). The reaction mixture was washed with water (3 x 50 mL) and brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: hexane) yielded the title compound (0.156 g, 0.73 mmol, 73%) as a colourless oil.

**1H NMR (300 MHz, CDCl₃):** δ 7.28-7.15 (5H, m, Ar-H), 5.16 (1H, qt, J = 16.8, 2.6, Hb), 2.62-2.46 (2H, m, Hj), 2.41 (1H, m, Hd), 2.25 (1H, m, Hd), 1.73-1.45 (9H, m), 1.07 (3H, s, Hh) ppm.

**13C NMR (75 MHZ, CDCl₃):** δ 150.92 (C, Cc), 143.53 (C, Ck), 128.24 (CHx4), 125.43 (CH, Cn), 113.17 (CH, Cb), 44.99 (C, Cg), 43.24 (CH₂), 39.47 (CH₂), 31.48 (CH₂, Cj), 29.30 (CH₂, Cd), 26.67 (CH₂, Ce), 22.31 (CH₃, Ch), 14.63 (CH₂, Ca) ppm.

**IR νmax/cm⁻¹ (film):** 1603 (w), 1495 (m), 1454 (m), 748 (m), 697 (s).

**LRMS (EI, CH₂Cl₂):** 214 ([M⁺], 20%), 109 (100%).

**HRMS (EI):** C₁₆H₂₂ [M⁺] calculated, 214.1722 found 214.1715.
To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at –78 °C was added n-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of DMAP (0.268 g, 2.2 mmol) in THF (5 mL) was added. The solution was warmed to rt and stirred for a further 1 h before a solution of 2-methylhept-1-en-5-yne (0.116 g, 0.95 mmol) in THF (2 mL) was added dropwise over 1 h. The solution was re-cooled to –78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) dropwise. The solution continued to stir for a further 10 min before warming to rt. The solution was stirred for a further 5 h before the addition of 2 M HCl (aq) in Et₂O (5 mL). The reaction mixture was stirred for a further 18 h at rt, extracted with Et₂O (50 mL), washed with water (3 x 50 mL) and brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: hexane) yielded the title compound (0.112 g, 0.53 mmol, 53%) as a colourless oil.

¹H NMR (300 MHz, CDCl₃): δ 7.37-7.14 (5H, m, Ar-H), 6.30 (1H, d, J = 15.9, Hj), 6.17 (1H, d, J = 16.2, Hi), 5.21 (1H, m, Hb), 2.35-2.33 (2H, m, CH₂), 1.80-1.47 (7H, m, CH₂, CH₃), 1.21 (3H, s, Hh) ppm

¹³C NMR (75 MHz, CDCl₃): δ 148.41 (C, Cc), 139.53 (CH, Ci), 138.02 (C, Ck), 128.41 (CHx2, Cm), 126.66 (CH, Cj), 126.03 (CHx3, Cl, n), 115.51 (CH, Cb), 48.26 (C, Cg), 41.28 (CH₂, Cf), 28.84 (CH₂, Cd), 25.61 (CH₃, Ch), 22.44 (CH₂, Ce), 14.69 (CH₃, Ca) ppm.

IR vₘₐₓ/cm⁻¹ (film): 1600 (w), 1495 (m), 1447 (m), 966 (s), 745 (s), 691 (s).

LRMS (EI, CH₂Cl₂): 212 ([M⁺], 100%), 91 (90%).

HRMS (EI): C₁₆H₂₀[M⁺] calculated 212.1565, found 212.1556.
5.65 Optimisation of the zirconene mediated co-cyclisation of 2-methylhept-1-en-5-yne

To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at –78 °C was added n-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of DMAP (0.268 g, 2.2 mmol) in THF (5 mL) was added. The solution was warmed to x °C (see table for temperature) and stirred for a further 1 h before a solution of 2-methylhept-1-en-5-yne (see table for amount) in THF (2 mL) was added dropwise over 1 h. Samples (0.1 mL) were removed from the reaction mixture and quenched with 2 M HCl (aq) (1.5 mL) at timed intervals. Et₂O (1 mL) was added to the quenched sample. The Et₂O layer was separated and passed through a short plug of MgSO₄ in Pasteur pipette. The samples were analysed by GC.

<table>
<thead>
<tr>
<th>Experiment</th>
<th>1</th>
<th>2</th>
<th>3</th>
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</thead>
<tbody>
<tr>
<td>Enyne amount</td>
<td>0.122 g, 1 mmol</td>
<td>0.134 g, 1.1 mmol</td>
<td>0.110 g, 0.9 mmol</td>
</tr>
<tr>
<td>Temperature °C</td>
<td>0</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

**GC conditions and retention times**

Standard GC conditions and column – see general experimental for details.

**GC method:**

Injector temperature: 200 °C

Initial temperature: 40 °C held for 2 min

Ramp 1: 10 °C per min to 70 °C

Ramp 2: 25 °C per min

Final temperature: 250 °C held for 4 min

**Retention times:**

Quenched zirconacycle 141 – 5.01 min

Starting enyne 140 – 6.27 min

Intermolecular cyclisation products 145a-c – 8.40 min, 8.52 min and 8.63 min
Synthesis of **146** was carried out using a procedure published by Begley et al.\(^8^3\) To a stirred suspension of NaH (60% suspension in mineral oil) (2.40 g, 60 mmol) in THF (100 mL) at 0 °C was added methylallyl chloride (5.40 g, 60 mmol) in THF (10 mL) dropwise. The resulting solution was stirred at rt for 72 h before being quenched with H\(_2\)O (50 mL) and extracted with Et\(_2\)O (3 x 100 mL). The combined organic extracts were washed with H\(_2\)O (3 x 50 mL), brine (50 mL), dried (MgSO\(_4\)) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 10% Et\(_2\)O in hexane) yielded the title compound (3.47 g, 16 mmol, 27%) as a colourless oil.

All data was consistent with published data.\(^8^3\)

\(^1^H\) NMR (300 MHz, CDCl\(_3\)): \(\delta\) 4.78 (1H, s, \(\text{Hg}\)), 4.73 (1H, s, \(\text{Hg}\)), 4.19 (4H, q, \(J = 6.9\), \(\text{Hb, j}\)), 3.57 (1H, t, \(J = 7.8\), \(\text{Hd}\)), 2.62 (2H, d, \(J = 7.5\), \(\text{He}\)), 1.75 (3H, s, \(\text{Hh}\)), 1.26 (6H, t, \(J = 6.9\), \(\text{Ha, k}\)) ppm.

\(^1^3^C\) NMR (75 MHz, CDCl\(_3\)): \(\delta\) 169.07 (C\(_x2\), C\(_i\)), 141.66 (C, C\(_f\)), 112.23 (CH\(_2\), C\(_g\)), 61.36 (CH\(_2\)\(_x2\), C\(_b\), j), 50.52 (CH, C\(_d\)), 36.46 (CH\(_2\), C\(_e\)), 22.52 (CH\(_3\), C\(_h\)), 14.04 (CH\(_3\)\(_x2\), C\(_a\), k) ppm.

**IR** \(\nu_{\text{max}}/\text{cm}^{-1}\) (film): 1731 (s), 1652 (w), 1446 (m), 1147 (s), 1048 (s), 1028 (s).

**LRMS** (ES, MeCN): \(m/z\) 237 ([M + Na]\(^+\), 100%).
5.67 Diethyl 2-(hex-2-ynyl)-2-(2-methylallyl)malonate 147

Synthesis of 1-bromohex-2-yne was carried out using a procedure published by Lu et al.\textsuperscript{84} PPh\textsubscript{3} (13.4 g, 51 mmol) was dissolved in CH\textsubscript{2}Cl\textsubscript{2} (100 mL) and cooled to 0 ºC before bromine (2.6 mL, 8.2 g, 51 mmol) was added dropwise. The resulting solution was stirred for 30 min at 0 ºC. Hex-2-yn-1-ol (5.6 mL, 5.0 g, 51 mmol) was added dropwise at 0 ºC and stirred for a further 1 h before the addition of pentane (300 mL). The resulting suspension was passed through a short silica pad and washed with pentane (50 mL). The solvent was removed \textit{in vacuo} to yield the compound (7.1 g, 44 mmol, 86%) as a colourless oil.

Data was consistent with published data.\textsuperscript{84}

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \(\delta 3.93 (2H, t, J = 2.2, \text{Hf}), 2.22 (2H, tt, J = 7.0, 2.2, \text{Hc}), 1.58-1.54 (2H, m, \text{Hb}), 0.99 (3H, t, J = 7.4, \text{Ha})\) ppm.

IR \(\nu_{\text{max/cm}}\) (film): 2232 (m), 1642 (m), 1206 (m), 606 (s).

Synthesis of diethyl 2-(hex-2-ynyl)-2-(2-methylallyl) malonate 147: Sodium (0.83 g, 36 g-atom) was added portion-wise to ethanol (20 mL) at 0 ºC. Once complete dissolution was observed a solution of the substituted diethyl malonate 146 (3.47 g, 16 mmol) in ethanol (5 mL) was added dropwise and the solution was stirred for 15 min at 0 ºC. A solution of 1-bromohex-2-yne (3.20 g, 20 mmol) in ethanol (5 mL) was added dropwise and the reaction mixture was warmed to rt and stirred for a further 18 h. The reaction mixture was poured onto H\textsubscript{2}O (50 mL) and extracted with Et\textsubscript{2}O (3 x 50 mL). The combined organic extracts were washed with H\textsubscript{2}O (3 x 50 mL), brine (50 mL), dried (MgSO\textsubscript{4}) and the solvent removed \textit{in vacuo}. Purification by column chromatography on silica gel (eluent: 10% Et\textsubscript{2}O in hexane) yielded the title compound (4.07 g, 13.9 mmol, 87%) as a colourless oil.

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \(\delta 4.89 (1H, m, \text{Hg}), 4.84 (1H, m, \text{Hg}), 4.27-4.11 (4H, m, \text{Hb, p}), 2.82 (2H, s, \text{He}), 2.79 (2H, t, J = 2.4, \text{Hi}), 2.10 (2H, tt, J = 6.0, 2.4, \text{Hl}), 1.68

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(3H, s, Hh), 1.48 (2H, sxt, J = 7.2, Hm), 1.25 (6H, t, J = 7.2, Ha, q), 0.95 (3H, t, J = 7.5, Hn) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$): δ 170.41 (C=x2, Cc, o), 140.27 (C, Cf), 115.86 (CH$_2$, Cg), 83.61 (C, Ck), 74.83 (C, Cj), 61.41 (CH$_2$x2, Cb, p), 56.75 (C, Cd), 39.31 (CH$_2$, Ce), 23.35 (CH$_3$, Ch), 22.91 (CH$_2$), 22.33 (CH$_2$), 20.66 (CH$_2$), 13.99 (CH$_3$x2, Ca, q), 13.38 (CH$_3$, Cn) ppm.

IR $\nu_{\text{max}}$/cm$^{-1}$ (film): 1732 (s), 1646 (w), 1202 (s), 1180 (s), 107 (m), 1058 (m).

LRMS (ES, MeCN): m/z 317 ([M + Na]$^+$, 100%).
Synthesis of 2-(hex-2-ynyl)-2-(2-methylallyl)propane-1,3-diol:
To a stirred suspension of LiAlH₄ (1.82 g, 48 mmol) in Et₂O (100 mL) at 0 °C was added substituted malonate 147 (4.06 g, 13.8 mmol) in Et₂O (20 mL). The solution was warmed to rt and stirred for 18 h before the dropwise addition of 2 M NaOH (aq) (10 mL) followed by water (20 mL). The mixture was poured onto 2 M HCl (aq) (30 mL) and extracted with Et₂O (3 x 100 mL). The combined organic extracts were washed with H₂O (3 x 50 mL) brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo to yield the 2-(hex-2-ynyl)-2-(2-methylallyl)propane-1,3-diol as a colourless oil (2.59 g, 12.3 mmol, 89%). No further purification was required.

¹H NMR (300 MHz, CDCl₃): δ 4.19 (1H, m, He), 4.80 (1H, m, He), 3.68-3.58 (4H, m, Ha, m), 2.76 (2H, s, OH), 2.23 (2H, s, Hc), 2.17-2.08 (4H, m, Hg, j), 1.81 (3H, s, Hf), 1.51 (2H, sxt, J = 7.3, Hk), 0.97 (3H, t, J = 7.3, Hl) ppm.

Synthesis of 4,4-bis(methoxymethyl)-2-methyldec-1-en-6-yne 148:
To a stirred suspension of NaH (60% suspension in mineral oil) (1.48 g, 37 mmol) in THF (80 ml) at 0 °C was added the 2-(hex-2-ynyl)-2-(2-methylallyl)propane-1,3-diol (2.59 g, 12.3 mmol) in THF (10 mL) dropwise. After 30 min MeI (1.15 mL, 2.63 g, 18.5 mmol) in THF (5 mL) was added and the solution was stirred at 0 °C for 30 min. The remaining MeI (1.15 mL, 2.63 g, 18.5 mmol) in THF (5 mL) was added and the solution was warmed to rt and stirred for 18 h. The reaction mixture was quenched with the dropwise addition of MeOH (10 mL) poured onto H₂O (50 mL) and extracted with Et₂O (3 x 70 mL). The combined organic extracts were washed with H₂O (3 x 50 mL), brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent gradient: 5 - 10% Et₂O in hexane) yielded the title compound (2.14 g, 9.0 mmol, 73%) as a colourless oil.

¹H NMR (300 MHz, CDCl₃): δ 4.90 (1H, s, Hf), 4.77 (1H, s, Hf), 3.32 (6H, s, Ha, o), 3.26-3.20 (4H, m, Hb, n), 2.17-2.13 (6H, m, Hd, h, k), 1.78 (3H, s, Hg), 1.53 (2H, sxt, J = 7.0, Hi), 0.99 (3H, t, J = 7.3, Hm) ppm.
\(^{13}\)C NMR (75 MHz, \text{CDCl}_3): \(\delta\) 142.11 (C, Ce), 114.74 (CH\_2, Cf), 82.36 (C, Cj), 76.81 (C, Ci), 74.37 (CH\_2\times2, Ch, n), 59.05 (CH\_3\times2, Ca, o), 42.45 (C, Cc), 38.30 (CH\_2), 25.02 (CH\_3, Cg), 22.64 (CH\_2\times2), 20.84 (CH\_2), 13.53 (CH\_3, Cm) ppm.

IR \(v_{\text{max}}/\text{cm}^{-1}\) (film): 1641 (w), 1456 (m), 1103 (s), 896 (m).

LRMS (ES, MeCN): \(m/z\) 261 ([M + Na]\(^+\), 100%).

HRMS (ES): \(C_{15}H_{26}NaO_2\) [M + Na]\(^+\) calculated 261.1825, found 261.182530.
5.69 \((E)\)-2-Butylidene-4,4-bis(methoxymethyl)-1,1-dimethylcyclopentane

To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at –78 °C was added \(n\)-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of 4,4-bis(methoxymethyl)-2-methyldec-1-en-6-yne (0.238 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h before being quenched with 2 M HCl (aq) (5 mL). The reaction mixture was stirred for 18 h before being extracted with Et\(_2\)O (50 mL), washed with water (3 x 50 mL) and brine (50 mL), dried (MgSO\(_4\)) and the solvent removed \textit{in vacuo}. Purification by column chromatography on silica gel (eluent: 5% Et\(_2\)O in hexane) yielded the title compound (0.167 g, 0.70 mmol, 70%) as a colourless oil.

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 5.11 (1H, tt, \(J = 7.3, 2.2\), Hh), 3.32 (6H, s, Ha, e), 3.22 (4H, q, \(J = 8.8\), Hb, d), 2.25-2.24 (2H, m, Hf), 1.94 (2H, q, \(J = 7.3\), Hi), 1.48 (2H, s, Hl), 1.34 (2H, sxt, \(J = 7.3\), Hj), 1.07 (6H, s, Hn), 0.87 (3H, t, \(J = 7.3\), Hk) ppm.

\(^13\)C NMR (75 MHz, CDCl\(_3\)): 150.40 (C, Ch), 119.19 (CH, Cg), 76.74 (CH\(_2\)x2, Cb, d), 59.16 (CH\(_3\)x2, Ca, e), 46.82 (CH\(_2\), Cl), 45.24 (C, Cc), 40.85 (C, Cm), 35.40 (CH\(_2\), Cf), 31.20 (CH\(_2\), Ci), 31.10 (CH\(_3\)x2, Cn), 22.96 (CH\(_2\), Cj), 13.64 (CH\(_3\), Ck) ppm.

IR \(\nu_{\text{max}}/\text{cm}^{-1}\) (film): 1454 (m), 1104 (s), 966 (m).

LRMS (ES, MeCN): \(m/z\) 263 ([M + Na]\(^+\), 100%).

HRMS (ES): \(C_{15}H_{28}NaO_2\) [M + Na]\(^+\) calculated 263.1982, found 263.1985.
To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at –78 °C was added n-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of 4,4-bis(methoxymethyl)-2-methyldec-1-en-6-yne 148 (0.238 g, 1.0 mmol) in THF (2 mL) was added dropwise. After a further 10 min the reaction mixture was warmed to rt for 2 h. The solution was re-cooled to –78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) dropwise. The solution continued to stir for a further 5 min at -78 °C before before the addition of 2 M HCl in Et₂O (5 mL). The solution was stirred for a further 18 h while warming to rt before being diluted with Et₂O (50 mL). The reaction mixture was washed with water (3 x 50 mL) and brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: 5% Et₂O in hexane) yielded the title compounds (0.215 g, 0.65 mmol, 65%) as a colourless oil.

**¹H NMR (300 MHz, CDCl₃):** 7.28-7.13 (5H, m, Ar-H), 5.13 (1H, tt, J = 7.3, 2.2, Hh), 3.33 (3H, s, Ha/e), 3.32 (3H, s, Ha/e), 3.29-3.16 (4H, m, Hb,d), 2.61-2.44 (2H, m, Hm), 2.34 (1H, d, J = 15.7), 2.14 (1H, d, J = 15.7), 1.96 (2H, q, J = 7.3, Hi), 1.71-1.54 (3H, m), 1.44 (1H, d, J = 13.4), 1.35 (2H, sxt, J = 7.3, Hj), 1.12 (3H, s, Hs), 0.87 (3H, t, J = 7.3, Hk) ppm.

**¹³C NMR (75 MHz, CDCl₃):** 148.90 (C, Cg), 143.36 (C, Co), 128.34 (CHx2, Cp/q), 128.28 (CHx2, Cp/q), 125.49 (CH, Cr), 120.58 (CH, Ch), 77.181 (CH₂, Ch/d), 76.39 (CH₂, Ch/d), 59.23 (CH₃, Ca/e), 59.20 (CH₃, Ca/e), 45.62 (CH₂, Cl), 45.16 (C, Cc), 44.37 (CH₂), 44.30 (C, Cm), 35.86 (CH₂), 31.57 (CH₂), 31.31 (CH₂), 28.37 (CH₃, Cs), 23.04 (CH₂), 13.75 (CH₃, Ck) ppm.

**IR v_max/cm⁻¹ (film):** 1456 (m), 1104 (s), 698 (s).

**LRMS (ES, MeCN):** m/z 353 ([M + Na]⁺, 100%).

**HRMS (ES):** C₂₂H₃₄NaO₂ [M + Na]⁺ calculated 353.2457, found 353.2457.
5.71 \((E)-2-((E)-2-\text{Butylidene}-4,4-\text{bis(methoxymethyl)}-1-\text{methylcyclopentyl)}\text{vinyl})\text{benzene}\) 153

To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at −78 °C was added \(n\)-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of 4,4-bis(methoxymethyl)-2-methyldec-1-en-6-yne 148 (0.238 g, 1.0 mmol) in THF (2 mL) was added dropwise. After a further 10 min the reaction mixture was warmed to rt for 2 h. The solution was re-cooled to −78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) dropwise. The solution continued to stir for a further 10 min before warming to rt. The solution was stirred for 24 h at rt before the addition of 2 M HCl (aq) (5 mL). The reaction mixture was stirred for a further 18 h at rt before being extracted with \(\text{Et}_2\text{O}\) (50 mL), washed with water (3 x 50 mL) and brine (50 mL), dried (MgSO\(_4\)) and the solvent removed \textit{in vacuo}. Purification by column chromatography on silica gel (eluent: 5% \(\text{Et}_2\text{O}\) in hexane) yielded the title compound (0.282 g, 0.86 mmol, 86%) as a colourless oil.

\(^1\)H NMR (300 MHz, CDCl\(_3\)): 7.37-7.16 (5H, m, \(\text{Ar-H}\)), 6.33 (1H, d, \(J = 16.0, \text{Hm}\)), 6.22 (1H, d, \(J = 16.0, \text{Hn}\)), 5.21 (1H, tt, \(J = 7.3, 2.0, \text{HH}\)), 3.36 (3H, s, \(\text{Ha/e}\)), 3.30 (3H, s, \(\text{Ha/e}\)), 3.28-3.21 (4H, m, \(\text{Hb/d}\)), 2.34 (1H, d, \(J = 16.4, \text{CH}_2\)), 2.23 (1H, d, \(J = 16.4, \text{CH}_2\)), 2.01 (2H, q, \(J = 7.3, \text{Hi}\)), 1.91 (1H, d, \(J = 16.4, \text{CH}_2\)), 1.54 (1H, d, \(J = 16.4, \text{CH}_2\)), 1.40 (2H, sxt, \(J = 7.3, \text{Hj}\)), 1.26 (3H, s, \(\text{Hs}\)), 0.91 (3H, t, \(J = 7.3, \text{Hk}\)) ppm.

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)): 147.42 (C, \(\text{Cg}\)), 140.60 (C, \(\text{Co}\)), 137.98 (CH, \(\text{Cn}\)), 128.45 (CHx2, \(\text{Cq}\)), 126.74 (CH, \(\text{Cm}\)), 126.08 (CHx2, \(\text{Cp}\)), 125.40 (CH, \(\text{Cr}\)), 122.57 (CH, \(\text{Ch}\)), 77.07 (CH, \(\text{Bh/d}\)), 76.03 (CH, \(\text{Bh/d}\)), 59.24 (CH, \(\text{Ca/e}\)), 59.17 (CH, \(\text{Ca/e}\)), 47.44 (C, \(\text{Cm}\)), 45.58 (CH, \(\text{Cl}\)), 45.58 (C, \(\text{Cc}\)), 35.61 (CH, \(\text{Cs}\)), 31.37 (CH, \(\text{Cp}\)), 28.11 (CH, \(\text{Cq}\)), 22.91 (CH, \(\text{Cj}\)), 13.79 (CH, \(\text{Ck}\)) ppm.

\(\text{IR } \nu_{\text{max}}/\text{cm}^{-1} \text{ (film): } 1447 \text{ (m), 1103 (s), 966 (s), 747 (s), 693 (s)}.\)
LRMS (ES, MeCN): m/z 351 ([M + Na]$^+$, 100%).

HRMS (ES): C$_{22}$H$_{32}$NaO$_2$ [M + Na]$^+$ calculated 351.2295, found 351.2292.
Sodium (1.3 g, 53.4 g-atom) was added portion-wise to ethanol (100 mL) at 0 °C. Once complete dissolution was observed a solution of diethyl malonate (6.5 mL, 42.7 mmol) was added dropwise and the solution was stirred for 15 min at 0 °C. A solution of 2-methylenehex-5-enyl methanesulfonate 104 (6.8 g, 35.6 mmol) in ethanol (50 mL) and 20% NaI (1.04 g, 7 mmol) in ethanol (5 mL) was added. The solution was warmed to rt and stirred for a further 3 h before being poured onto H₂O (500 mL) and extracted with Et₂O (3 x 200 mL). The combined organic extracts were washed with H₂O (3 x 100 mL), brine (2 x 100 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: 10% Et₂O in hexane) yielded the title compound (3.2 g, 13 mmol, 37%).

**¹H NMR (300 MHz, CDCl₃):** δ 5.81 (1H, ddt, J = 16.3, 10.2, 5.9, Hj), 5.06-4.81 (4H, m, Hk, g), 4.19 (4H, q, J = 7.1, Hb, m), 3.58 (1H, t, J = 7.8, Hd), 2.63 (2H, d, J = 7.8, He), 2.22-2.12 (4H, m, Hh, i), 1.26 (6H, t, J = 7.1, Ha, n) ppm.

**¹³C NMR (75 MHz, CDCl₃):** δ 169.07 (C₂, Cc, l), 145.00 (C, Cf), 137.97 (CH, Cj), 114.78 (CH₂, Ck), 111.27 (CH₂, Cg), 61.39 (CH₂x2, Cb, m), 50.59 (CH₂, Cd), 35.23 (CH₂), 34.77 (CH₂), 31.78 (CH₂), 14.05 (CH₃x2, Ca, n) ppm.

**IR v_max/cm⁻¹ (film):** 1731 (s), 1642 (w), 14456 (m), 1147 (s).

**LRMS (ES, MeCN):** 277 ([M+Na⁺], 100%).
5.73 Diethyl 2-(hex-2-yn-1-yl)-2-(2-methylenehex-5-en-1-yl)malonate 155

Synthesis of hex-2-ynyl methanesulfonate: To a stirred solution of hex-2-yn-1-ol (1.66 g, 17 mmol) and triethylamine (3.6 mL, 2.6 g, 26 mmol) in CH$_2$Cl$_2$ (40 mL) at –10 °C was added methanesulfonyl chloride (2.4 g, 1.6 mL, 20 mmol) dropwise. After 30 min at –10 °C the reaction mixture was poured onto H$_2$O (30 mL). The aqueous layer was separated and re-extracted with CH$_2$Cl$_2$ (3 x 30 mL). The combined organic layers were washed with 2M HCl (aq) (30 mL), H$_2$O (30 mL), NaHCO$_3$ (30 mL) and brine (30 mL). The organic layer was dried (MgSO$_4$) and solvent removed in vacuo to yield hex-2-ynyl methanesulfonate (2.82 g, 16 mmol, 94%). No further purification was required.

$^1$H NMR (300 MHz, CDCl$_3$): 4.85 (2H, s, Hb), 3.11 (3H, s, Ha), 2.23 (2H, t, J = 7.2, He), 1.56 (2H, sextet, J = 7.2, Hf), 0.99 (3H, t, J = 7.2, Hg) ppm.

Synthesis of diethyl 2-(hex-2-yn-1-yl)-2-(2-methylenehex-5-en-1-yl)malonate 155: To a stirred suspension of NaH (60% suspension in mineral oil) (0.626 g, 16.3 mmol) in THF (30 mL) at 0 °C was added malonate 154 (1.74 g, 13 mmol) in THF (10 mL) dropwise. The solution was stirred for a further 15 min before the addition of hex-2-ynyl methanesulfonate (2.82 g, 16 mmol) in THF (10 mL) and NaI (0.51 g, 3.4 mmol) in THF (10 mL). The solution was warmed to rt and stirred for 24 h before being quenched by the dropwise addition of NH$_4$Cl (50 mL). The reaction mixture was extracted with Et$_2$O (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried (MgSO$_4$) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent gradient: 0-10% Et$_2$O in hexane) yielded the title compound (3.13 g, 9.4 mmol, 72%) as a colourless oil.

$^1$H NMR (300 MHz, CDCl$_3$): δ 5.78 (1H, ddt, J = 16.8, 10.2, 6.3, Hj), 5.04-4.89 (4H, m, Hg, k), 4.27-4.10 (4H, m, Hb, s), 2.83 (2H, s, Hq), 2.79 (2H, t, J = 2.1, He), 2.23-2.00 (6H, m, CH$_2$), 1.48 (2H, sxt, J = 7.5, Hm), 1.25 (6H, t, J = 7.2, Ha, t), 0.96 (3H, t, J = 7.5, Hl) ppm.
$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 170.83 (Cx2, Cc, r), 143.64 (C, Cf), 130.08 (CH, Cj), 114.94 (CH$_2$, Ck), 114.59 (CH$_2$, Cg), 83.74 (C, Cp/o), 74.85 (C, Cp/o), 61.43 (CH$_2$x2, Cb, s), 56.97 (C, Cd), 37.09 (CH$_2$) 35.94 (CH$_2$), 32.18 (CH$_2$), 22.88 (CH$_2$), 22.32 (CH$_2$), 20.66 (CH$_2$), 13.98 (CH$_3$x2, Ca, t), 13.39 (CH$_3$, Cl) ppm.

IR $\nu_{\text{max}}$/cm$^{-1}$ (film): 1733 (s), 1641 (w), 1445 (m), 1180 (s), 1096 (s), 1051 (s), 905 (s).

LRMS (ES, MeCN): $m/z$ 357 ([M + Na]$^+$, 100%).
5.74 7,7-Bis(methoxymethyl)-5-methylenetridec-1-en-9-yne 156

Synthesis of 2-(hex-2-yn-1-yl)-2-(2-methylenehex-5-en-1-yl)propane-1,3-diol: To a stirred suspension of LiAlH$_4$ (1.1 g, 18.2 mmol) in Et$_2$O (50 mL) at 0 °C was added malonate 155 (3.12 g, 9.4 mmol) in Et$_2$O (10 mL). The solution was warmed to rt and stirred for 3 h before the dropwise addition of 2 M NaOH (aq) (5 mL) followed by water (20 mL). The mixture was poured onto 2 M HCl (aq) (20 mL) and extracted with Et$_2$O (3 x 50 mL). The combined organic extracts were washed with H$_2$O (3 x 50 mL), dried (MgSO$_4$) and the solvent removed in vacuo to yield the compound as a colourless oil (2.2 g, 8.8 mmol, 94%). No further purification was required.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 5.88-5.75 (1H, m, Hh), 5.06-4.89 (4H, m, He, i), 3.69-3.59 (4H, m, Ha, p), 2.52 (2H, t, $J = 5.7$, Hc), 2.24-2.15 (8H, m), 2.13 (2H, br s, OH), 1.52 (2H, sxt, $J = 7.2$, Hk), 0.98 (3H, t, $J = 7.2$, Hl) ppm.

Synthesis of 7,7-bis(methoxymethyl)-5-methylenetridec-1-en-9-yne 156: To a stirred suspension of NaH (60% suspension in mineral oil) (1.1 g, 28.2 mmol) in THF (80 ml) at 0 °C was added the diol (2.2 g, 8.8 mmol) in THF (10 mL) dropwise. After 30 min MeI (1.62 g, 14.1 mmol) in THF (5 mL) was added and the solution was stirred at 0 °C for 30 min. The remaining MeI (1.62 g, 14.1 mmol) in THF (5 mL) was added and the solution was warmed to rt and stirred for 4 h. The solution was quenched with the dropwise addition of MeOH (20 mL) poured onto H$_2$O (50 mL) poured onto H$_2$O (50 mL) before being extracted with Et$_2$O (3 x 30 mL). The combined organic extracts were washed with brine (50 mL), dried (MgSO$_4$) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: 5% Et$_2$O in hexane) yielded the title compound (2.15 g, 7.7 mmol, 88%) as a colourless oil.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 5.83 (1H, ddt, $J = 16.5, 10.2, 6.0$, Hi), 5.05-4.84 (4H, m, Hf, j), 3.31 (6H, s, Ha, r), 3.25-3.18 (4H, m, Hb, q), 2.19-2.12 (10H, m), 1.52 (2H, sxt, $J = 7.2$, Hl), 0.99 (3H, t, $J = 7.2$, Hk) ppm.
$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 145.34 (C, Ce), 138.62 (CH, Ci), 114.32 (CH$_2$, Cj), 113.95 (CH$_2$, Cf), 82.41 (C, Co/n) 76.81 (C, Co/n), 74.20 (CH$_2$x2, Ch,q), 59.0 (CH$_3$x2, Ca, r), 42.55 (C, Ce), 37.14 (CH$_2$), 36.23 (CH$_2$), 32.64 (CH$_2$), 22.57 (CH$_2$), 22.51 (CH$_2$), 20.83 (CH$_2$), 13.55 (CH$_3$, Ck) ppm.

IR $\nu_{\text{max}}$/cm$^{-1}$ (film): 1733 (s), 1639 (w), 1445 (m), 1180 (s), 1096 (s), 1051 (s), 905 (s).

LRMS (ES, MeCN): $m/z$ 301 ([M + Na]$^+$, 100%).

HRMS (ES): C$_{18}$H$_{30}$NaO$_2$ [M + Na]$^+$ calculated 301.2138, found 301.2142.
5.75 \((E)-1-(\text{But-3-en-1-yl})-2\text{-butylidene-4,4-bis(methoxymethyl)-1-methylcyclopentane}\ 158\)

To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at \(-78 \, ^\circ\text{C}\) was added \(n\text{-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol)}\) dropwise over 5 min. After 10 min a solution of 7,7-bis(methoxymethyl)-5-methylenetridec-1-en-9-ynye 156 (0.278 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h before being quenched with 2 M HCl (aq) (5 mL). The reaction mixture was was stirred for 18 h at rt before being extracted with \(\text{Et}_2\text{O (50 mL)}\). The organic layer was washed with water (3 x 50 mL) and brine (50 mL), dried (MgSO\(_4\)) and the solvent removed \textit{in vacuo}.

Purification by column chromatography on silica gel (eluent: 5% \(\text{Et}_2\text{O in hexane})\) yielded the title compound (0.259 g, 0.93 mmol, 93%) as a colourless oil.

\(^1\text{H NMR (300 MHz, CDCl}_3\)): \(\delta 5.82 (1\text{H, ddt, } J = 17.0, 10.3, 6.5, \text{ Hq}), 5.09 (1\text{H, tt, } J = 7.3, 2.2, \text{ Hh}), 5.0-4.89 (2\text{H, m, Hr}), 3.35 (3\text{H, s, Ha/e}), 3.33 (3\text{H, s, Ha/e}), 3.28-3.15 (4\text{H, m, Hb, d}), 2.33 (1\text{H, m}), 2.12 (1\text{H, m}), 2.02-1.93 (4\text{H, m}), 1.61 (1\text{H, m}), 1.51-1.30 (5\text{H, m}), 1.06 (3\text{H, s, Hn}), 0.88 (3\text{H, t, } J = 7.3, \text{ Hk}) \text{ ppm.}\)

\(^{13}\text{C NMR (75 MHz, CDCl}_3\)): \(\delta 148.95 (\text{C, Cg}), 139.64 (\text{CH, Cq}), 120.43 (\text{CH, Ch}), 113.74 (\text{CH}_2, \text{ Cr}), 77.22 (\text{CH}_2, \text{ Ch/d}), 76.30 (\text{CH}_3, \text{ Ch/d}) 59.23 (\text{CH}_3, \text{ Ca/e}), 59.18 (\text{CH}_3, \text{ Ca/e}), 45.09 (\text{C, Ce}), 44.41 (\text{CH}_2, \text{ Cl}), 44.05 (\text{C, Cm}), 42.54 (\text{CH}_2, \text{ Co}), 35.82 (\text{CH}_2, \text{ Cf}), 31.26 (\text{CH}_2), 29.42 (\text{CH}_2), 28.32 (\text{CH}_2), 23.00 (\text{CH}_3, \text{ Cn}), 13.71 (\text{CH}_3, \text{ Ck}) \text{ ppm.}\)

\(\text{IR } \nu_{\text{max}}/\text{cm}^{-1} (\text{film})\): 1640 (w), 1456 (m), 1105 (s).

\(\text{LRMS (ES, MeCN): } m/z 303 ([M + Na]^+, 100\%).\)

\(\text{HRMS (ES): } \text{C}_{18}\text{H}_{32}\text{NaO}_2 [M + Na]^+ \text{ calculated 303.2295, found 303.2295.}\)
5.76 (E)-(2-(1-(But-3-en-1-yl)-2-butylidene-4,4-bis(methoxymethyl)cyclopentyl)ethyl)benzene 160

To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at –78 °C was added n-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of 7,7-bis(methoxymethyl)-5-methylenetridec-1-en-9-yne 156 (0.278 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. The solution was re-cooled to –78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) dropwise. The solution continued to stirred for a further 5 min at –78 °C before the addition of 2 M HCl in Et2O (5 mL). The solution was stirred for a further 20 h while warming to rt before being diluted with Et2O (50 mL). The reaction mixture was washed with water (3 x 50 mL) and brine (50 mL), dried (MgSO4) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: 5% Et2O in hexane) yielded the title compound (0.288 g, 0.78 mmol, 78%) as a colourless oil.

1H NMR (300 MHz, CDCl3): δ 7.32-7.26 (2H, m, Ar-H), 7.20-7.16 (3H, m, Ar-H), 5.85 (1H, ddt, J = 17.0, 10.3, 6.5, Hv), 5.14 (1H, tt, J = 7.3, 2.0, Hh), 5.06-4.93 (2H, m, Hw), 3.37 (3H, s, Ha/e), 3.35 (3H, s, Ha/e), 3.29-3.20 (4H, m, Hb, d), 2.56-2.50 (2H, m, Ho), 2.26 (2H, br s), 2.06-1.95 (4H, m), 1.81-1.55 (5H, m), 1.45-1.36 (3H, m), 0.92 (3H, t, J = 7.3, Hk) ppm.

13C NMR (75 MHz, CDCl3): 146.47 (C, Cg), 143.30 (C, Cp), 139.45 (CH, Cv), 128.33 (CHx4), 125.56 (CH), 121.64 (CH, Ch), 113.95 (CH2, Cw), 76.90 (CH2,Cb/d), 76.79 (CH2, Cb/d), 59.19 (CH3x2, Ca/e), 47.61 (C, Cc), 44.71 (C, Cm), 42.71 (CH2), 41.95 (CH2), 38.85 (CH2), 35.92 (CH2), 31.31 (CH2), 31.23 (CH2), 29.11 (CH2), 23.08 (CH2), 13.79 (CH3, Ck) ppm.

IR v_max/cm⁻¹ (film): 1640 (w), 1454 (m), 1104 (s), 698 (s).
LRMS (ES, MeCN): \( m/z \) 393 ([M + Na]\(^+\), 100%).

HRMS (ES): \( \text{C}_{25}\text{H}_{38}\text{NaO}_2 \) [M + Na]\(^+\) calculated 393.2764, found 393.2760.
To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at –78 °C was added n-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of 7,7-bis(methoxymethyl)-5-methylenetridec-1-en-9-yne (0.278 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. The solution was re-cooled to –78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) was added. The solution continued to stir for a further 10 min before warming to rt. The solution was stirred for 24 h at rt before the addition of 2 M HCl (aq) (5 mL). The reaction mixture was stirred for a further 18 h at rt before being extracted with Et₂O (50 mL). The organic layer was washed with water (3 x 50 mL) and brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: 5% Et₂O in hexane) yielded the title compound (0.110 g, 0.30 mmol, 30%) as a colourless oil.

**¹H NMR (300 MHz, CDCl₃):** δ 7.37-7.28 (3H, m, Ar-H), 7.23-7.14 (2H, m, Ar-H), 6.37 (1H, d, J = 16.1, Ho), 6.23 (1H, d, J = 16.1, Hm), 5.82 (1H, tdd, J = 16.8, 10.6, 6.6, Hv), 5.28 (1H, tt, J = 7.1, 2.4, Hh), 5.04-4.90 (2H, m, Hw), 3.37 (3H, s, Ha/e), 3.33-3.21 (7H, m, Ha/e, b, d), 2.25 (2H, br s), 2.10-1.98 (5H, m), 1.76-1.53 (3H, m), 1.46-1.38 (2H, m), 0.93 (3H, t, J = 7.3, Hk) ppm.

**¹³C NMR (75 MHz, CDCl₃):** δ 146.73 (C, Cg), 139.28 (CH), 139.10 (CH), 137.97 (C, Cp), 128.48 (CHx2), 126.80 (CH), 126.43 (CH), 126.11 (CHx2), 122.82 (CH, Ch), 114.00 (CH₂, Cw), 77.28 (CH₂, Cb/d), 77.38 (CH₂, Cb/d), 59.28 (CH₃, Ca/e), 59.08 (CH₃, Ca/e), 50.66 (C, Cm), 45.42 (C, Ce), 41.36 (CH₂), 41.26 (CH₂), 36.08 (CH₂), 31.42 (CH₂), 29.45 (CH₂), 22.91 (CH₂, Cj), 13.83 (CH₃, Ck) ppm.
IR \( \nu_{\text{max}}/\text{cm}^{-1} \) (film): 1640 (w), 1495 (m), 1448 (m), 1103 (s), 693 (s).

LRMS (ES, MeCN): \( m/z \) 391 ([M + Na]\(^+\), 100\%).

HRMS (ES): \( \text{C}_{25}\text{H}_{36}\text{NaO}_2 \) [M + Na]\(^+\) calculated 391.2608, found 391.2607.
To a stirred solution of zirconocene dichloride (0.164 g, 0.56 mmol) in THF (2 mL) at −78 °C was added n-BuLi (2.5 M solution in hexanes) (0.45 mL, 1.12 mmol) dropwise over 5 min. After 10 min a solution of **162** (0.103 g, 0.28 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 3 h before being quenched with MeOH (2 mL) followed by sat NaHCO₃ (aq) (2 mL). The reaction mixture was stirred for a further 20 h at rt. The reaction mixture was extracted with Et₂O (50 mL). The combined organic layers were washed with water (3 x 50 mL) and brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: 5% Et₂O in hexane) yielded the title compounds (0.071 g, 0.19 mmol, 68%) as a colourless oil. NMR revealed that the title compound had been formed in a 1:1 ratio of diastereoisomers. Separation of the 2 diastereoisomers was achieved by preparative HPLC.

**Diastereoisomer A:**

**¹H NMR (300 MHz, CDCl₃):** δ 7.26-7.14 (5H, m, Ar-H), 5.31 (1H, tt, J = 17.3, 2.0, Hh), 3.37 (3H, s, Ha/e), 3.35 (3H, s, Ha/e), 3.32-3.21 (4H, m, Hb, d), 2.57-2.55 (2H, CH₂), 2.30-2.23 (2H, m), 2.07-1.90 (5H, m), 1.79 (2H, m), 1.62-1.51 (2H, m, CH₂), 1.39 (2H, sxt, J = 7.53, Hj), 1.29 (1H, m), 0.93-0.89 (6H, m, Hk, w) ppm.

**¹³C NMR (75 MHz, CDCl₃):** δ 149.32 (C, Cg), 142.36 (C, Cp), 128.70 (CHx2), 128.11 (CHx2), 125.40 (CH), 119.91 (CH, Ch), 77.48 (CH₂, Ch/d), 75.32 (CH₂, Ch/d), 59.33 (CH₃, Ca/e), 59.14 (CH₃, Ca/e), 54.79 (C, Cm), 54.73 (CH, Cn), 46.11 (C, Cc), 43.82 (CH₂), 39.62 (CH₂), 36.99 (CH₃), 32.74 (CH₂), 32.44 (CH, Cu), 32.25 (CH₂), 31.48 (CH₂), 23.06 (CH₂, Cj), 18.07 (CH₃, Cw), 13.78 (CH₃, Ck) ppm.

**IR ν_max/cm⁻¹ (film):** 1640 (w), 1495 (m), 1455 (m), 1103 (s), 699 (s).

**LRMS (ES, MeCN):** m/z 393 ([M + Na]⁺, 100%).
HRMS (ES): $\text{C}_{25}\text{H}_{38}\text{NaO}_2 \ [\text{M} + \text{Na}]^+$ calculated 393.2764, found 393.2764.

Diastereoisomer B:

$^1\text{H NMR (300 MHz, CDCl}_3\text{): } \delta$ 7.24-7.13 (5H, m, Ar-H), 5.29 (1H, tt, $J = 7.3, 2.3$, Hh), 3.36 (3H, s, Ha/e), 3.34 (3H, s, Ha/e), 3.31-3.21 (4H, m, Hb, d), 2.71 (1H, dd, $J = 13.4, 3.4$), 2.42 (1H, dd, $J = 13.6, 8.5$), 2.26 (1H, d, $J = 16.3$), 2.02-1.87 (4H, m), 1.72-1.58 (5H, m), 1.47 (1H, d, $J = 13.8$), 1.37 (2H, sxt, $J = 7.3$, Hj), 1.91 (1H, m), 0.90 (3H, t, $J = 7.3$, Hk), 0.65 (3H, d, $J = 6.27$, Hw) ppm.

$^{13}\text{C NMR (75 MHz, CDCl}_3\text{): } \delta$ 147.73 (C, Cg), 142.53 (C, Cp), 129.06 (CHx2), 127.93 (CHx2), 125.39 (CH), 120.31 (CH, Ch), 77.21 (CH$_2$,Cb/d), 75.56 (CH$_2$,Cb/d), 59.31 (CH$_3$, Ca/e), 59.15 (CH$_3$, Ca/e), 59.15 (CH, Cn), 56.59 (C, Cm), 45.59 (C, Cc), 42.15 (CH$_2$), 38.78 (CH, Cu), 37.80 (CH$_2$), 37.20 (CH$_2$), 36.77 (CH$_2$), 31.90 (CH$_2$), 31.40 (CH$_2$), 22.50 (CH$_2$, Cj), 21.21 (CH$_3$, Cw), 13.78 (CH$_3$, Ck) ppm.

IR $\nu_{\text{max}}$/cm$^{-1}$ (film): 1640 (w), 1495 (m), 1455 (m), 1103 (s), 698 (s).

LRMS (ES, MeCN): $m/z$ 393 ([M + Na]$^+$, 100%).

HRMS (ES): $\text{C}_{25}\text{H}_{38}\text{NaO}_2 \ [\text{M} + \text{Na}]^+$ calculated 393.2764, found 393.2764.
5.79 (E)-1-Benzyl-6-butylidene-8,8-bis(methoxymethyl)-2-methylspiro[4.4]nonane 164 and ((E)-2-((E)-1-(But-3-en-1-yl))-2-butylidene-4,4-bis(methoxymethyl)cyclopentyl)vinyl)benzene 162

To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at –78 °C was added n-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of 7,7-bis(methoxymethyl)-5-methylenetridec-1-en-9-yne 156 (0.278 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. The solution was re-cooled to –78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LiTMP (formed by treating 2,2,6,6-tetramethylpiperidine (0.22 mL, 0.184 g, 1.3 mmol) in THF (2 mL) at 0 °C with n-BuLi (2.5 M solution in hexanes) (0.52 mL, 1.3 mmol) dropwise). The solution continued to stir for 10 min at –78 °C before being warmed to rt. The solution was stirred for 24 h at rt before the addition of 2 M HCl (aq) (5 mL). The reaction mixture was stirred for a further 18 h at rt before being extracted with Et₂O (50 mL). The organic layer was washed with water (3 x 50 mL) and brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: 5% Et₂O in hexane) yielded the title compounds (0.259 g, 0.70 mol, 70%) as an inseparable mixture of spirocycle 164 and alkene 162 in a 2:1 ratio. Only diasterisomer A of spirocycle 164 was isolated.

For alkene 162 data analysis see experimental 5.75.

For spirocycle 164 data analysis see experimental 5.76.
6 References


66. Whitby, R. J., unpublished work, **2009**.


