UNIVERSITY OF SOUTHAMPTON

Carbenoid Insertion into Organozirconocene Complexes

By Emma Thomas

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ABSTRACT

FACULTY OF ENGINEERING, SCIENCE & MATHEMATICS
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Doctor of Philosophy

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By Emma Victoria Thomas

The synthesis of zirconacycles and organochlorozirconocene complexes is well established and the potential for their further elaboration is of interest to the organic chemist. This thesis focuses on elaboration through carbenoid insertion into the carbon zirconium bond.

The regioselectivity of alkyl and alkenyl carbenoid insertion into unsymmetrical zirconacycles has been investigated. In most cases studied complete regioselectivity was observed. The origins of regioselectivity were investigated using zirconacycles with distinct substitution patterns and carbenoids with different electronic properties. Results were used to support a model that explains regioselectivity through steric hindrance and the rate of 1,2-metallate rearrangement of the intermediate 'ate' complex.

The insertion of cyclopropyl carbenoids into organochlorozirconocenes results in the synthesis of vinylcyclopropanes and in alkylidenecyclopropanes. The technique was applied to the synthesis of di-vinylcyclopropanes. Investigations into the mechanism of these reactions revealed that the initial transmetallation from lithium to zirconium probably occurs with inversion of configuration. The insertion of cyclopropyl carbenoids generated *in situ* into organochlorozirconocenes was shown to be a viable synthetic technique.

The sequential addition of 1-halo-1-lithioalkenes and acetylides to zirconacyclopent-enes and -anes results in highly elaborated bicyclo-[3.3.0]-octenes and –octanes. These are thought to be generated *via* an unusual 1,3-alkyl shift resulting in a zirconocene-alkenylidene complex.

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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 citation of literature examples are indicated.

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Last, but by no means least I like to thank my sister, Sarah, for always being there and for finding me and Barney a place to live. Thanks to my Mum and Dad for all their love and encouragement, and a special thanks to my Grandma for being such an amazing lady.

List of Abbreviations

Techniques

CI	Chemical Ionisation
COSY	Correlation Spectroscopy
DEPT	Distortionless Enhancement by Polarisation Transfer
EI	Electron Impact Ionisation
ES	Electrospray
GC	Gas Chromatography
GCMS	Gas Chromatography Mass Spectrometry
GOESY	Gradient Enhanced Nuclear Overhauser Effect Spectroscopy
HRMS	High Resolution Mass Spectrometry
IR	Infra-Red Spectroscopy
LRMS	Low Resolution Mass Spectrometry
NOE	Nuclear Overhauser Effect
NMR	Nuclear Magnetic Resonance
TLC	Thin Layer Chromatography

Reagents

n-BuLi	*n*-Butyllithium
sec-BuLi	*sec*-Butyllithium
t-BuLi	*tert*-Butlyllithium
DMF	Dimethyl Formamide
DMAP	4-DimethylAmino Pyridine
DME	Dimethoxyethane
HMPA	Hexamethylphosphoroamide
LDA	Lithium Diisopropylamide
LiTMP	Lithium 2,2,6,6-tetramethylpiperidide
NBS	*N*-Bromosuccinimide
PMA	Phosphomolybdic Acid
PPTS	Pyridinium *para*-Toluene Sulfonate
TBAF	Tetrabutylammonium Fluoride
TBDMS	*tert*-Butyldimethylsilyl
THF	Tetrahydrofuran
TMEDA	*N*, *N*, *N*, *N*-Tetramethylethylenediamine
TMS	Trimethylsilyl

Chemical Groups

Ac	Acyl
Ar	Aryl
Bu	Butyl
Bn	Benzyl
Cp	Cyclopentadieneyl
Cy	Cyclohexyl
Et	Ethyl
Hex	Hexyl
LG	Leaving Group

Me	Methyl
Ms	Methanesulfonyl
Oct	Octyl
Pr	Propyl

Others

aq.	Aqueous
°C	Degrees Celsius
cat.	Catalytic
δ	Chemical Shift, in Parts Per Million
d	Doublet
eq	Equivalent(s)
fs	Fine Splitting (NMR spectra)
g	Gram
hr	Hour(s)
m	Multiplet
M	Moles per litre
mg	Milligram(s)
MHz	Megahertz
mL	Millilitre
min	Minute(s)
mmol	Millimole(s)
mol	Mole(s)
m/z	Mass Charge Ratio
RT	Room Temperature
s	Singlet
t	Triplet

Chapter 1 Introduction

1.1 Overview

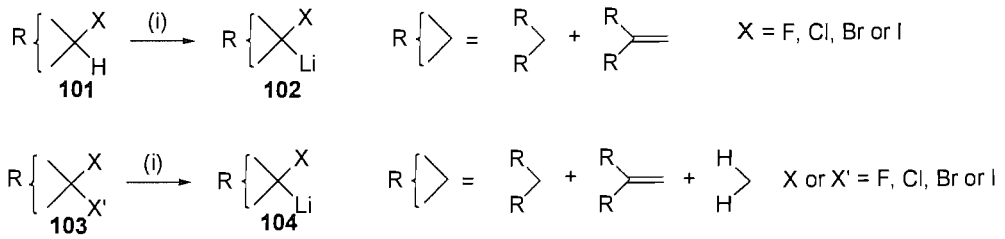
The results described in this thesis focus on the insertion of carbenoids into organozirconocene complexes. The aims of the research were to explore novel methodology for, and to gain a better understanding of, this synthetically useful carbon-carbon bond forming reaction. Chapter 1 presents a brief description of the formation, properties and reactions of carbenoids and organozirconocene complexes. The two topics are then brought together and there follows a discussion on general precedent for the results presented in chapters 2-4. Each of these discussion chapters includes a more targeted introduction to that particular area of research.

1.2 Carbenoids

Carbenoids are molecules in which a single carbon atom is substituted with a leaving group and a metal atom. The term carbenoid was first used as a noun by Closs and Moss[1] to describe intermediates which exhibit reactions qualitatively similar to those of carbenes. Though carbenoids with metal atoms such as potassium, sodium and tin are known[2] the focus of this section will be on lithium halocarbenoids.

1.2.1 Synthesis of Carbenoids

Lithium halocarbenoids are thermally unstable and are therefore formed at low temperatures to avoid decomposition. There are two main ways of making carbenoids (Scheme 1-1). The first is deprotonation of an organohalides using an amide or organolithium base (**101** to **102**).[3] The main limitation of this method is often the low acidity of the proton, which makes removal at the low temperatures required for the stability of the product difficult. The second method is halogen lithium exchange between an organolithium reagent and a gem-dihalo-compound. This is a very fast process which occurs at low temperatures (**103** to **104**).[4] The drawbacks associated with this method are competing side reactions such as α-metallation.[5]



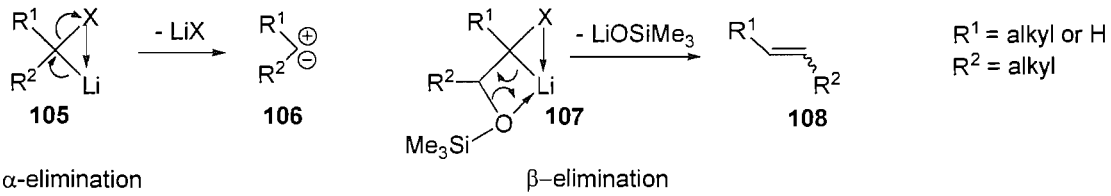
101 102 103 104

(i) 1.0 eq R_2NLi, < - 70 °C; (ii) 1.0 eq RLi, ~ -100 °C

Scheme 1-1 Methods for carbenoid formation

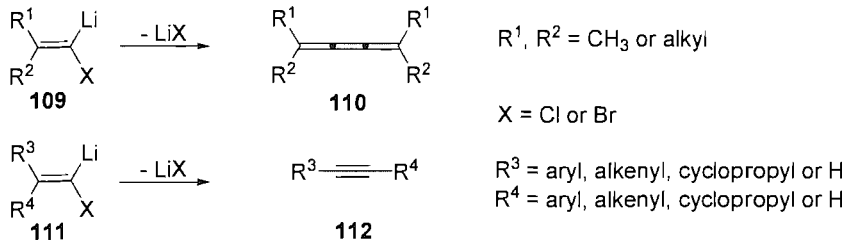
1.2.2 Decomposition of Carbenoids

Studies have shown that carbenoids decompose through a number of routes (Scheme 1-2). The most important route is α-elimination, which results in the formation of a carbene with the loss of lithium halide (**105** to **106**).[6] There are also other more specific decomposition routes that are associated with particular carbenoids. β-Elimination of lithium and a substituent at the β-position with respect to the carbenoid **107** can result in formation of alkenes **108**.[6]



Scheme 1-2 Decomposition pathways for carbenoids

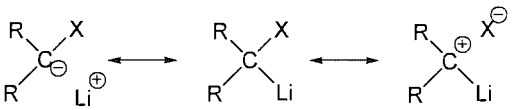
When alkenyl carbenoids **109** decompose by α-elimination they may form cumulenes **110** (Scheme 1-3).[7,8] Alkenyl carbenoids **111** can also undergo the Fritsch-Buttenberg-Weichell rearrangement to form disubstituted acetylenes **112** (Scheme 1-3).[8,9] This process was initially used in the synthesis of tolanes from 2,2-diarly-1-haloethenes.[9] However, more significantly, it will also occur for 1-halo-1-lithio alkenes **111** where at least one of the β-substituents is an aryl, alkenyl or cyclopropyl group.[8]



Scheme 1-3 Decomposition pathways for alkenyl carbenoids

1.2.3 Properties of Carbenoids

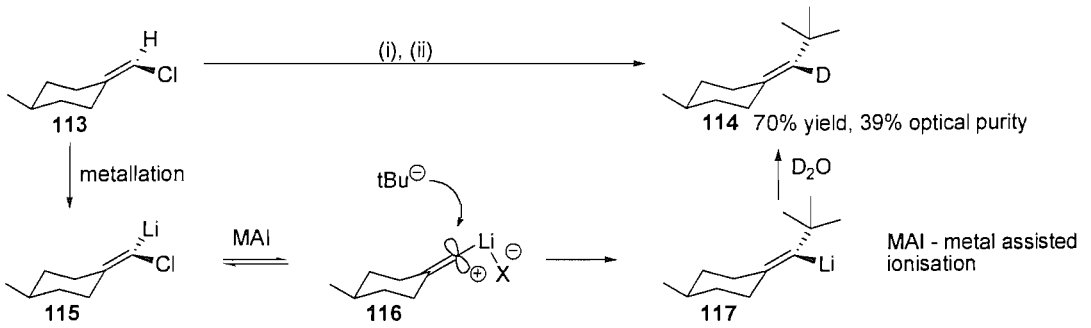
Carbenoids are of particular interest in organic synthesis due to their ambiphilic nature. They can behave as both nucleophiles and as electrophiles but usually behave as both (Scheme 1-4).[2] Nucleophilic behaviour includes reactions such as alkylations[10] and acylations.[11]



Scheme 1-4 Carbenoid viewed as nucleophiles and electrophiles

Bosch and Lohrenz have recently reviewed the electrophilic nature of carbenoids.[12] Investigations using NMR revealed the electron deficient nature of the carbenoid carbon.[13] This was shown by the large deshielding that occurred upon replacement of the proton with lithium in the metallation process. Further evidence for the electrophilic nature of carbenoids in the elongated carbon halogen bond which was observed in the x-ray structure of an alkenyl carbenoid.[14] This evidence may explain why carbenoids react with nucleophiles.[12]

A study of chiral vinyl and cyclopropyl carbenoids by Walborsky and co-workers has extended the understanding the electrophilic nature of carbenoids and led to the development of the metal assisted ionisation theory.[2,15-17] This explains the stereoselectivity observed upon reaction of nucleophiles with carbenoids. In this case chloro **115** and bromo carbenoids undergo nucleophilic substitution with inversion of configuration (Scheme 1-5).



Scheme 1-5 Example of metal assisted ionisation of a carbenoid followed by nucleophilic addition

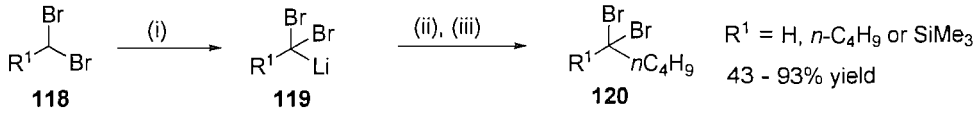
Metal assisted ionisation explains the process through which a nucleophilic reagent **115** can become electrophilic **116**.[2] During the ionisation, through loss of the halide, the carbenoid undergoes rehybridisation placing the developing positive charge in a p-orbital and producing a tight ion pair **116**. The halide remains blocking one face of the carbenoid directing nucleophilic attack to the other face, affording **117**. Alternatively this reaction could also be viewed as a 1,2-metallate rearrangement, especially if the chelating effect of the solvent is taken into account.

Carbenoids do not always retain their stereochemical integrity. Harada *et al.* reported that carbenoids might isomerise through halogen lithium exchange with unreacted dihalides present in the reaction.[18] Metal assisted ionisation (MAI) may help to explain the quick loss in stereochemical integrity observed in β,β-di-substituted alkenyl carbenoids when compared to β-mono-substituted alkenyl carbenoids observed by Whitby *et al.*[19] β-Mono-substituted alkenyl carbenoids would isomerise slower through MAI because the cationic component would be less stabilised by the β-substituents and the loss of the halogen would not result in a very significant relief of steric strain.[19]

1.2.4 Reactions of Alkyl Carbenoids

Alkyl carbenoids have been shown to react with nucleophiles and electrophiles.[20] Villieras *et al.* carried out some pioneering work in this field.[3,21-23] Unfunctionalised alkyl carbenoids **119** with two halogens present at the carbenoid carbon were initially

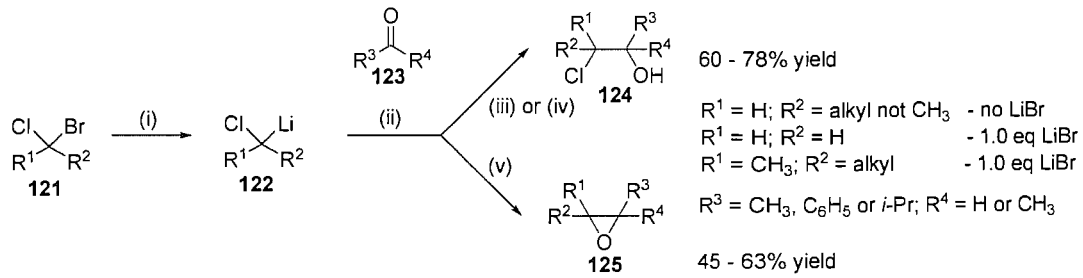
synthesised using metallation with lithium diisopropylamide.[3] These were reacted with alkyl iodides to afford alkylated products **120** (Scheme 1-6).



(i) 0.91 eq LDA, -90 °C, 15 min; (ii) $CH_3(CH_2)_2CH_2I$, -90 to -55 °C over 4 hr; (iii) 2 N HCl aq..

Scheme 1-6 Alkylation of alkyl carbenoid

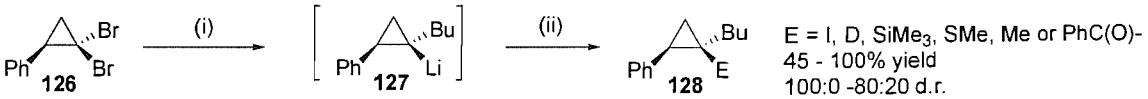
Villieras *et al.* later found that the use of halogen lithium exchange gave access to a number of carbenoids **122** that only had one halogen at the carbenoid carbon.[23] The reaction of these alkyl carbenoids with esters[23] afforded α-haloketones and with carbonyl compounds **123**[21] afforded epoxides **125** or halohydrins **124** depending on the conditions used (Scheme 1-7).



(i) 1.0 eq *n*-BuLi, < -113 °C, THF/diethyl ether/pentane 6:4:3, in some cases 1.0 eq LiBr; (ii) 0.96 eq **123**, -115 °C; (iii) NH_4 Cl aq., RT (no LiBr); (iv) NH_4Cl aq., -95 °C (with LiBr); (v) NH_4Cl aq. RT (with LiBr).

Scheme 1-7 Acylation of alkyl carbenoid

Alkyl carbenoids have been shown to act as electrophiles. The stereoselective alkylation of cyclopropyl carbenoids **127** resulted from the use of an excess of organometallic reagent and afforded elaborated cyclopropanes **128** upon further reaction (Scheme 1-8).[24-26]



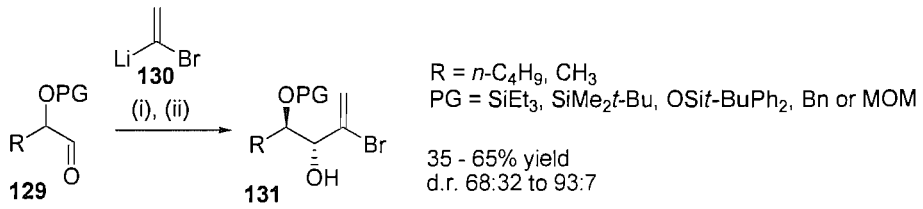
(i) 2.0 eq *n*-BuLi; (ii) E^+.

Scheme 1-8 Reaction of cyclopropyl carbenoid with excess organolithium

Alkyl carbenoids where the carbenoid carbon is bonded to a heteroatom are synthetically significant and of particular interest in the context of the results presented later in this thesis (Chapters 2 – 4). An example with silicon in the α-position was described in Scheme 1-6. Those with sulfur[27] and phosphorous[28] have also found synthetic uses.[20]

1.2.5 Reactions of Alkenyl Carbenoids

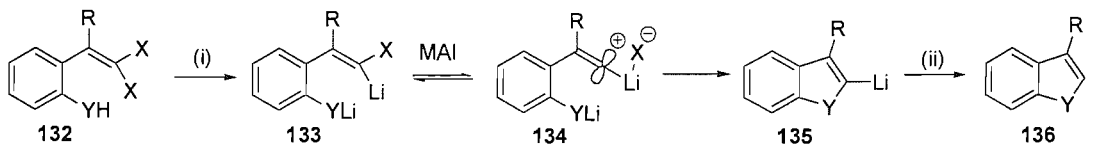
Alkenyl carbenoids have also been shown to behave as nucleophiles and electrophiles.[9] 1-Bromo-1-lithioethene **130** has recently been shown to undergo diastereoselective 1,2-addition to a series of aldehydes and ketones affording 2-bromo-1-alkene-3-ols **131** in moderate yields (Scheme 1-9).[29]



(i) 0.23 eq **130**, -110 to -105 °C, 30 min; (ii) AcOH in Trapp solvent, -105 °C to RT.

Scheme 1-9 Acylation of alkenyl carbenoid

Alkenyl carbenoids have also been used as electrophiles in the synthesis of fused hetererocycle compounds **136** in variable yields (Scheme 1-10).[30] The vinyl carbenoids were shown to undergo intramolecular substitution reactions with oxygen, nitrogen and sulfur, which were present as ortho substituents in the aromatic rings.



R = H or CH_3; Y = O, NH or S; X = Cl or Br.

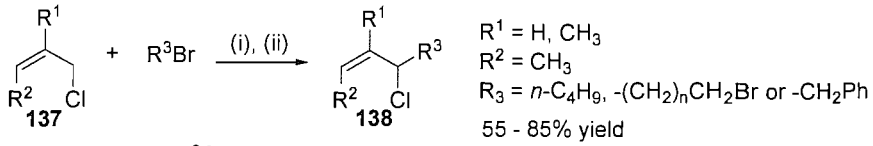
30 - 70% yield

(i) 2.0 eq *n*-BuLi, -100 °C, then -70 °C over 2 hr, (ii) MeOH, RT.

Scheme 1-10 Reaction of alkenyl carbenoid with nucleophiles

1.2.6 Reactions of Allyl and Benzyl Carbenoids

The carbenoid generated by deprotonation of allyl chloride undergoes regiospecific α-alkylation with primary alkyl bromides, affording elaborated allyl chlorides **138** (Scheme 1-11).[31] Allyl and benzyl carbenoids generated with LDA and LiTMP have also been trapped *in situ* with trimethylsilyl chloride.[32]

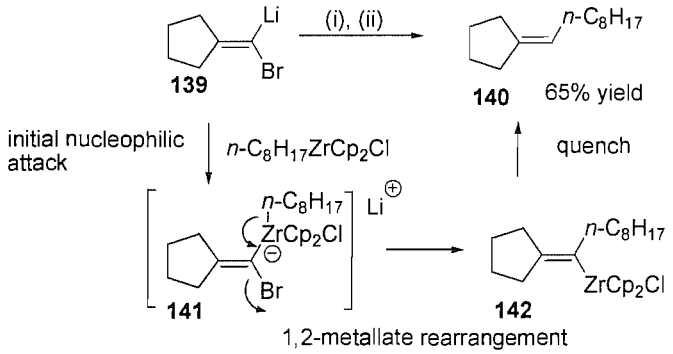


(i) 1.0 eq LDA, -78 °C, 15 min; (ii) NH_4Cl aq.

Scheme 1-11 Alkylation of allyl carbenoids

1.2.7 Reactions of Carbenoids with Organozirconocene Complexes

The direct precedent upon which many of the results described in this thesis are based (Chapters 2 – 4) was set by Negishi *et al.*[33] The report on carbon-carbon bond forming reactions of organotransition metals with α- or γ- haloorganolithium reagents describes the migratory insertion of carbenoids **139** into organochlorozirconocenes (Scheme 1-12). Prior to this publication migratory insertion had been dominated by a small number of reagents such as carbon monoxide and isonitriles.[33]



(i) 1.0 eq n-$C_8H_{17}ZrCp_2Cl$, -78 °C, 1 hr; (ii) 2 N HCl aq.

Scheme 1-12 First example of carbenoid insertion into organochlorozirconocenes

The ambiphilic properties of carbenoids, discussed in section 1.2.3, are thought to be responsible for the migratory insertion behaviour observed upon the reaction of carbenoids and organotransition metals. In the proposed mechanism for the insertion of carbenoids into organochlorozirconocenes the initial role of the carbenoid, which is

seen as the nucleophile, involves the donation of an electron pair into the empty orbital on the metal affording 'ate' complex **141**. This is followed by a 1,2-metallate rearrangement with the loss of the leaving group from the carbenoid moiety **142**. 1,2-Metallate rearrangement was first described by Matteson[34] in the context of boron chemistry and has since found synthetic utility[35] with both main group[36] and transition metals.[33] However, carbenoid insertion into organozirconocene complexes could also be seen in terms of a nucleophilic attack by the carbon zirconium bond on the electrophilic carbenoid carbon.[37]

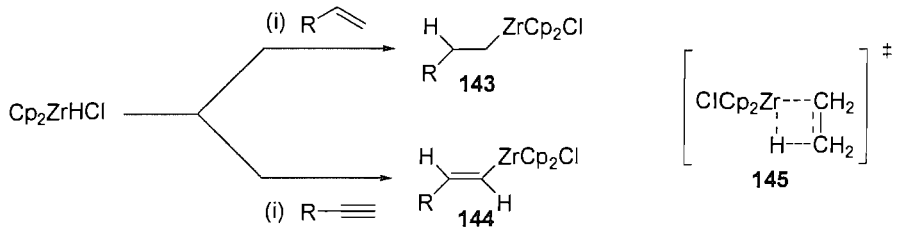
1.3 Organozirconocene Complexes

The results discussed in this thesis (Chapters 2-4) are based on carbenoid insertion into organozirconium complexes. Having discussed some relevant aspects of carbenoid chemistry (Section 1.2) this section will focus on the synthesis and some relevant reactions of acyclic organozirconium species and zirconacycles.

It is important first of all to note the properties of zirconocenes that make them suitable for stoichiometric organometallic synthesis.[38] Zirconium is a group four transition metal, which is both relatively cheap and non-toxic. Zirconocene complexes are most electronically stable when they have sixteen electrons in their valance shell. The empty orbital this leaves on the metal is key in understanding its reactivity.[38]

1.3.1 Synthesis of Acyclic Organozirconium Complexes

Acyclic organochlorozirconocenes can be synthesised *via* hydrozirconation of alkenes and alkynes with the Schwartz reagent (Scheme 1-13). The Schwartz reagent was first synthesised by Wailes and Wigold[39] in 1970 and used for hydrozirconation by Schwartz *et al.* in 1974.[40] Organochlorozirconocenes were shown to react with electrophiles such as halides and acid chlorides as well as with carbenoids such as carbon monoxide.[40,41] Hydrozirconation occurs *via* a 4-member transition state **145**[42] and is a formally allowed process due to the empty orbitals on zirconium (Scheme 1-13).[43]



(i) 1.0 eq alkene/alkyne, RT.

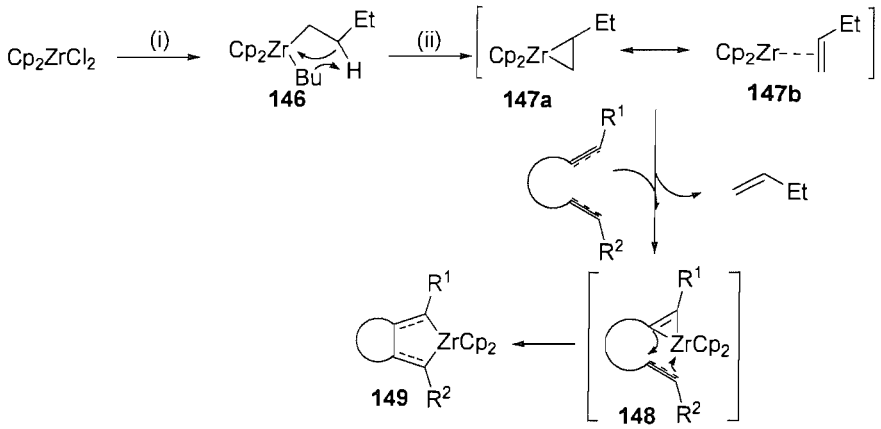
Scheme 1-13 Hydrozirconation of alkenes and alkynes

In the case of di-substituted alkynes the steric bulk of the substituents dictate the direction of zirconium hydride cis β-addition.[44] Hydrozirconation is most favoured for a terminal alkyne > terminal mono-substituted alkene ≈ internal alkyne > internal di-substituted alkene ≈ 2,2-disubstituted alkene ≈ conjugated polyene > tri-substituted alkene.[42]

1.3.2 Synthesis of Zirconacycles

There are two main strategies available for the synthesis of zirconacycles. The first is the co-cyclisation of 1,*n*-dienes, -enynes and –diynes using a '$ZrCp_2$' equivalent and the second is trapping zirconocene η^2 –alkenes, -alkynes and benzynes with alkenes and alkynes.[45]

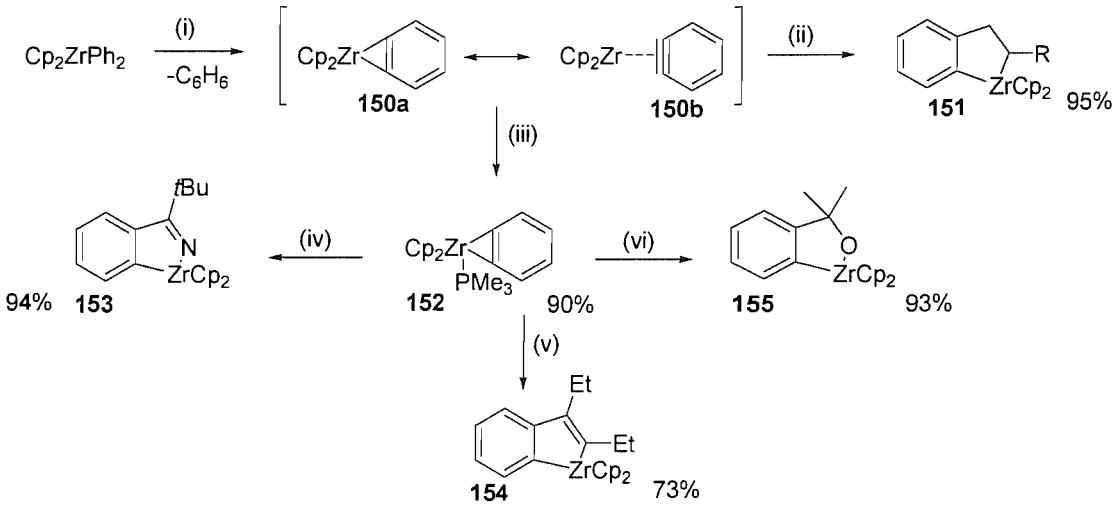
Co-cyclisation using a '$ZrCp_2$' equivalent zirconocene(1-butene) **147** was developed by Negishi *et al.*[46] and has largely replaced methods for its generation where the metal was reduced using reagents such as mercury and magnesium amalgam.[47] Zirconocene(1-butene) **147** can be generated *in situ* by reaction of zirconocene dichloride with two equivalents of *n*-butyllithium followed by warming to room temperature (Scheme 1-14). Zirconocene(1-butene) **147** is formed *via* a non-dissociative mechanism with the loss of butane through β-hydride elimination from **146**.[48] The butene ligand is weakly bound to the metal centre and can easily be replaced by another ligand. This method has been used to synthesise both carbocyclic and heterocyclic zirconacycles for further elaboration.[45,49,50]



(i) 2.0 eq *n*-BuLi, -78 °C; (ii) -78 °C to RT.

Scheme 1-14 Mechanism for co-cyclisation of dienes, enynes and diynes

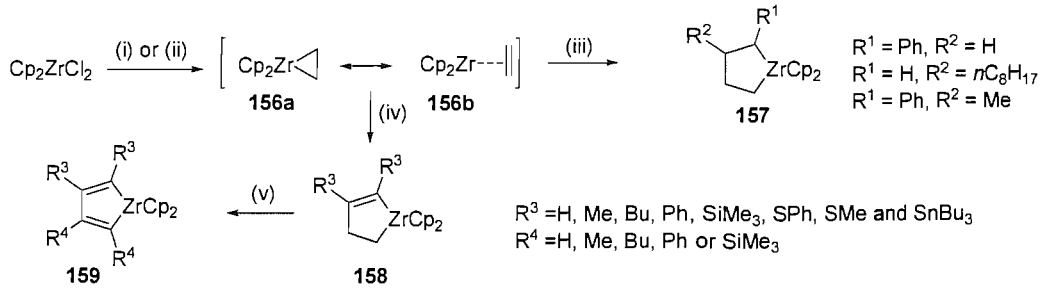
Zirconacycles can be synthesised by trapping alkenes and alkynes with zirconocene η^2 –alkene and alkyne complexes.[45] Some of the initial work in this area was carried out by Erker and involved generating and trapping zirconocene complexes of benzyne **150** to afford zirconabicycles **151** (Scheme 1-15).[51] The benzyne complex **150** was found to be stabilised by addition of trimethylphosphine and in this form **152** reacted with ketones, nitriles and alkynes to afford highly elaborated products **153-155** in good yields.[50]



(i) 70 °C; (ii) $RCHCH_2$; (iii) PMe_3; (iv) *t*-BuCN; (v) EtCCEt; (vi) $CH_3C(O)CH_3$.

Scheme 1-15 Synthesis of zirconacycles from benzyne complexes

Zirconocene ethylene **156** has been used in the same manner as the benzyne complex **150** to synthesise zirconacyclopentanes **157**, zirconacyclopentenes **158** and zirconacyclopentadienes **159** by reaction with alkenes and alkynes (Scheme 1-16).[52-54] Zirconocene ethylene can be generated by either treating zirconocene dichloride with ethyl magnesiumbromide[52] or by synthesising zirconocene(1-butene) **147** under an atmosphere of ethylene gas.[53]



(i) 2.0 eq *n*-BuLi, -78 °C to RT, under an atmosphere of ethene; (ii) 2.0 eq EtMgBr, -78 °C, 1 hr; (iii) 1.0 eq alkene, 0 °C; (iv) 1.0 eq R^3CCR^3, 0 °C; (v) 1.0 eq R^4CCR^4, under atmosphere N_2, 50 °C.

Scheme 1-16 Synthesis of zirconacycles by trapping zirconocene ethylene complexes

The regiochemistry of the zirconacycles formed using this method appear to follow some patterns: it was found that alkyl substituents prefer to be β to zirconium whereas aryl, alkenyl, alkynyl and silyl groups prefer to be α to the metal (Scheme 1-16).[45] Two regioisomers of zirconacyclopentene **158** were isolated in some cases where the two R^3 substituents were different. Regioisomers were also observed in some of the zirconacyclopentadienes **159**.

1.3.3 Reactions of Organozirconocene Complexes

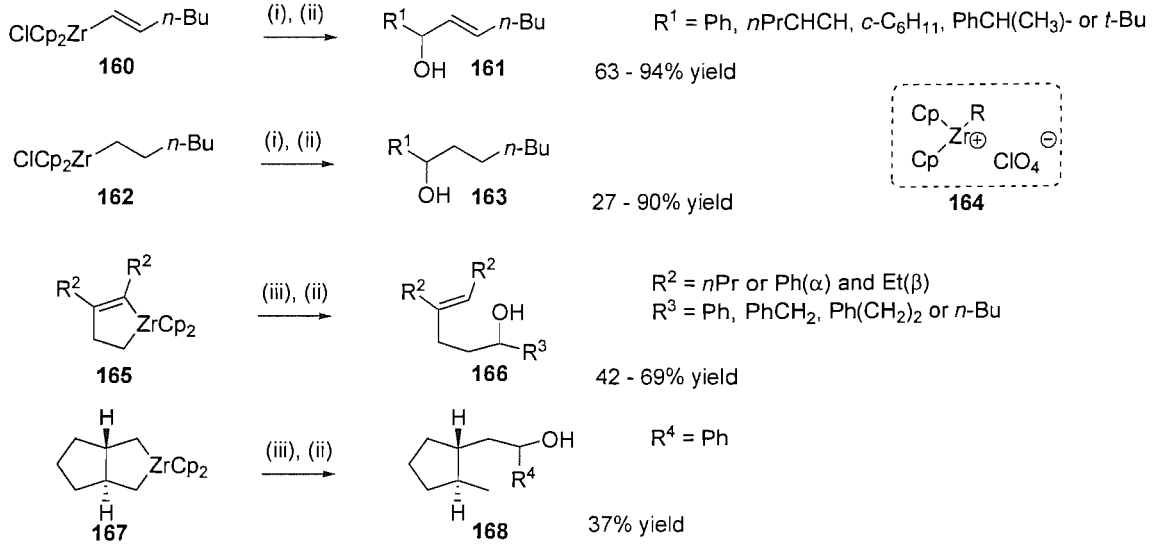
Organozirconocene complexes have been elaborated using many strategies. The carbon zirconium bond in the organozirconium complex can be broken very simply by protonation,[40] through addition of aqueous acid or methanol and aqueous sodium hydrogencarbonate. These conditions can be selected to suit the stability of the product to acidic/basic conditions.

Wipf and Jahn reviewed the synthetic applications of organochlorozirconocenes.[42] These include transmetallation of zirconium to a wide variety of other metals, as well as reactions with oxygen and carbon monoxide.[42] Zirconacycles have also been

elaborated using many strategies including transmetallation,[55] metathesis to main group elements,[56] reactions with carbon monoxide[57] and halogenolysis.[58] Selective mono-halogenation is described in Chapter 2.1.1.

The remainder of this section provides a brief insight into the reaction of organozirconocenes with aldehydes and isonitriles. These elaboration strategies have been used as part of the research presented in this thesis (Chapters 2 – 4). Section 1.4 will focus on the elaboration of organozirconocene complexes using carbenoids.

The addition of aldehydes to organozirconium complexes results in the isolation of alcohols. Suzuki *et al.* have shown that the reaction of alkenyl- **160** and alkylchlorozirconocenes **162** with aldehydes is accelerated by the presence of catalytic silver perchlorate and affords alcohols **161** and **163** respectively.[59] Silver perchlorate is thought to accelerate the reaction by making the zirconocene complex cationic **164**, which activates the aldehyde towards nucleophilic attack. Negishi *et al.* have shown that zirconacyclopentenes **165** and zirconacyclopentanes **167** react with aldehydes to afford alcohols **166** and **168** respectively in the absence of Lewis acids.[60]

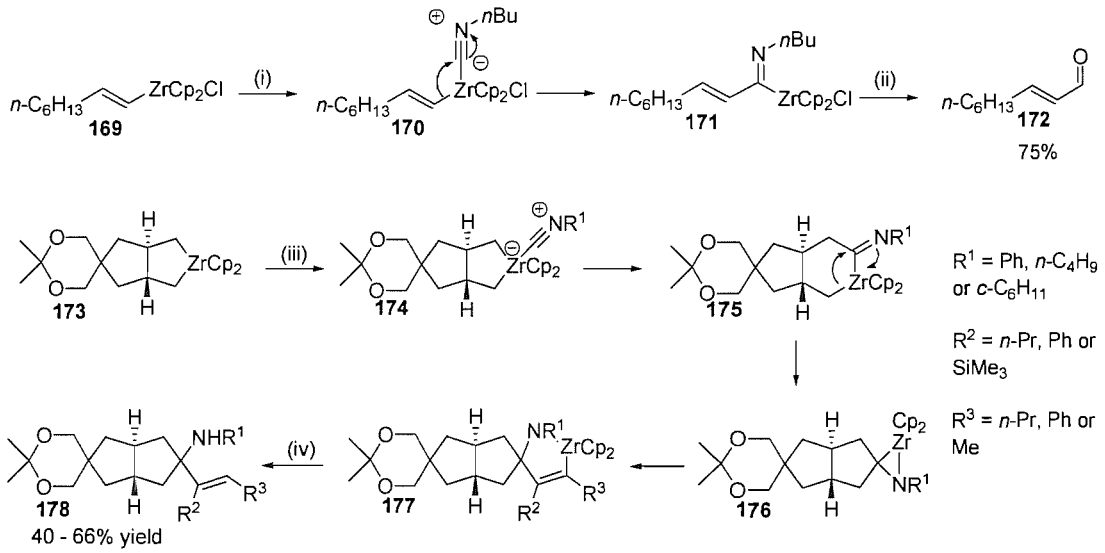


(i) 0.81 eq R^1CHO, 5 mol % $AgClO_4$, RT, 10 min; (ii) HCl aq.; (iii) 1.1 eq R^3CHO or R^4CHO, <25 °C, 3 hr.

Scheme 1-17 Addition of aldehydes to organozirconium complexes

The addition of isonitriles to organochlorozirconocenes **169** results in the formation of iminoacyl complexes **171**. The stability of the iminoacyl group depends on the

isonitrile used, but it is generally acid labile. Treatment of the intermediate iminoacyl complex **171** with dilute acetic acid afforded one-carbon homologated aldehyde **172** very reliably.[61] The iminoacyl complexes formed upon the insertion of isonitriles into zirconacycles can result in the isolation of amines or aldehydes. It was found that iminoacyl complexes **175**, especially those formed using *n*-butyl, cyclohexyl, or phenyl isonitrile rearrange to η^2-imine complexes **176**, which upon trapping with alkynes followed by protonolysis afford amines **178** in modest yields.[62,63] Iminoacyl complexes formed with *tert*-butyl isonitrile do not undergo the same rearrangement to the η^2-imine complex and therefore allows aldehydes to be isolated, using the same methodology.[64]



(i) 1.0 eq *n*-BuNC, 0 - 45 °C, 3 hr; (ii) HOAc aq., -78 °C; (iii) 1.0 eq R^1NC, 1.5 eq R^2CCR^3, 67 °C, 3 hr; (iv) MeOH, RT.

Scheme 1-18 Isonitrile insertion into organozirconocene complexes

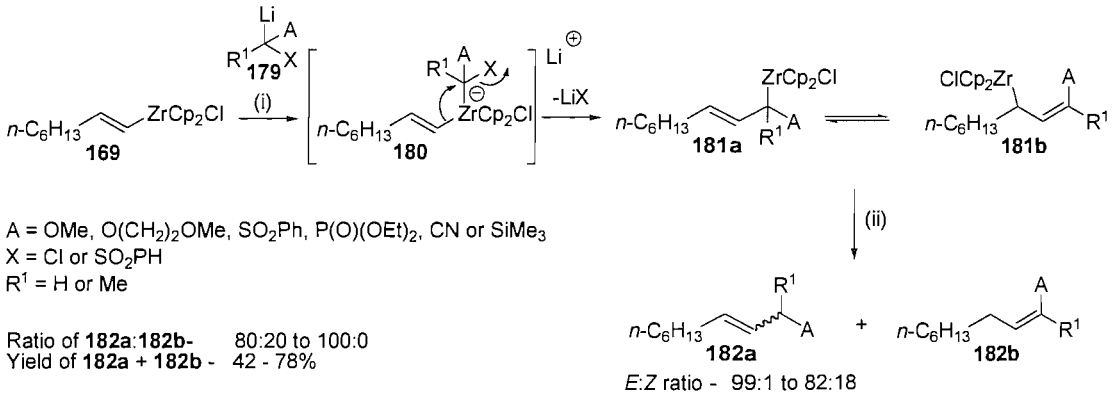
1.4 Carbenoid Insertion into Organozirconium Complexes

Carbenoids were first inserted into carbon zirconium bonds by Negishi *et al.*[33] The first examples of this novel carbon-carbon bond forming reaction were described in Section 1.2.7. This area of research has been taken on by Whitby who has extended the methodology to include the insertion of many different carbenoids into zirconacycles as well as organochlorozirconocene complexes.

1.4.1 Carbenoid Insertion into Organochlorozirconocenes

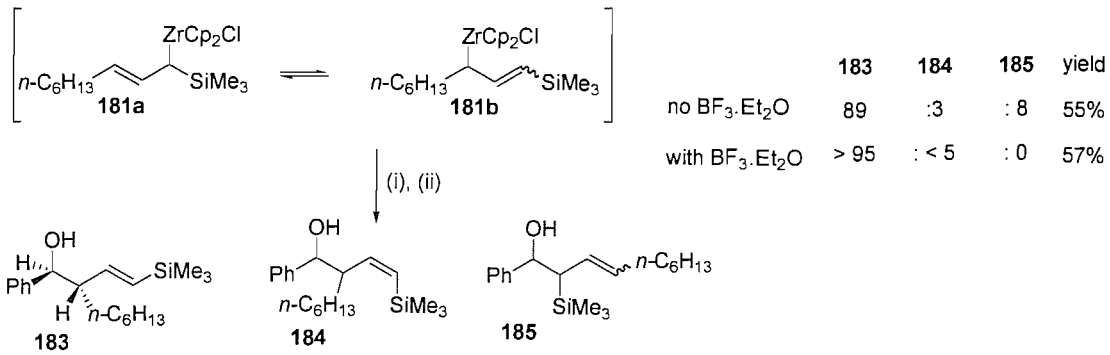
Carbenoid insertion into organochlorozirconocenes has been used in the synthesis of substituted alkenes, dienes, trienes and dienynes. The intermediates resulting from carbenoid insertion have also been elaborated further through addition of electrophiles to afford alcohols and organohalides.

The insertion of alkyl carbenoids **179** into alkenylchlorozirconocene **169** (a number of these have been studied, though 1-octenylchlorozirconocene is shown in Scheme 1-19) results in the formation of allylmetalic **181**.[65,66] Due to the allylic nature of the organometallic reagent, protonation usually gives rise to two alkene products **182a** and **182b**. Compound **182a** can be present as either (*E*) or (*Z*) isomer.



Scheme 1-19 Insertion of alkyl carbenoids into organochlorozirconocenes

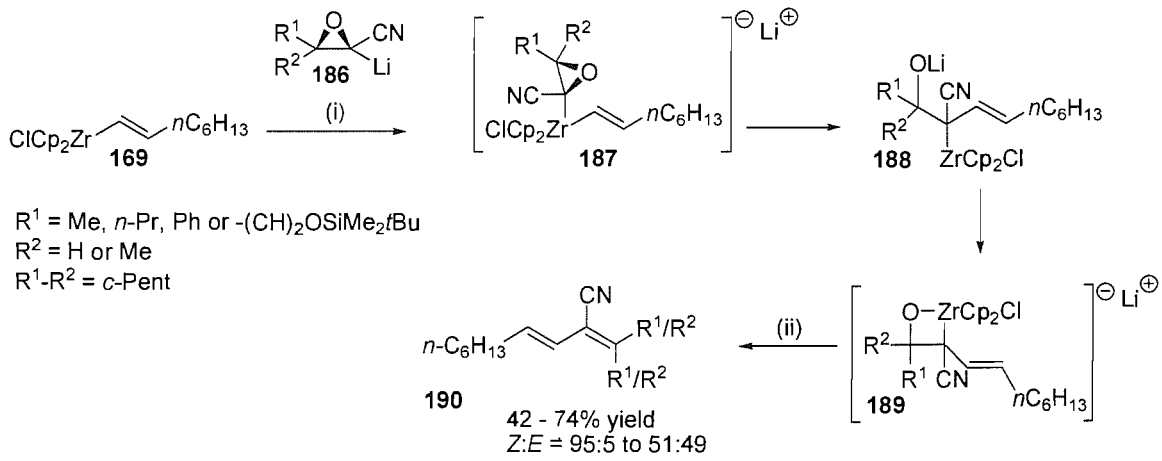
Allylmetallics can be further elaborated by addition of aldehydes.[65,66] The selectivity of aldehyde addition can be improved through the presence of a Lewis acid. In the example shown in Scheme 1-20, the addition of boron trifluoride etherate during the reaction of allylmetallic **181** with benzaldehyde resulted in a very high selectivity for (*E*)-vinylsilane **183**.



(i) 1.3 eq PhCHO, $BF_3.Et_2O$, -78 to 20 °C, 18 hr; (ii) $NaHCO_3$ aq..

Scheme 1-20 Elaboration of allylmetallics with aldehydes

Lithiated expoxynitriles **186** insert efficiently into alkenylchlorozirconocenes *via* a 1,2-metallate rearrangement to afford substituted dienes.[67] In the example shown in Scheme 1-21 intermediate **189** eliminates $Cp_2ZrCl(O)^-$ to afford substituted 2-cyano-1,3-dienes **190**. Insertion lacks stereoselectivity due to the loss of stereochemical integrity of the carbenoid **186** when it is initially formed.

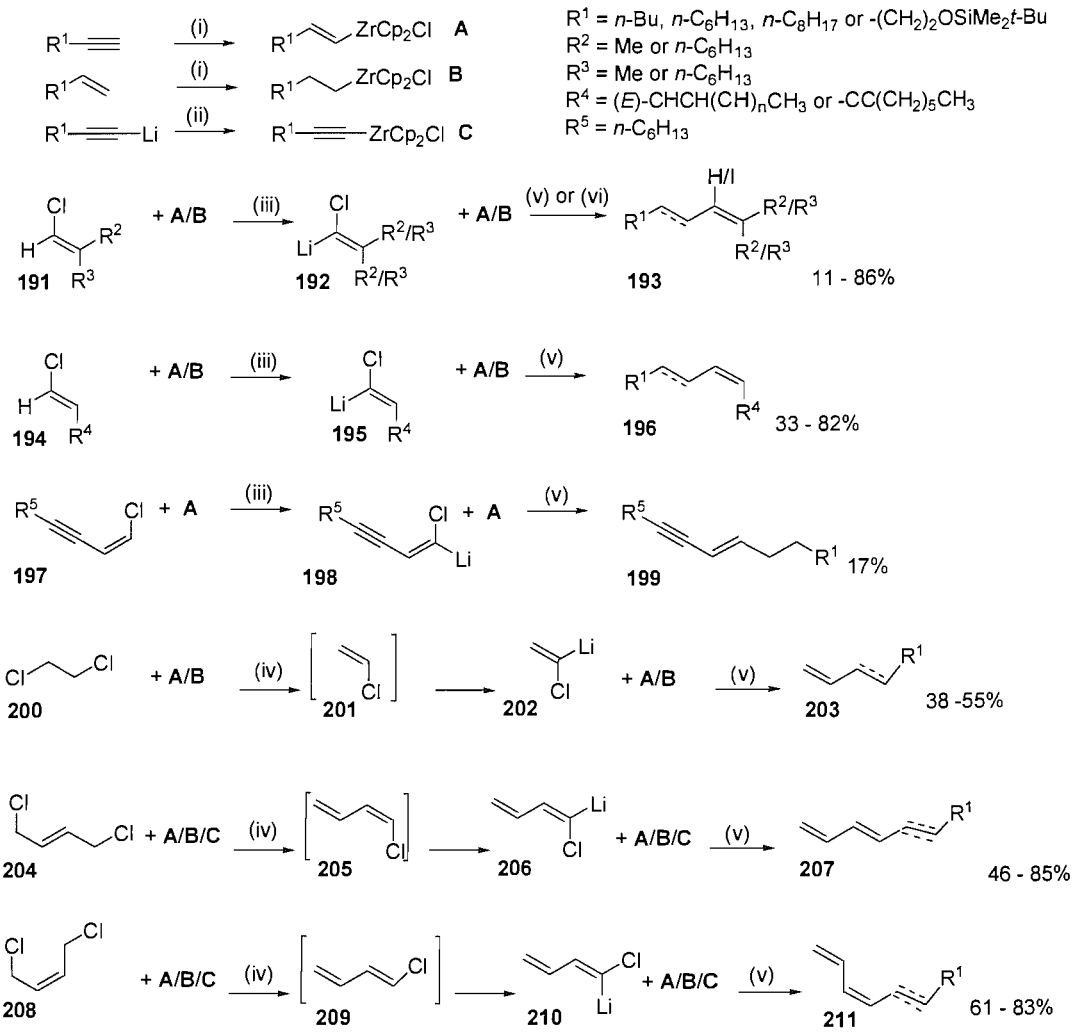


(i) 1.3 eq **186**, -90 to -60 °C, over 1hr; (ii) HCl aq., RT.

Scheme 1-21 Insertion of metallated epoxynitriles into organochlorozirconocenes

Alkenyl carbenoids, formed *in situ*, have been inserted into alkyl-, alkenyl- and alkynyl-chlorozirconocenes (Scheme 1-22).[19,68] This methodology was shown to be useful in the synthesis of dienes, trienes and diynes, often with very good stereocontrol. The exchange of the acidic quench that afforded protonated organozirconium intermediates by an electrophilic quench with iodine yielded iodides **193** (Scheme 1-22). Other halides were synthesised by addition of different halogenating agents and aldehydes were isolated by addition of isonitriles followed by

an acidic quench. The carbenoid insertion reactions were expected to result in inversion of configuration at the carbenoid carbon. Inversion of configuration was observed with 2-monosubstituted vinyl carbenoids **195**, **198**, **206** and **210**. However, poor stereocontrol was observed for 2,2-disubstituted vinyl carbenoid **192**. This is believed to be due to rapid isomerisation of the carbenoid. The reasons for this were discussed in section 1.2.3.



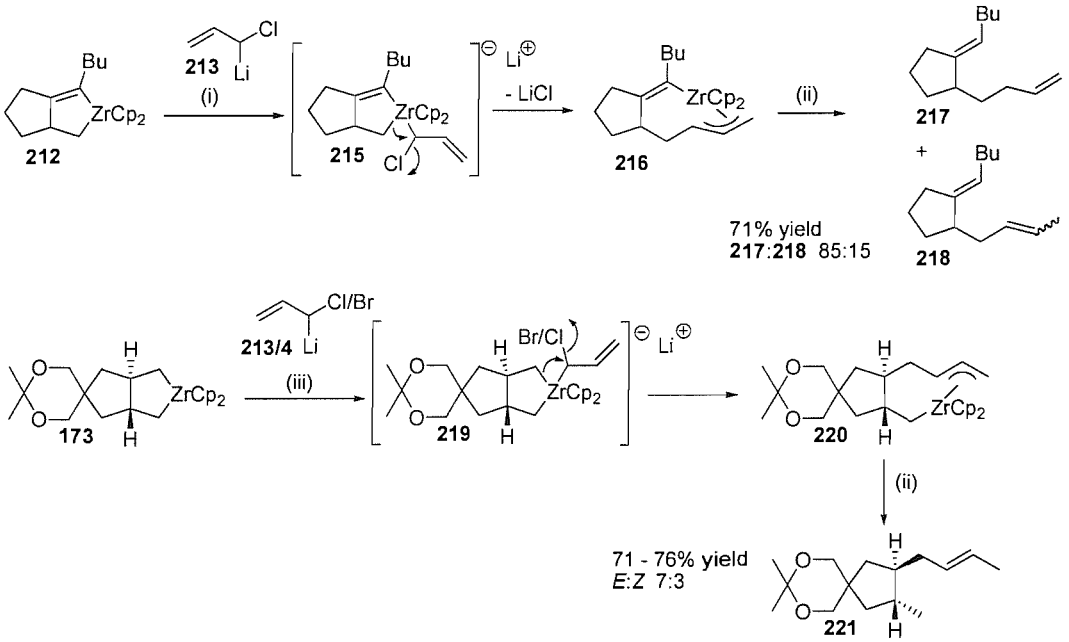
(i) 1.2 eq Cp_2ZrHCl, 20 °C, 1 hr; (ii) 1.0 eq Cp_2ZrCl_2, -20 °C, then 0 °C, 2 hr; (iii) carbenoids formed *in-situ*, 1.0 eq LiTMP, -90 to - 80 °C, 15 min; (iv) carbenoids formed *in-situ*, 2.0 eq LiTMP, -90 to -80 °C, 15 min; (v) H^+aq.; (vi) 3.0 eq I_2, 0 °C, 30 min.

Scheme 1-22 Insertion of vinyl carbenoids into organochlorozirconocenes

1.4.2 Carbenoid Insertion into Zirconacycles

Allyl carbenoids insert into the alkyl carbon zirconium bond of mono- and bi-cyclic zirconacyclopentenes[69,70] and into a carbon zirconium bond in zirconacyclopentanes[70-

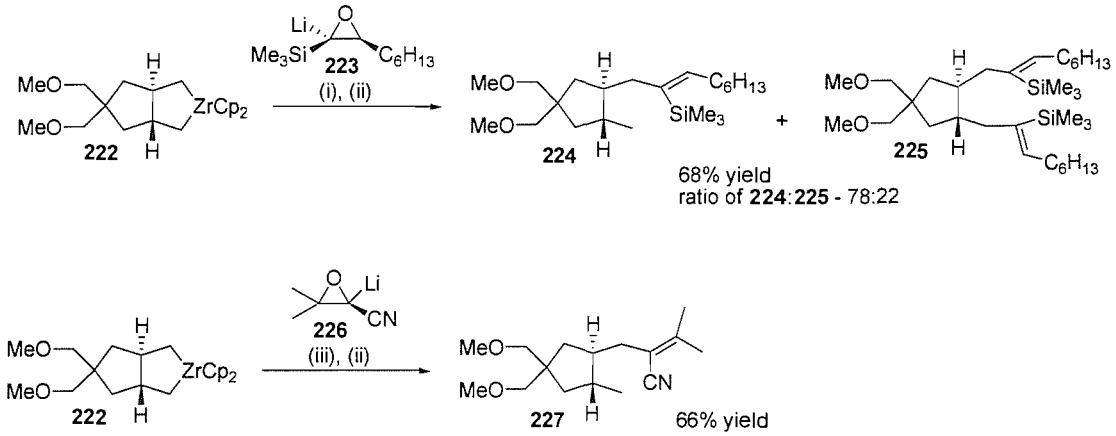
[72] to afford allyl zirconium complexes. These complexes can be protonated to afford diene products, or elaborated further through addition of different electrophiles. Scheme 1-23 shows a simple example where the insertion of lithium haloallylide **213/4** into a zirconacyclopentene **212** and zirconacyclopentane **173** affords dienes **217/218** and **221** respectively upon protonation. Allyl zirconacyclopentane systems have been elaborated using a number of different electrophiles: ketones,[71] sulfur-based electrophiles,[73] iminium ions[73] and through the Lewis acid catalysed addition of aldehydes,[71] acetals,[73] and orthoesters.[73] Allyl zirconacyclopentene systems have been elaborated using the Lewis acid catalysed addition of aldehydes to afford alcohols as a mixture of diastereomers.[69] Allyl carbenoid insertion into zirconacyclopentanes has also been used as the key step in the construction of the bicyclo[9.3.0]tetradecane Dolabellane skeleton,[74] present in diterpenoid natural products, most of which exhibit antimicrobial activity and specifically in the synthesis of naturally occurring diterpene (±)acetoxyodontoschismenol.[75] The same methodology was also used in conjunction with intramolecular Diels-Alder to create the tri-cyclic ring systems present in Pisiferanol and Dolastane skeletons.[76] Recently the methodology has found application in the synthesis of terpenoid and terpene-polyketide natural products.[77]



(i) 1.1 eq CH_2CHCH_2Cl, 1.1 eq LiTMP, -78 to -60 °C over 1 hr; (ii) MeOH, 20 °C, 24 - 48 hr; (iii) 1.2 eq CH_2CHCH_2Cl/Br, 1.2 eq LDA, -78°C, 20 °C.

Scheme 1-23 Elaboration of zirconacyclopentanes and –enes with allyl carbenoids

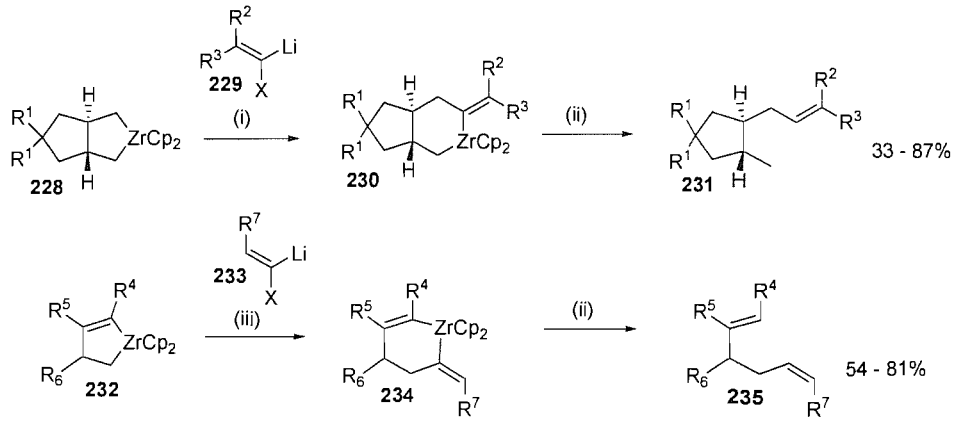
Substituted alkenes have also been synthesised using carbenoids in the form of lithiated epoxides (Scheme 1-24).[78] Insertion of the electron rich α-silyl-α-lithium epoxide carbenoid **223** often resulted in a mixture of products. In the example shown in Scheme 1-24, the two products are the result of single **224** and double **225** carbenoid insertion. The insertion of the electron poor α-cyano-α-lithium substituted carbenoid **226** into the same zirconacycle **222** afforded only one product **227**. The effect of the different electronic properties of carbenoids has been explored further in Chapter 2. The proposed mechanism for carbenoid insertion involves initial 1,2-metallate rearrangement followed by elimination of $Cp_2Zr(R)O^-$ similar to that discussed in Section 1.4.1 (Scheme 1-21).



(i) 1.3 eq **223**, -100 to -30 °C, 2 hr; (ii) HCl aq.; (iii) 1.3 eq **226**, -90 to -60 °C, 1 hr.

Scheme 1-24 Elaboration of zirconacycles with lithiated epoxynitriles

Alkenyl carbenoids inserted into zirconacyclopentanes **228** and zirconacyclopentenes **232** to afford alkenes **231** and dienes **235** respectively (Scheme 1-25).[79] Double carbenoid insertion was only observed in the saturated zirconacycle systems. This can be explained by the steric crowding in the diene zirconocene intermediate **234** compared to intermediate **230**. In the diene intermediate **234** the empty orbital on zirconium is blocked from both sides.

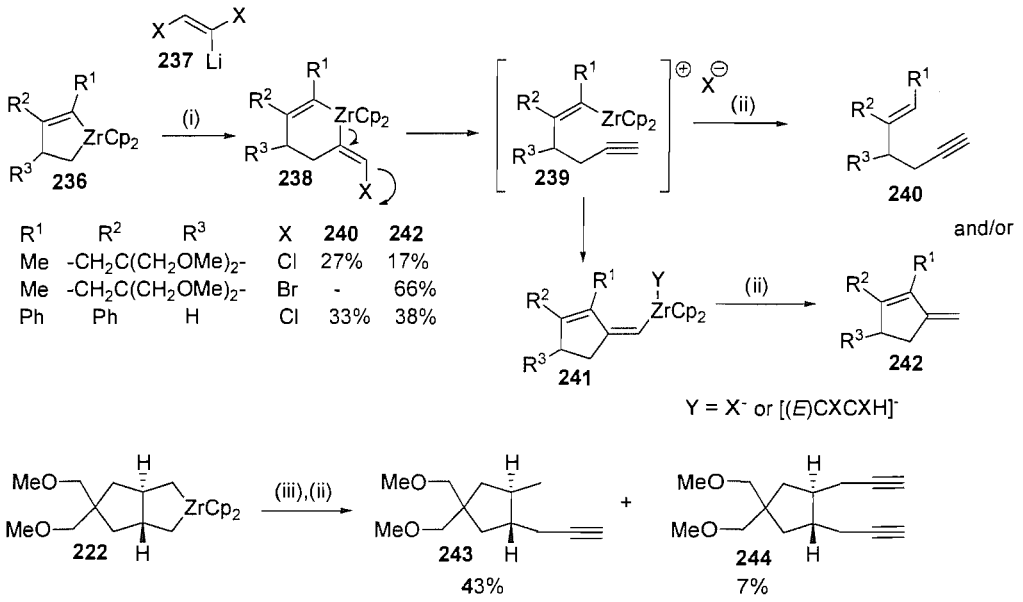


R^1 = $-CH_2OMe$; or R^1-R^1 = $-CH_2OCMe_2OCH_2-$; R^2 = H, Me, Ph, $-CHCH_2$ or $-CCn$-Bu; R^3 = H, Me or $-CHCH_2$; X = Cl or Br
R^4 = Et, *n*-Pr or *n*-Bu; R^5 = *n*-Pr; R^5-R^6 = $-CH_2C(CH_2OMe)_2CH_2-$ or $-(CH_2)_3-$, R^6 = H; R^7 = Ph, $-CHCH_2$ or $-CCn$-Bu.

(i) 1.1 - 5.0 eq $R^2R^3CHCH_2X$, 1.1 - 5.0 eq LDA/ LiTMP, -90/-78 °C, 5 min to 1 hr; (ii) MeOH, $NaHCO_3$ aq.; (iii) 1.2 - 3.0 eq (*E*)-R^7CCHX, 1.2 - 3.0 eq LDA/LiTMP, -90/-78 °C, 20 - 45 min.

Scheme 1-25 Elaboration of zirconacycles with alkenyl carbenoids

A special example of alkenyl carbenoid insertion into zirconacycles is the insertion of (*E*)-(1,2-dihalovinyl)lithium **237**, to afford alkynes and/or methylene cyclopentanes (Scheme 1-26).[80] Initial carbenoid insertion is followed by elimination of the halide to give an alkyne **240**. In the unsaturated zirconacyclopentene systems **236** the resulting intermediate then may or may not insert the alkyne intramolecularly into the carbon zirconium bond to afford a methylene cyclopentane **242**. Partial insertion was observed for chlorocarbenoids (mixture of **240** and **242** isolated), whereas complete insertion was observed for bromocarbenoids (only **242** isolated). Evidence for the proposed cationic intermediate **239** was sought though the addition of anion traps; however, these were not successful.[81] This intramolecular insertion process was not observed with zirconacyclopentanes where only alkyne product **243** was isolated. Some double carbenoid insertion, however, was observed in the saturated systems resulting in the isolation of a bis-alkyne **244**.

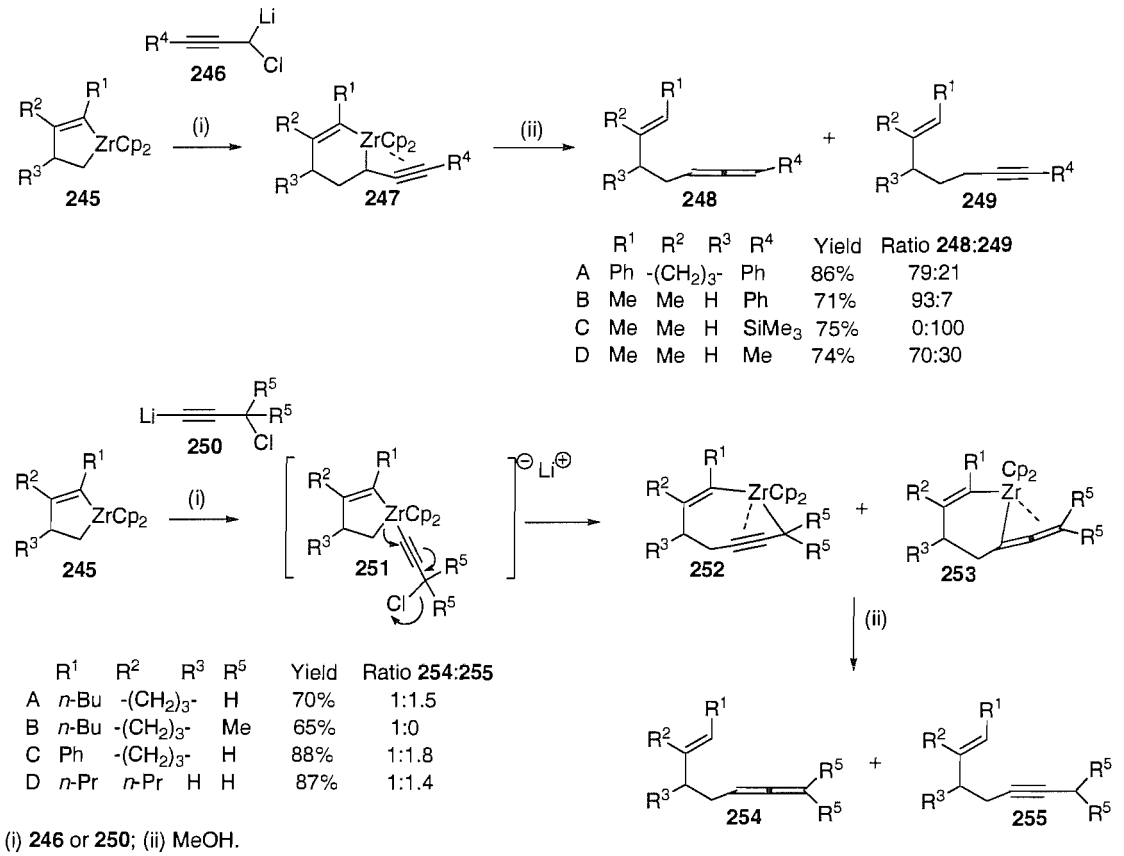


R^1	R^2	R^3	X	240	242
Me	$-CH_2C(CH_2OMe)_2-$		Cl	27%	17%
Me	$-CH_2C(CH_2OMe)_2-$		Br	-	66%
Ph	Ph	H	Cl	33%	38%

(i) 2.0 eq Cl = (*E*)HClCCHCl, Br = 1:2 (*E*):(*Z*) HBrCCHBr, 2.0 eq LDA, -78 °C; (ii) MeOH, $NaHCO_3$ aq.; (iii) 2.0 eq (*E*) HClCCHCl, 2.0 eq LDA, -78 to -50 °C, 30 min.

Scheme 1-26 Insertion of (*E*)-(1,2-dihalovinyl)lithium into zirconacycles

Allenes and alkynes have been synthesised through the insertion of propargyl **246** and allenyl **250** carbenoids into zirconacycles (Scheme 1-27).[82,83] Quenching of the η^3-pro-2-ynyl/allenyl complexes formed through propargyl cabenoid insertion into zirconacyclopentanes proved problematic as the zirconium complexes were very stable; however, those derived from zirconacyclopentenes **245** afforded mixtures of allenes **248a-d** and alkynes **249a-d** in good yields.[83] Insertion of allenyl carbenoids **250** into zirconacyclopentenes **245** favoured the formation of internal alkynes **255a-d** over allenes **254a-d** (Scheme 1-27).[82]

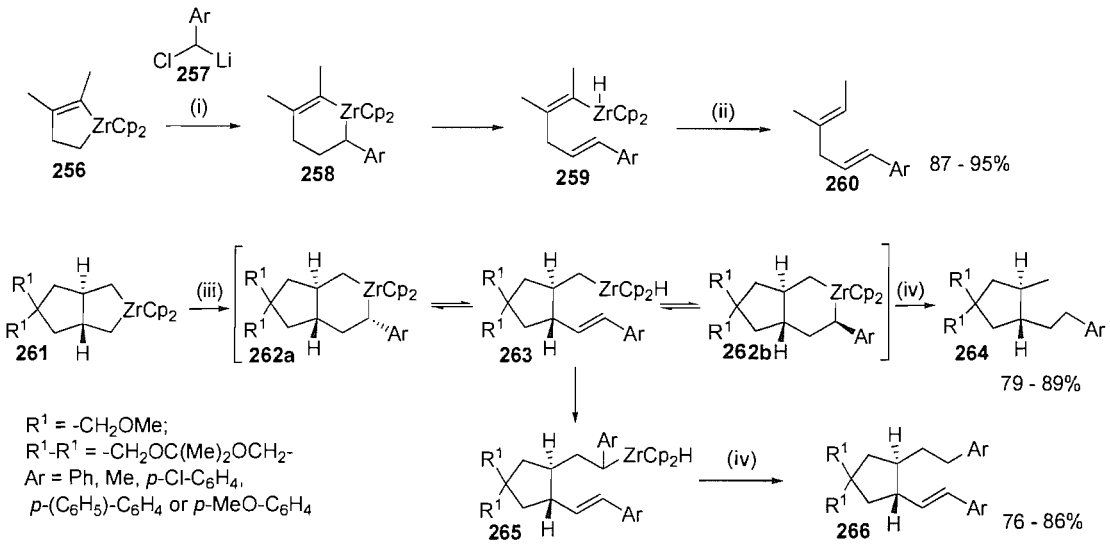


	R^1	R^2	R^3	R^4	Yield	Ratio 248:249
A	Ph	$-(CH_2)_3-$		Ph	86%	79:21
B	Me	Me	H	Ph	71%	93:7
C	Me	Me	H	$SiMe_3$	75%	0:100
D	Me	Me	H	Me	74%	70:30

	R^1	R^2	R^3	R^5	Yield	Ratio 254:255
A	*n*-Bu	$-(CH_2)_3-$		H	70%	1:1.5
B	*n*-Bu	$-(CH_2)_3-$		Me	65%	1:0
C	Ph	$-(CH_2)_3-$		H	88%	1:1.8
D	*n*-Pr	*n*-Pr	H	H	87%	1:1.4

Scheme 1-27 Insertion of propargyl and allenyl carbenoids into zirconacycles

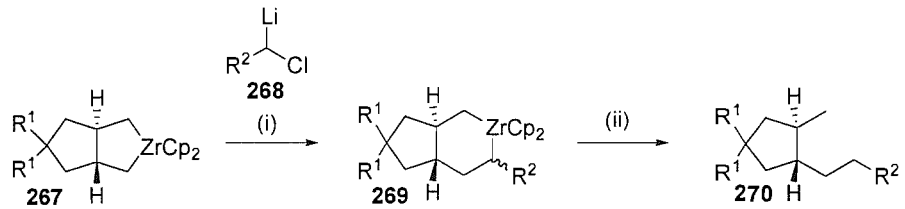
Elaboration of zirconacyclopentanes and zirconacyclopentenes was also achieved through insertion of benzyl carbenoids **257** (Scheme 1-28).[84] Insertion into zirconacyclopentene **256** resulted in the isolation of dienes **260**. β-Hydride elimination is believed to be responsible for the stereospecific formation of the second alkene in dienes **260**. In the saturated system, interesting behaviour was observed on double carbenoid insertion. The proposed mechanism for this transformation sees the second carbenoid being inserted into a zirconocene hydride intermediate **263**.



(i) 2.0 eq $ArCH_2Cl$, 2.0 eq LDA, -78 °C for 30 min then RT for 1 hr; (ii) HCl aq., MeOH, RT, 1 hr; (iii) For **264** 1.1 eq $ArCH_2Cl$, 1.1 eq LDA, -78 °C, 1hr; for **265** 10 eq $ArCH_2Cl$, 10 eq LDA, -78 °C to RT, 1 hr; (iv) MeOH, RT, 16 hr.

Scheme 1-28 Elaboration of zirconacycles with benzyl carbenoids

The insertion of alkyl carbenoids **268** into zirconacycles results in potential useful functionalisation of the carbon zirconium bond. Allyl carbenoid insertion into zirconacyclopentanes, to afford functionalised products **270**, is a well-established technique for both electron rich and electron poor carbenoids (Scheme 1-29).[79] The insertion of alkyl carbenoids into zirconacyclopentenes has been investigated as part of the work described in this thesis and is included in Chapter 2.



R^1 = $-CH_2OMe$, H or R^1-R^1 = $-CH_2OCMe_2OCH_2-$
Electron rich carbenoids R^2 = $SiMe_3$, $SiMe_2Ph$, $SnBu_3$, SPh, OEt - 11 - 78% yields
Electron poor carbenoids R^2 = $P(O)(OEt)_2$, SO_2Ph, CN - 24 - 74% yields

(i) 1.0 to 4.0 eq $CHCH_2R^2$, 1.0 to 4.0 eq LDA/LiTMP, -90/-78 °C; (ii) MeOH, $NaHCO_3$ aq. or HCl aq.

Scheme 1-29 Elaboration of zirconacyclopentanes with alkyl carbenoids

1.5 Conclusion

Carbenoid insertion into organozirconocene complexes is a useful synthetic tool, which through further development could realise its potential in organic synthesis.

The following chapters address different aspects of carbenoid insertion into cyclic and acyclic organozirconocene complexes.

Chapter 2 Regiochemistry of Carbenoid Insertion into Unsymmetrical Zirconacycles

This chapter presents an investigation into the regioselectivity of alkyl and alkenyl carbenoid insertion into unsymmetrical zirconacycles. In most cases complete regioselectivity is observed with a single product isolated. The origins of selectivity are probed using zirconacycles with distinct substitution patterns and carbenoids with different electronic properties. Further regiochemical information is gained through isonitrile insertion and mono-deuteration experiments. The results are used to provide evidence to support a model that may explain regioselectivity.

2.1 Background

In order to promote efficient use of zirconacycles in organic synthesis, selective means of elaborating carbon zirconium bonds are required. Carbenoid insertion,[70] monohalogenation,[85] isocyanide insertion[64] and transmetallation[52,86] have all been used to differentially elaborate carbon zirconium bonds in zirconacycles.

2.1.1 Elaboration of Zirconacyclopentenes

Carbenoids

A study of allyl carbenoid (lithium chloroallylide) insertion into zirconacyclopentenes resulted in good regioselectivity observed in all cases (Figure 2-1). Complete selectivity for the alkyl zirconium bond was observed when the vinyl carbon α- to zirconium was substituted (R' = *n*-Pr, Ph, $SiMe_3$, *n*-Bu, $SnBu_3$, SPh) (zirconacycles **301-306**).[70,69] Incomplete selectivity for the alkyl zirconium bond was observed when the vinyl carbon α- to zirconium was unsubstituted (R' = H) (zirconacycle **307**). This effect was enhanced by a move to a zirconacyclopentene **308** where substitution at the alkyl carbon α- to zirconium resulted in complete regioselectivity for the alkenyl zirconium bond. However, it was subsequently shown that the nature of substitution at the alkyl carbon was also significant. In tricyclic zirconacyclopentenes **309** and **310** selectivity for the zirconium alkyl bond was observed despite substitution at the alkyl carbon.

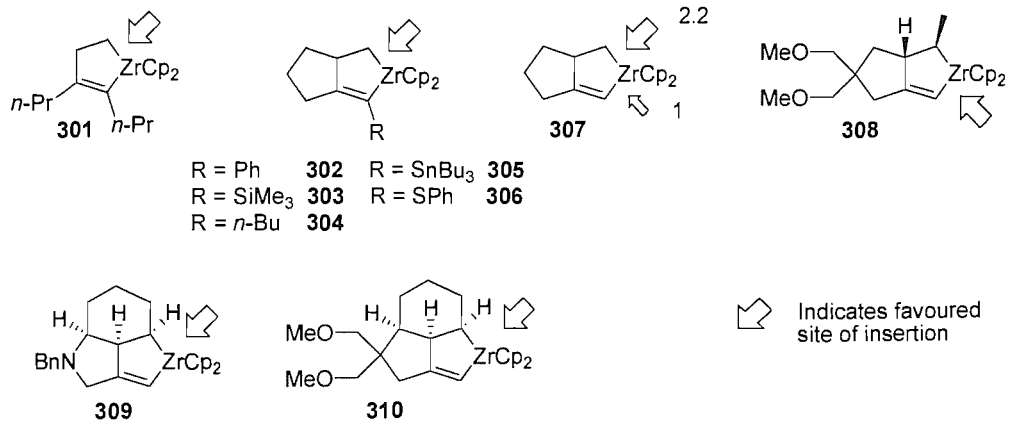


Figure 2-1 Elaboration of zirconacyclopentenes with lithium chloroallylide/methylchloroallylide

Alkenyl carbenoids (1-halo-1-lithio-alkenes) have been inserted into zirconacyclopentenes **301**, **304**, **311** with complete regioselectivity for the alkyl zirconium bond (Figure 2-2). Insertion only occurs once even in the presence of a five fold excess of the carbenoid.[79]

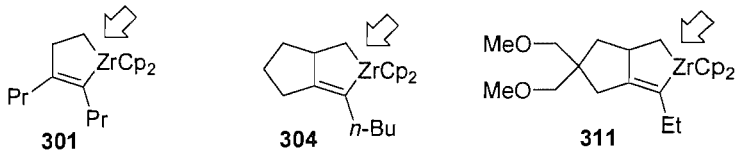
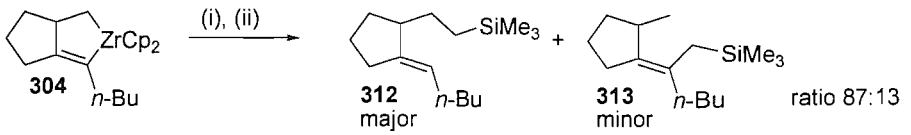


Figure 2-2 Elaboration of zirconacyclopentenes with 1-halo-1-lithioalkenes

The silicon substituted carbenoid $Me_3SiCHLiCl$ displayed incomplete regioselectivity for the alkyl zirconium bond in **304**, and afforded a mixture of alkenes **312** and **313** in a 87:13 ratio (Scheme 2-1).[79] The behaviour of other alkyl carbenoids is examined in the results and discussion section of this chapter (Section 2.2).



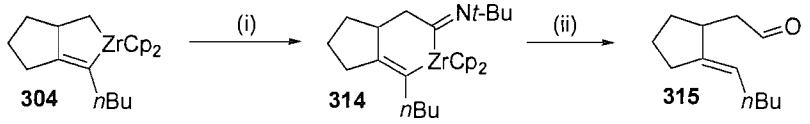
(i) 1.1 eq Me_3SiCH_2Cl, LDA, -78 °C for 30 min, then to RT; (ii) MeOH, sat. $NaHCO_3$ aq., 16 hr, RT.

Scheme 2-1 Insertion of $Me_3SiCHLiCl$ into zirconacyclopentene

Isonitriles

Insertion of phenyl- and trimethylsilyl-isocyanide into zirconacyclopentenes affords iminoacyl complexes which rearrange to give α,β- unsaturated zirconocene η^2-imine complexes.[64] These complexes do not retain the information regarding the

regiochemistry of insertion. A move to *tert*-butyl isocyanide prevents the rearrangement of the intermediate iminoacyl complex **314** preventing the loss of regiochemical information. Acidic quench of complex **314** resulted afforded aldehyde **315** (Scheme 2-2).[64]

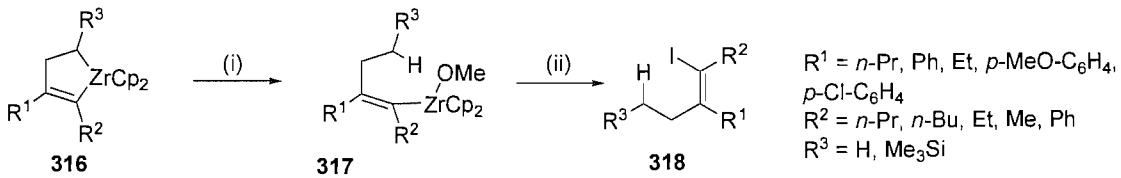


(i) 1.0 eq *t*-BuNC, RT; (ii) 2 M HCl aq., RT.

Scheme 2-2 *Tert*-butyl isocyanide insertion into zirconacyclopentenes

Selective Protonation and Monohalogeneation

Takahashi has developed methodologies for the monohalogenation of zirconacyclopentenes.[87] Halogenation can be chemoselective for the alkyl or alkenyl bond depending on the reagents used.[58,88] Selective protonation of the zirconium alkyl bond was observed when zirconacyclopentenes **316** were treated with methanol (Scheme 2-3). Treatment of the alkoxy zirconocene intermediate **317** with iodine resulted in alkenyl iodides **318** in excellent yields.[85]



(i) 1.0 eq MeOH, RT, 1 hr; (ii) I_2, RT.

Scheme 2-3 Alkenyl iodides resulting from selective protonation

2.1.2 Elaboration of Zirconacyclopentanes

Carbenoids

Allyl carbenoid insertion into α- and β- substituted saturated zirconacycles is well established (Figure 2-3).[70] α-Substitution resulted in insertion into the unsubstituted carbon zirconium bond (e.g. **319** and **321**). Exceptions were noted with the tricyclic zirconacyclopentanes **322** and **323** where selectivity for the α-substituted carbon zirconium bond was observed. β-Substitution with regard to zirconium, as in **324-326** resulted in selective insertion into the more hindered carbon zirconium bond.

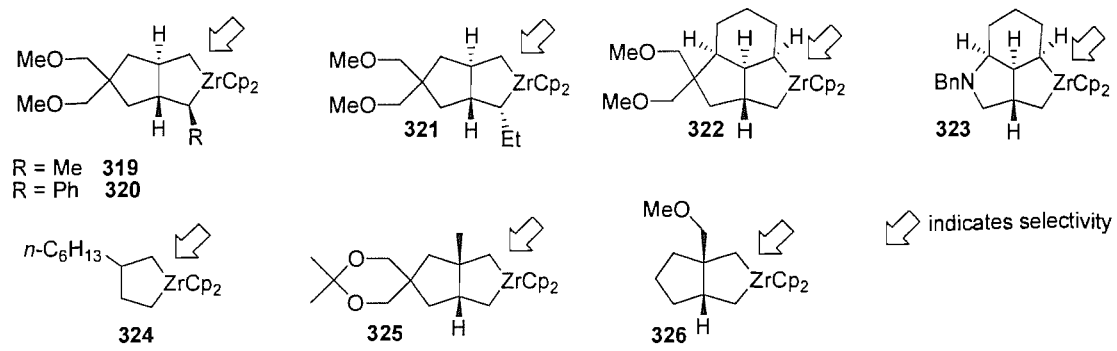
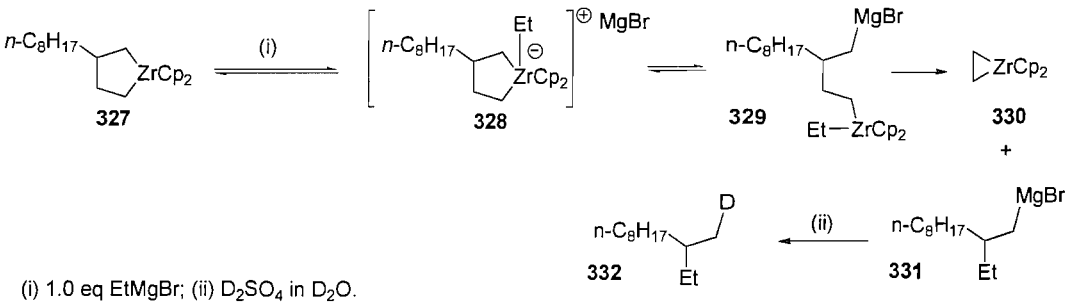


Figure 2-3 Elaboration of zirconacyclopentanes with lithium chloroallylide/chloromethylallylide

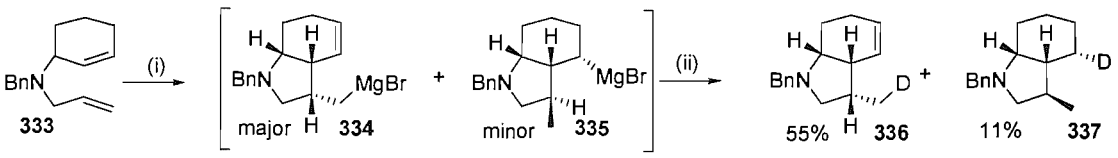
Transmetallation

Transmetallation from zirconium to magnesium using Grignard reagents has been responsible for the differentiation of the two carbon zirconium bonds in zirconacyclopentanes. Negishi reported that treatment of zirconacycle **327** with one equivalent of ethyl magnesiumbromide, followed by a D_2SO_4 in D_2O quench, resulted in the isolation of mono-deuterated alkane **332** (Scheme 2-4).[52] Transmetallation was regiospecific, inhibiting the formation of a second deuterated product.



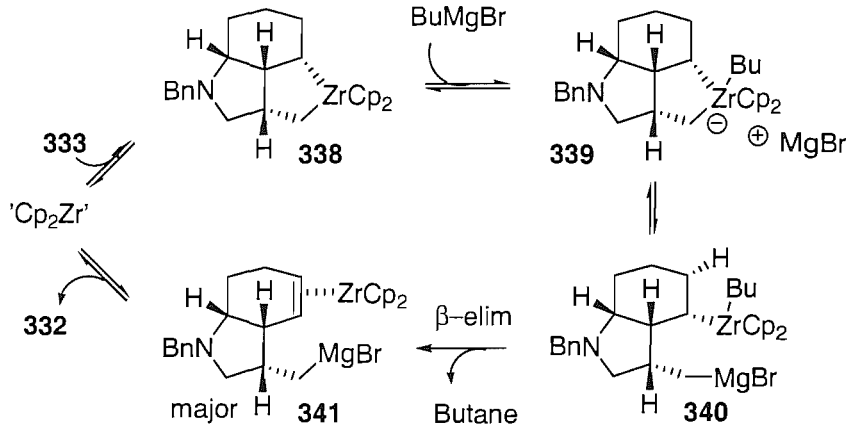
Scheme 2-4 Transmetallation of zirconium for magnesium using Grignard reagent

Mori also reported selective transmetallation from zirconium to magnesium when the cyclisation of **333** was carried out in the presence of catalytic zirconocene dichloride and butyl magnesium bromide as the reducing agent (Scheme 2-5).[86]



Scheme 2-5 Reductive cyclisation of 333 results in selective transmetallation to Mg

Scheme 2-6 illustrates the proposed mechanism for the formation of the major product **334** (Scheme 2-5), which on deuteration gives **336**.[86]



Scheme 2-6 Mechanism for transmetallation of Zr to Mg as proposed by *Mori* –kinetic pathway

1.1.1 Models Used to Explain Regioselectivity

Different models can be used to explain the regiochemistry of carbenoid insertion into zirconacycles.[70,37] Lateral attack is used to explain the path of carbenoid attack on zirconacycles (Figure 2-4). This model recognises that carbenoid attack must occur into an empty a2 orbital on zirconium and thus in the same plane as the carbon-zirconium-carbon atoms of the zirconacycle **342**. Steric hindrance in this plane blocks attack so the less hindered side is attacked. The model assumes that the regiochemistry of insertion is dictated by the kinetics of this initial attack, explained by a reaction course that minimises unfavourable steric interactions **343**.[37]

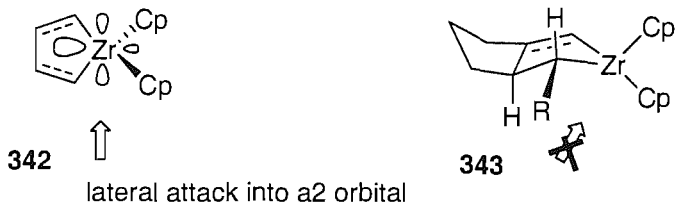
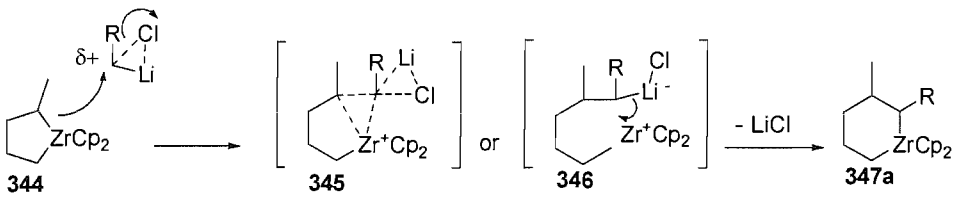


Figure 2-4 Steric interactions determine regiochemistry of carbenoid attack

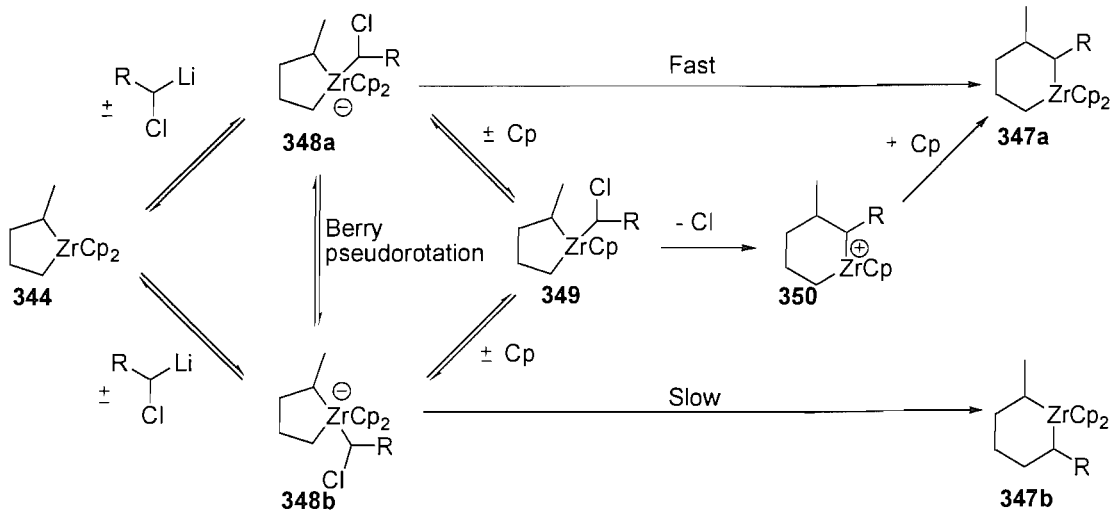
This model can explain the selectivity observed for zirconacycles **301-306**, **311** and **319-321** (Figure 2-1, Figure 2-2, Figure 2-3). However, in further α- and β-substituted zirconacycles **309**, **310** and **322-326** insertion into the more sterically hindered carbon zirconium bond is observed (Figure 2-1, Figure 2-3). These examples show that steric arguments cannot be used to explain the selectivity in all systems.

Electronic arguments can also be used to explain regioselectivity.[70,37] If a carbenoid is viewed as an electrophile,[12] (as has been indicated by theoretical calculations) it could be seen as interacting with the highest occupied molecular orbital of the zirconacycle. Calculations indicate that the HOMO has a larger coefficient on the more substituted carbon zirconium bond (Scheme 2-7). Carbenoid insertion into zirconacycles could occur as a concerted reaction *via* transition state **345** or through an electrophilic attack on the carbon zirconium bond and intermediate **346**.[37] This model can explain the selectivity observed for zirconacycles **322-326**; however, it does not explain the selectivity observed for α-substituted zirconacycles **319-321** (Figure 2-3).



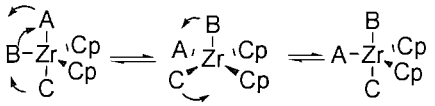
Scheme 2-7 Mechanism for carbenoid as an electrophile

In the third model, regioselectivity may be determined by the rate of 1,2-metallate rearrangement of the interconverting 'ate' complexes **348a-b**, rather than the rate of their formation.[37] When rearrangement is fast the direction of the initial carbenoid attack may determine the regiochemistry of the product (i.e. model 1 above). However, if the rate of 1,2-metallate rearrangement is slow, the relative populations of, and the rate of rearrangement of interconverting 'ate' complexes **348a-b** may determine the regioselectivity (Scheme 2-8).[37] Possible ways in which the 'ate' complexes **348a-b** may interconvert include: the reversible formation of the 'ate' complex (**348**↔**344**) or alternatively the loss and re-addition of the cyclopentadienyl anion[89] (**348**↔**349**). Loss of the cyclopentadienyl anion could result in the rearrangement of a common tetrahedral intermediate **349** favouring rearrangement of the more electron rich carbon zirconium bond (product **350**).



Scheme 2-8 Possible effect of slow 1,2-metallate rearrangement on regiochemical results

The isomerisation of the initial 'ate' complex **348** could also be influential in the case of slow 1,2-metallate rearrangement (Scheme 2-8). 5-Coordinate metal centres are known to undergo Berry pseudorotation (Scheme 2-9).[90,91] In this process the relative orientation of the substituents about the metal centre (Scheme 2-9) can be altered and may favour rearrangement of the more electron rich carbon zirconium bond.



Scheme 2-9 Representation of Berry pseudorotation

The behaviour of alkyl and alkenyl carbenoids towards unsymmetrical zirconacycles is examined in section 2.2. The results are used to support the view that the regiochemistry of insertion is indeed determined by the rate of 1,2-metallate rearrangement of the intermediate 'ate' complex.

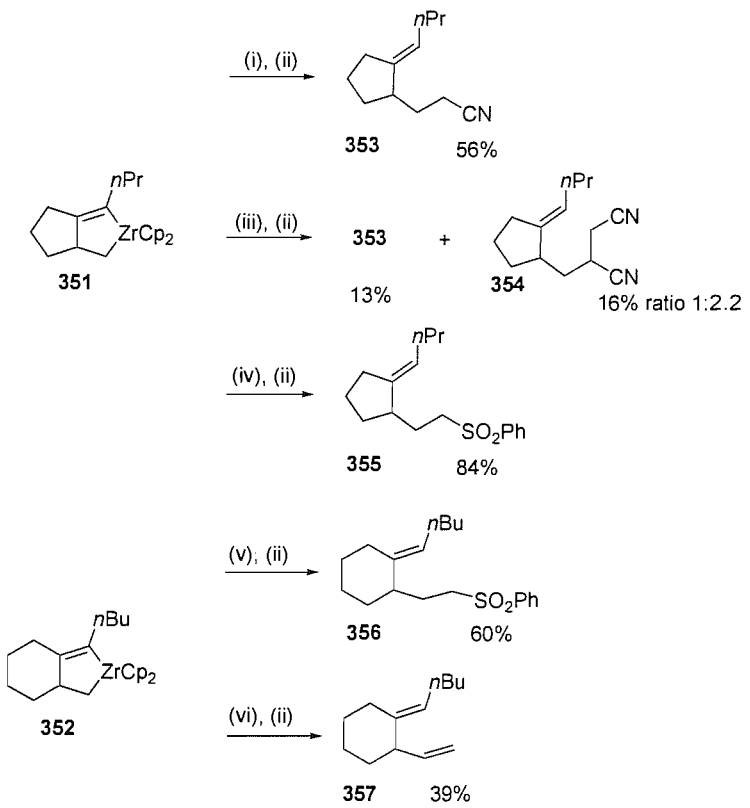
2.2 Results and Discussion

This section presents results from differential elaboration or zirconacyclopentanes and zirconacyclopentenes obtained through carbenoid and isonitrile insertions and mono-deuteration experiments.

2.2.1 Alkyl Carbenoid Insertion into α- Substituted Zirconacyclopentenes

The results from the insertion of electron rich and electron poor alkyl carbenoids into zirconacyclopentenes **351** and **352** (Scheme 2-10) were required to complete a series for publication.[79] The insertion of electron rich carbenoids into zirconacyclopentanes: lithiated chloromethyl methyl ether, 2-methoxyethoxymethyl chloride and chloromethyl phenyl sulfide was not forthcoming. This is thought to be due to the instability of the carbenoids.

The insertion of electron poor carbenoids, lithiated chloroacetonitrile and chloromethyl sulfone, into zirconacyclopentenes **351** and **352** was successful and afforded products **353-357** (Scheme 2-10). Regioselectivity for the alkyl zirconium bond was observed in all examples.



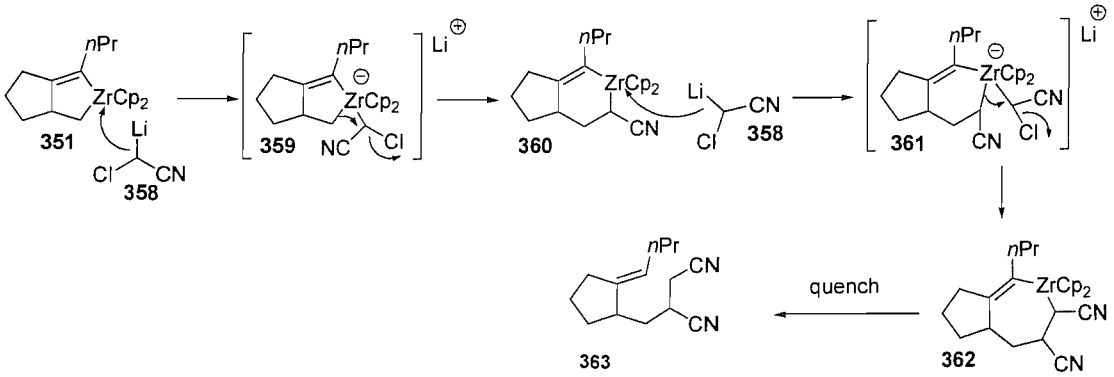
(i) 1.0 eq CH_2ClCN, LDA, -78 °C, 30 min; (ii) MeOH, sat. $NaHCO_3$ aq., RT, 16-24 hr; (iii) 5.0 eq CH_2ClCN, LDA, -78 °C, 45 min; (iv) 2.0 eq CH_2ClSO_2Ph, LDA, -78 °C to -20 °C over 1 hr, -20 °C for 4 hr, 0 °C for 2 hr; (v) 1.3 eq CH_2ClSO_2Ph, LDA, -78 °C, 2 hr; (vi) 1.5 eq CH_2ClSO_2Ph, LDA, -78 °C to RT over 16 hr.

Scheme 2-10 Alkyl carbenoid insertion into zirconacyclopentenes

Treatment of zirconacycle **351** with five equivalents of lithiated chloroacetonitrile resulted in double carbenoid insertion product **354**, isolated in low yield as a separable

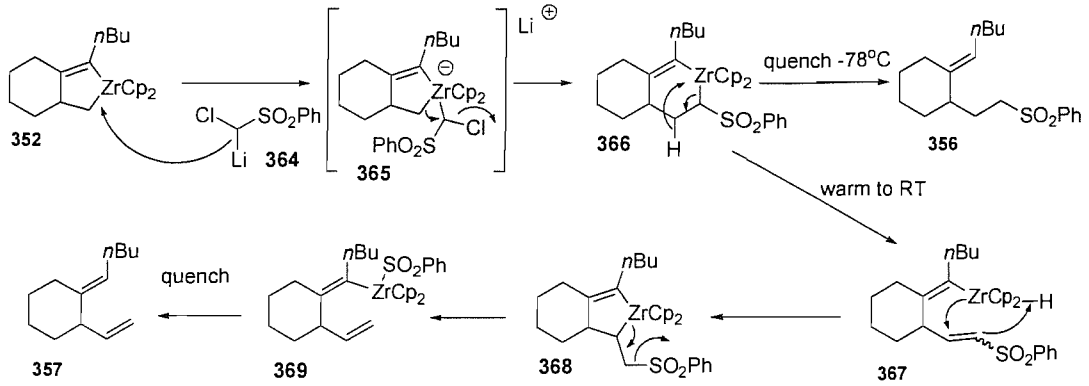
1:2.2 mixture of diastereisomers (Scheme 2-10). Dimerisation of the carbenoid made the work up and purification process difficult and goes some way to explaining the low product yield observed. The second carbenoid insertion was observed into the same side as the first. Previously, double insertion of lithiated chloroacetonitrile had been observed into the two opposite sides of the zirconium in symmetrical zirconacyclopentanes.[79]

A mechanism for double carbenoid insertion is shown in Scheme 2-11. The second carbenoid insertion into zirconacyclohexene **360** is thought to result in zirconacycloheptene **362**. This leads to the conclusion that in the case of α-substitution on the two carbon zirconium bonds, insertion is once again selective for the alkyl zirconium bond over the alkenyl zirconium bond.



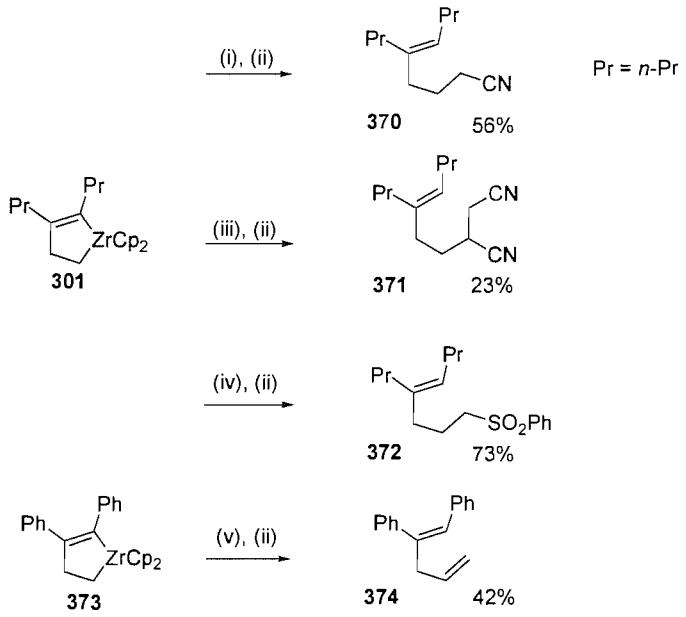
Scheme 2-11 Proposed mechanism for double carbenoid insertion

Different conditions were required for efficient insertion of lithiated chloromethyl phenyl sulfone **364** into zirconacycles **351** and **352** (Scheme 2-10). In the less constrained system **352** insertion occurred at –78 °C to afford sulfone **356**; however, for insertion into the more constrained system **351**, warming to 0 °C was required to afford sulfone **355**. Additionally when the reaction with zirconacyclopentene **352** was warmed to room temperature before quench a new product, diene **357** was isolated. This resulted from the elimination of the sulfone (Scheme 2-12). Elimination can be explained by the formation of a hydride intermediate **367**, which upon re-addition to form a new zirconacyclopentene **368** allows the sulfone group to be eliminated **369**. Similar hydride intermediates have been used to explain other aspects of carbenoid insertion into zirconacycles.[84]



Scheme 2-12 β-Hydride transfer mechanism for elimination

The insertion of lithiated chloroacetonitrile and chloromethyl phenyl sulfone into monocyclic zirconacyclopentene **301** was shown to be favourable and afforded products **370-372** (Scheme 2-13). As with the bicyclic example **351** (Scheme 2-10), lithiated chloroacetonitrile **359** was shown to double insert to afford the double inserted product **371** in low yield. The elimination of the sulfone was also observed. In this case a more polar zirconacyclopentene **373** aided in the difficult purification of diene **374**.

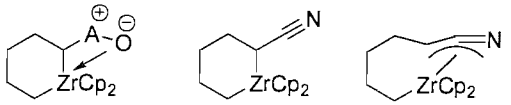


(i) 1.0 eq CH_2ClCN, LDA, -85 °C, 10 min; (ii) MeOH, sat. $NaHCO_3$ aq., RT, 16-24 hr; (iii) 3.2 eq CH_2ClCN, LDA, -78 °C, 2 hr, (iv) 2.2 eq CH_2ClSO_2Ph, LDA, -78 °C, 2.5 hr; (v) 1.0 eq CH_2ClSO_2Ph, LDA, -78 °C to RT, 16 hr.

Scheme 2-13 Insertion of alkyl carbenoids into zirconacyclopentenes

The different behaviour displayed by carbenoids **358** and **364** towards double insertion may be accounted for by donation of electrons from the lone pair on the

oxygen of the sulfone to the empty orbital on zirconium **375**, which prevent double insertion occurring (Figure 2-5). If the nitrile adopted an η^3-coordinated structure **377** it could also prevent double insertion occurring; however, calculations have shown the uncoordinated structure **376** to be more stable.[79]



375 **376** **377**

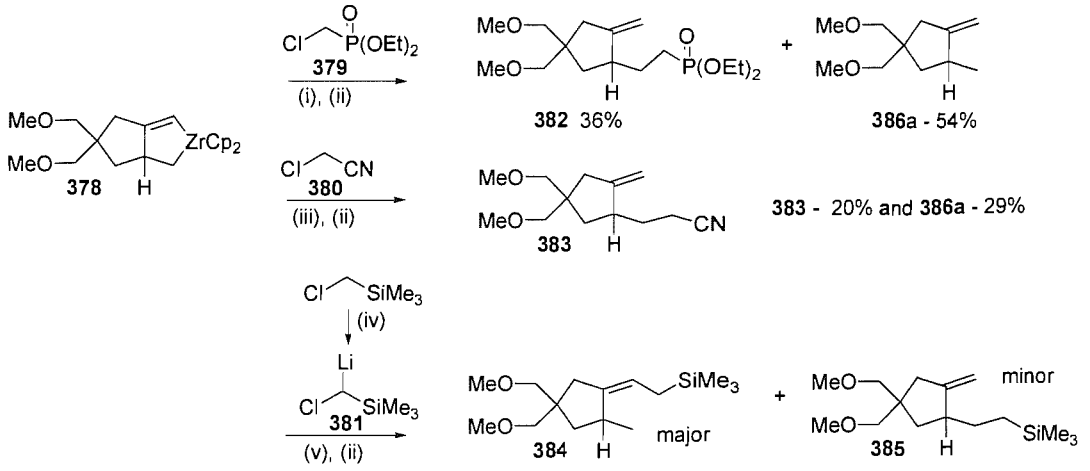
Figure 2-5 Electron donation to zirconium from functional groups of carbenoids

The results presented in this section show that alkyl carbenoid insertion into α-substituted zirconacyclopentenes is selective for the alkyl zirconium bond.

2.2.2 Alkyl and Alkenyl Carbenoid Insertion into Non α-Substituted Zirconacyclopentenes

Non α-substituted zirconacyclopentenes result from the co-cyclisation of terminally unsubstituted enynes. This type of co-cyclisation using a zirconocene equivalent is relatively disfavoured and will not proceed in the presence of zirconocene-1-butene.[92] Alternative conditions using a combination of activated magnesium and zirconocene dichloride do favour co-cyclisation. However, this process was found to be unrealiable and accounts for the poor yields often observed in the series based on zirconacycle **378**.

The regiochemistry of insertion of three alkyl carbenoids into zirconacyclopentene **378** is examined here (Scheme 2-14). Insertion of lithiated chloromethylphosphonate and chloroacetonitrile (electron poor carbenoids) resulted in insertion with complete regioselectivity for the alkyl zirconium bond (products **382** and **383** respectively). Whereas, the electron rich lithiated chloromethyl trimethylsilane **381** displayed moderate 3:1 selectivity for the alkenyl zirconium bond, affording an inseparable mixture of **384** and **385**.

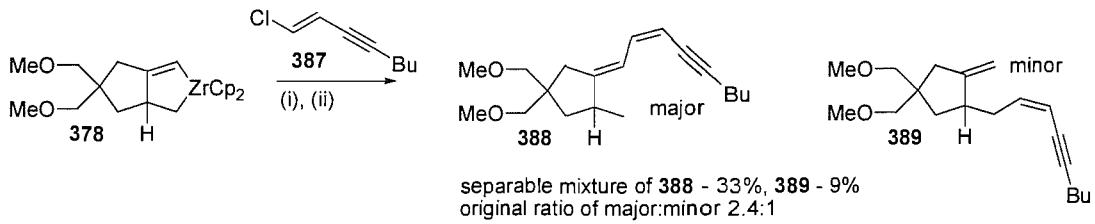


384 and **385** - inseparable mixture - 29% yield, ratio major: minor 3:1
also recovered 26% of **386a**

(i) 2.0 eq **379**, LiTMP, -78 °C to RT, 14 hr; (ii) MeOH, sat. $NaHCO_3$ aq., RT, 16 hr; (iii) 1.1 eq **380**, LiTMP, -78 °C, 15 min; (iv)1.0 eq sec-BuLi, TMEDA, -78°C, 30 min; (v) 1.39 eq **381**, -78 °C to RT, 16 hr.

Scheme 2-14 Alkyl carbenoid insertion into zirconacyclopentene

Moderate 2.4:1 regioselectivity for the alkenyl zirconium bond in zirconacyclopentene **378** was observed on the insertion of the alkenyl carbenoid lithiated (*E*)-1-chlorooct-1-en-3-yne (Scheme 2-15). Products from the reaction were a separable mixture of enynes **388** and **389**. The two products were separated by flash column chromatography using silver nitrate impregnated silica gel.



separable mixture of **388** - 33%, **389** - 9%
original ratio of major:minor 2.4:1

(i) 1.0 eq **387**, LiTMP, -78 °C for 1 hr then RT, 16 hr; (ii) 2M HCl aq., RT, 24 hr.

Scheme 2-15 Alkenyl carbenoid insertion into zirconacyclopentene

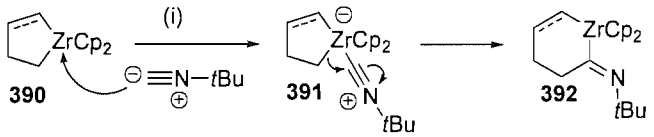
The differences between the phosphonate and nitrile carbenoids, and the silyl and alkenyl carbenoids (Scheme 2-14, Scheme 2-15) provide evidence to support the regioselectivity model where the relative rate of 1,2-metallate rearrangement determines the product observed.

Results from the phosphonate and nitrile carbenoids (Scheme 2-14) appear to indicate initial carbenoid insertion occurs on the side of the alkyl zirconium bond. This could be explained by the alkenyl proton being positioned in the direction of lateral attack, preventing initial attack on the alkenyl side of the zirconacycle **378**.

Unfavourable steric interactions do not explain the results obtained from the silyl and alkenyl carbenoids (Scheme 2-14, Scheme 2-15). These results can be explained by the isomerisation of the initial 'ate' complex due to slow 1,2-metallate rearrangement. The reason for slow rearrangement is different in the two cases. The β-silicon atom stabilises the 'ate' complex, formed from silyl carbenoid and zirconacycle **378**, slowing rearrangement and allowing the more electron rich carbon zirconium bond to migrate. While the insertion of the alkenyl carbenoid, derived from **387**, requires inversion at the sp^2 centre of the alkene for insertion, resulting in slower rearrangement and more opportunity for the electron rich alkenyl zirconium bond to effect the migration.

2.2.3 Mono-Deuteration and Isonitrile Insertion into Non α-Substituted Zirconacyclopentenes

Isonitriles and carbenoids have similar carbene like properties. It is believed that isonitrile insertion proceeds through a similar mechanism to carbenoid insertion.[63] A lone pair of electrons from the isonitrile is donated into the empty orbital of the zirconium metal **390**; the resulting complex **391** then undergoes a 1,2-metallate rearrangement to afford **392** (Scheme 2-16). Isonitrile insertion therefore provides a useful comparison to carbenoid insertion.



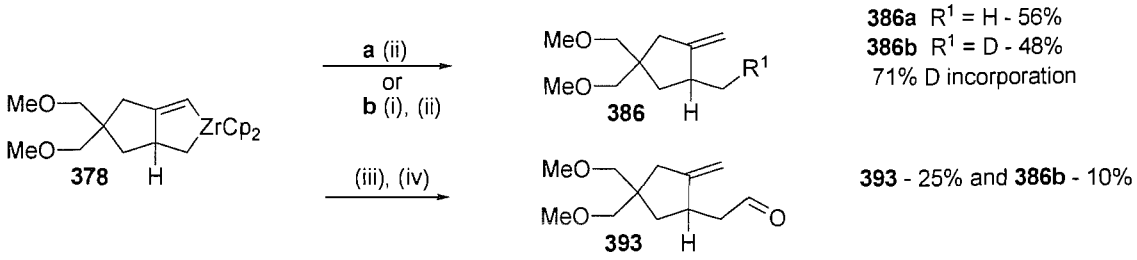
(i) 1.0 eq *t*BuNC, 0 °C to RT, 1.5 hr.

Scheme 2-16 Isonitrile insertion into zirconacycles

Protonation can provide evidence regarding the relative reactivities of the two carbon zirconium bonds present in zirconacycles. Breaking the first carbon zirconium bond in the zirconacycle is believed to be a fast process compared to breaking the second.[85]

This is due to the stability of the intermediate alkoxy zirconocene complex (see section 2.1.1)

Mono-deuteration of zirconacyclopentene **378** was achieved through treatment with one equivalent of deuterated methanol (Scheme 2-17). Deuterium incorporation was observed exclusively at the alkyl position **386b**. This trend in selectivity was mirrored by the insertion of *tert*-butyl isocyanide, which followed by an acidic quench, resulted in the isolation of aldehyde **393** (Scheme 2-17).



(i) 1.0 eq CD_3OD, RT, 1.5 hr; (ii) MeOH, sat. $NaHCO_3$ aq., RT, 16 hr; (iii) 1.0 eq *t*-BuNC, 0 °C to RT, 1.5 hr; (iv) 2 M HCl aq., RT, 16 hr.

Scheme 2-17 Mono-deuteration and isonitrile insertion

In conclusion, mono-deuteration and isonitrile insertion into zirconacyclopentene **378** resulted in regioselectivity for the alkyl zirconium bond.

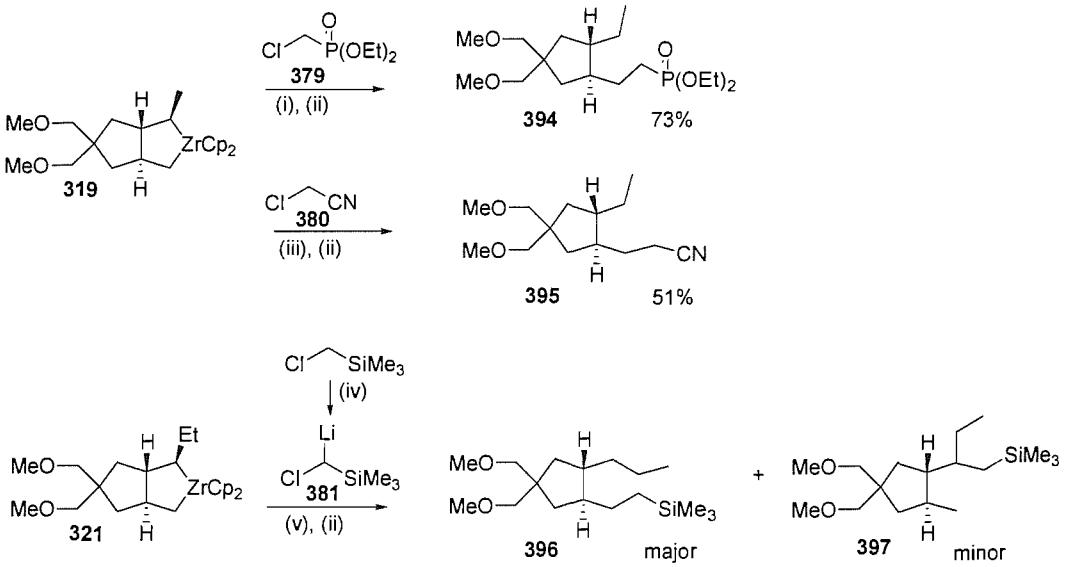
2.2.4 Alkyl and Alkenyl Carbenoid Insertion into Zirconacyclopentanes

The results presented in this section are based on a study of four zirconacycles. A few results regarding regiochemistry of alkyl and alkenyl carbenoid insertion into three of these systems already existed;[54] however, more examples were needed to understand the factors which influenced regioselectivity.

α-Substituted Zirconacyclopentanes

Initially the effect of two different α-substituents on the zirconacyclopentane were investigated. Methyl and phenyl substituted zirconacyclopentenes **319** and **321** (Scheme 2-18) (Scheme 2-20), represent two extremes with regard to steric bulk.

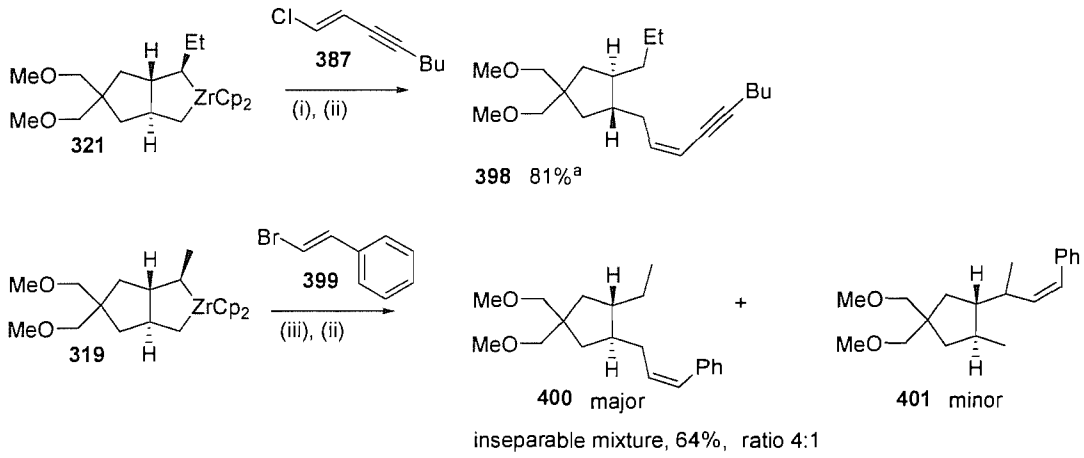
The electron poor carbenoids derived from lithiation of chloromethylphosphonate **379** and chloroacetonitrile **386** were inserted selectively into the unsubstituted alkyl zirconium bond of α-methyl substituted zirconacyclopentane **319** (Scheme 2-18). Incomplete selectivity (ratio 39:1 of **396** to **397**) had previously been observed by Dixon on the insertion of lithiated chloromethyltrimethyl silane **381** into α-ethyl substituted zirconacyclopentane **321**.[54]



(i) 2.0 eq **379**, LiTMP, -78°C to -70 °C, 10 min; (ii) MeOH, sat. $NaHCO_3$ aq., RT, 16 hr; (iii) 1.1 eq **380**, LiTMP, -78 °C, 10 min; (iv)1.0 eq sec-BuLi, TMEDA, -78°C to -65 °C, 30 min; (v) 1.1 eq **381**, -78 °C to RT, 16 hr.
[a]- result obtained by Dixon.

Scheme 2-18 Alkyl carbenoid insertion into α-substituted zirconacyclopentanes

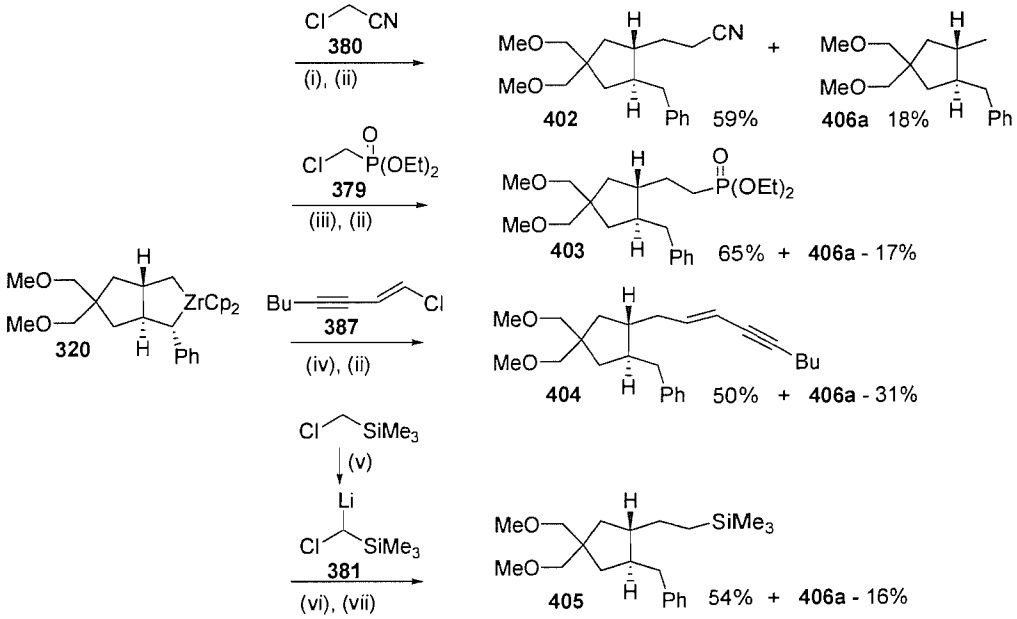
Alkenyl carbenoid insertion with lithiated (*E*)-1-chlorooct-1-en-3-yne had previously been shown by Dixon to be selective for the unsubstituted carbon zirconium bond of zirconacycle **321** resulting in the isolation of **398** (Scheme 2-19).[54] However, a change to a different alkenyl carbenoid lithiated (*E*)-β-bromostyrene eroded this selectivity and resulted in the isolation of an inseparable mixture of alkenes **400** and **401** (Scheme 2-19). This observation could be explained by the greater steric encumbrance presented by the second carbenoid.



(i) 1.0 eq **387**, LiTMP, -78 °C to -65 °C over 40 min; (ii) MeOH, sat. $NaHCO_3$ aq., RT, 12-16 hr; (iii) 1.1 eq **399**, LiTMP, -78 °C, 3hr.
[a]- result obtained by Dixon

Scheme 2-19 Alkenyl carbenoid insertion into α-substituted zirconacyclopentanes

The α-phenyl substituted zirconacyclopentane **320** was treated with an electron rich (**381**) and two electron poor (lithiated **379** and **380**) alkyl carbenoids and an alkenyl carbenoid (lithiated **387**) (Scheme 2-20). Selectivity for the unsubstituted carbon zirconium bond of the zirconacycle **320** was observed in all cases, resulting in moderate yields of products **402-405** (50 – 65%).

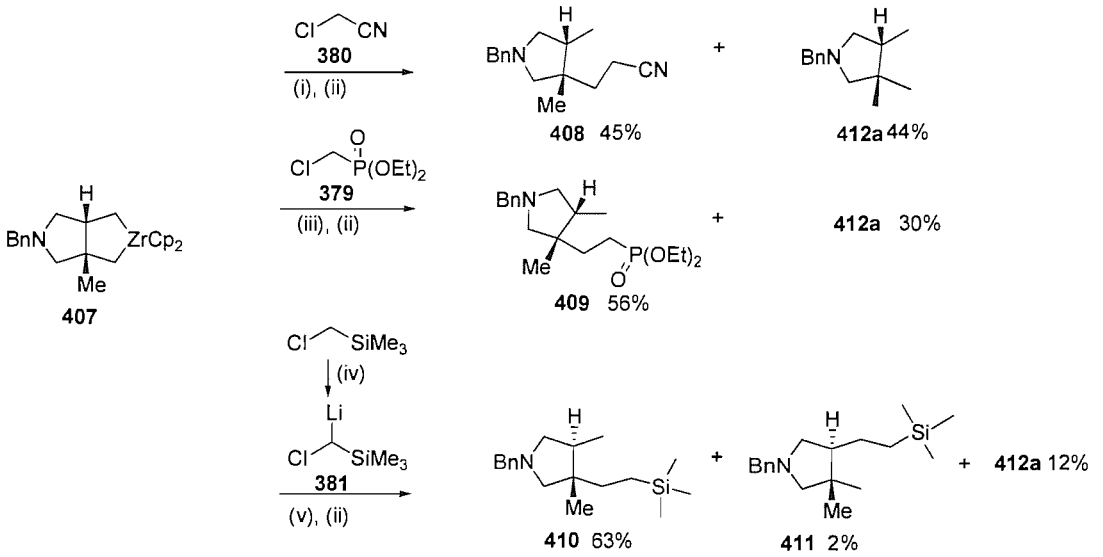


(i) 1.1 eq **380**, LiTMP, -78°C, 15 min; (ii) 2 M HCl aq., 3-16 hr; (iii) 2.0 eq **379**, LiTMP, -78 °C to RT, 16 hr; (iv) 1.0 eq **387**, LiTMP, -78 °C, 1.5 hr; (v) 1.0 eq sec-BuLi, TMEDA, -78 °C, 30 min; (vi)1.39 eq **381**, -78 °C to RT, 16 hr; (vii) MeOH, sat. $NaHCO_3$ aq., RT, 24 hr.

Scheme 2-20 Carbenoid insertion into α-substituted zirconacyclopentene

β-Substituted Zirconacyclopentane

When β-substituted zirconacyclopentane **407** was treated with electron poor carbenoids (lithiated **379** and **380**) selectivity was observed for the most hindered carbon zirconium bond (products **408** and **409**) (Scheme 2-21). This result was reflected in the insertion of the electron rich silyl carbenoid **381**, which displayed incomplete selectivity for the more hindered carbon zirconium bond affording silanes **410** and **411**. A sample of major silane **410** was isolated as a pure compound.



(i) 1.1 eq **380**, LDA, -78 °C, 10 min; (ii) MeOH, sat. $NaHCO_3$ aq., RT, 16-24 hr; (iii) 5.0 eq **379**, LDA, -78 °C, 1.5 hr; (iv) 1.0 eq *sec*-BuLi, TMEDA, -78 °C, 30 min; (v)1.39 eq **381**, -78 °C, 30 min.

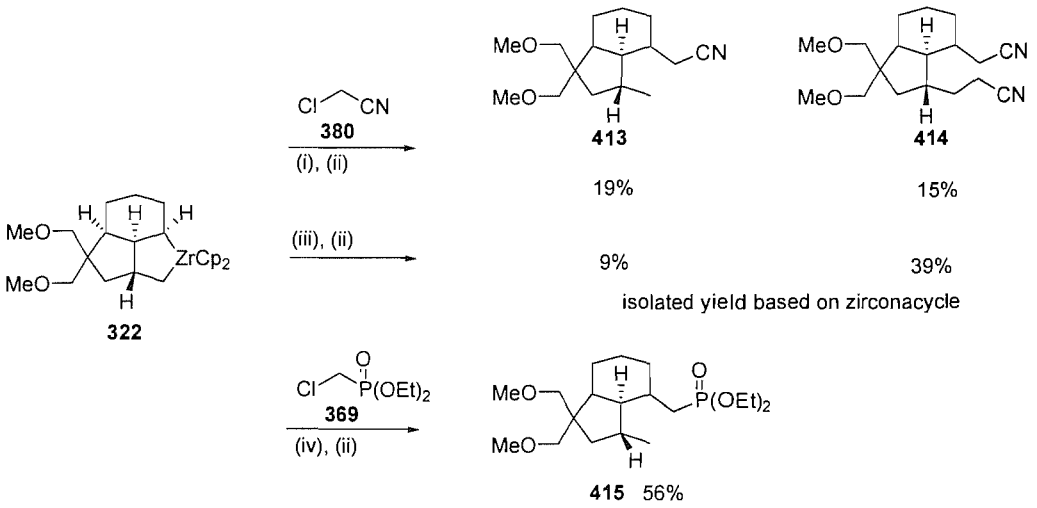
Scheme 2-21 Carbenoid insertion into β-substituted zirconacyclopentanes

Silyl carbenoid **381** had previously been inserted into zirconacyclopentane **407**; however, the products were isolated as a mixture of **410** and **411** in 43% yield, in a ratio of 1.7:1.[54] The reaction was repeated to isolate the major product as a single compound. The alkenyl carbenoid derived from **387**, had previously been inserted into zirconacyclopentane **407** and proceeded with a 5:1 selectivity for the most hindered carbon zirconium bond.[54]

Tricyclic Zirconacyclopentane

The regiochemistry of carbenoid insertion into zirconacycle **322** has previously displayed highly unexpected selectivity.[70] Allyl carbenoid insertion occurred into the

α-substituted carbon zirconium bond (Section 2.1.2). This unexpected selectivity was also observed on the insertion of electron rich alkyl carbenoids and alkenyl carbenoids.[54] In order to complete the analysis of this particular system **322**, it was important to find out whether electron poor alkyl carbenoids also followed the same trend with regard to the regiochemistry of carbenoid insertion. This section presents the results for electron poor carbenoid insertion into tricyclic zirconacycle **322** (Scheme 2-22).



(i) 0.5 eq **380**, LDA, -78 °C, 1 hr; (ii) MeOH, sat. $NaHCO_3$ aq., RT, 16-24 hr; (iii) 2.0 eq **380**, LDA, -78 °C, 1.5 hr; (iv) 2.0 eq **379**, LDA, -78 °C to RT over 16 hr.

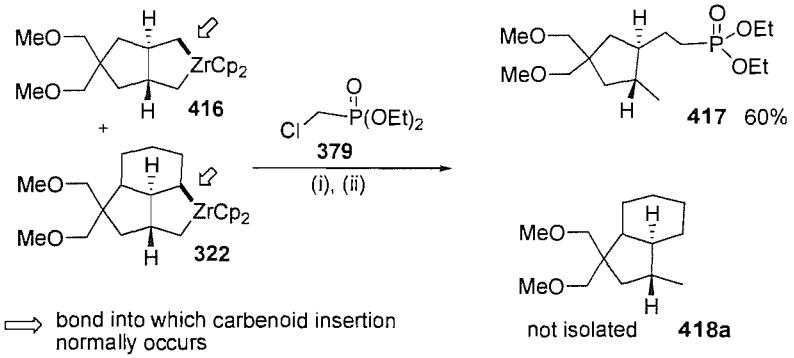
Scheme 2-22 Electron poor carbenoid insertion into tri-cyclic zirconacyclopentane

Nitrile carbenoid insertion into zirconacycle **322** could not be limited to a single insertion (Scheme 2-22). The regiochemistry of the first insertion was tentatively inferred through the use of half an equivalent of carbenoid. It is thought to occur into the α-substituted carbon zirconium bond, as the majority of product isolated was the mono-inserted product **413**. Selectivity for the α-substituted side was observed with the phosphonate carbenoid, affording phosphonate **415**.

Competition Experiment

The regiochemical results obtained for the tricyclic zirconacycle **322** suggested that the α-substituted carbon zirconium bond in this system was more reactive than the unsubstituted bond (Scheme 2-22). If this were the case this may explain why regioselectivity for the more hindered carbon zirconium bond in **322** was observed. A direct competition experiment was designed to test this theory (Scheme 2-23). The α-

substituted and a non-substituted zirconacyclopentanes, **322** and **416** respectively, were formed in the same reaction vessel. The mixture was treated with half an equivalent (with respect to equivalents of zirconacycles) of the phosphonate carbenoid (derived from **379**) and insertion monitored by gas chromatography. Insertion was only observed into the non-substituted zirconacycle **416**. This showed that α-substituted carbon zirconium bond was not more reactive than the unsubstituted carbon zirconium bond. Phosphonate **417** was isolated as it was an unknown compound.



(i) 0.5 eq **379**, LDA, -78°C to RT over 16 hr; (ii) MeOH, sat. $NaHCO_3$ aq., RT, 24 hr.

Scheme 2-23 Competition experiment

Summary

Carbenoid insertion resulted in complete regioselectivity for the unsubstituted carbon zirconium bond in the simple α-substituted zirconacyclopentanes **319** and **320** (Scheme 2-20, Scheme 2-21), and for the more hindered carbon zirconium bond in tricyclic zirconacyclopentane **322** (Scheme 2-22) and β-substituted zirconacyclopentane **407** (Scheme 2-21). Exceptions resulted from the insertion of silyl and alkenyl carbenoids where incomplete regioselectivity was recorded (Scheme 2-19, Scheme 2-20, Scheme 2-21). The competition experiment showed that α-substituted carbon zirconium bonds are not inherently more reactive towards carbenoids than unsubstituted carbon zirconium bonds (Scheme 2-23).

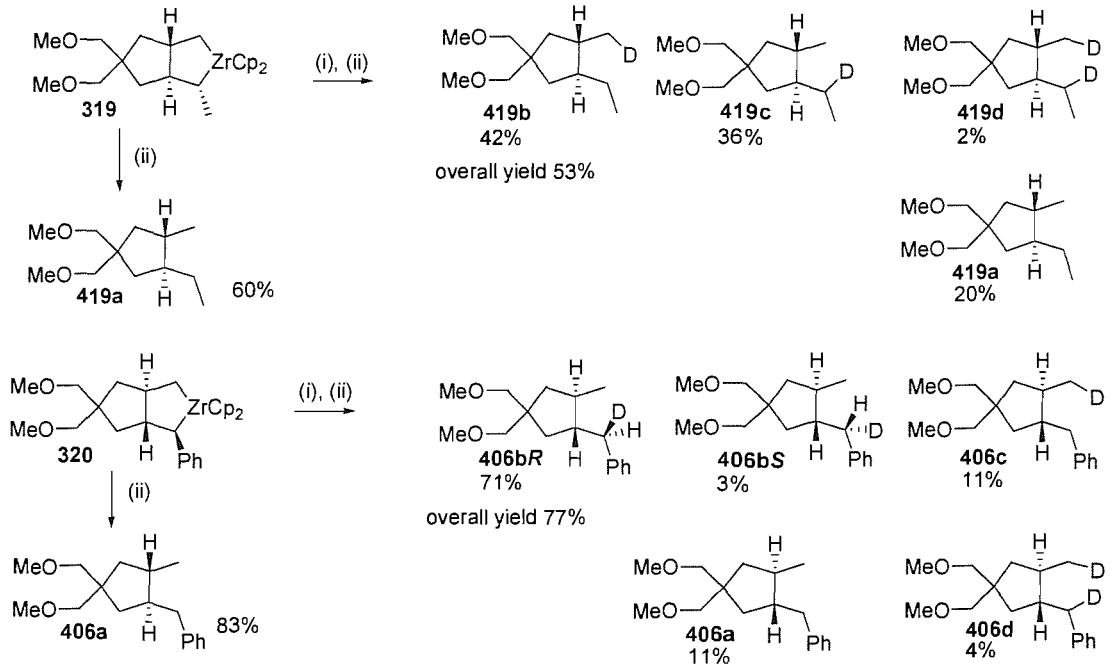
A few conclusions can be drawn from these results. The regiochemistry of carbenoid insertion observed is not determined by steric factors alone. Though it does appear to be an important influencing factor for systems such as the simple α-substituted zirconacycles **319** and **320**. The results from the competition experiment (Scheme 2-21) provide evidence that carbenoid insertion is not a concerted process, otherwise

insertion into the tricyclic system **322** over the symmetrical system **416** would have been observed. The pattern of results observed and consideration of the proposed mechanism of carbenoid insertion into zirconacycles would therefore lead to the conclusion that factors such as the rate of 1,2-metallate rearrangement have an important role in determining the regiochemistry of insertion observed.

2.2.5 Mono-Deuteration of Zirconacyclopentanes

Mono-deuteration of zirconacyclopentanes **319**, **320**, **322** and **407** provided more information regarding the general reactivity of the two carbon zirconium bonds in each zirconacycle (Scheme 2-24, Scheme 2-25).

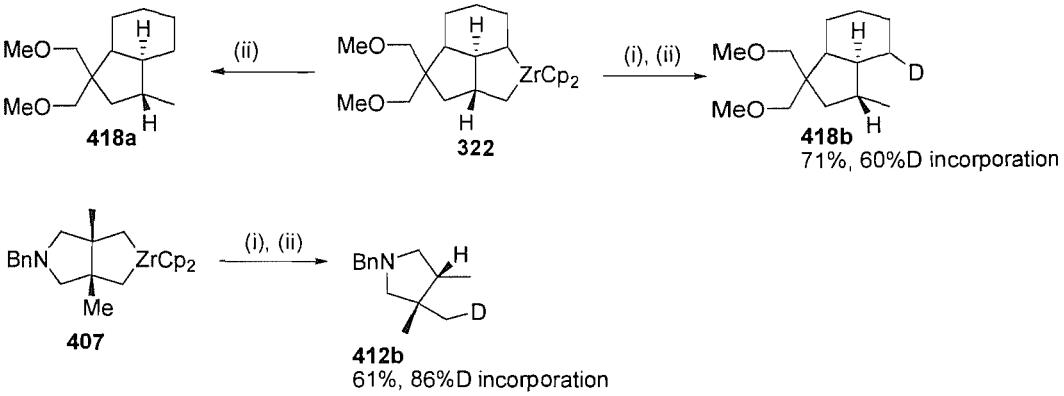
Initially the zirconacycles **319** and **320** were quenched to recover the cyclised products **419a**[79] and **406a** respectively (Scheme 2-24). Mono-deuteration of these α-substituted zirconacyclopentanes provided some interesting results, as complete selectivity for either side of the zirconacycles was not observed. The α-methyl substituent had a limited effect with a 42:36 (**419 b**:**c**) selectivity for the non-substituted carbon zirconium bond. In contrast, the α-phenyl substituent has a significant effect with a 74:11 (**406 b**:**c**) selectivity observed for the α-substituted carbon zirconium bond. This experiment was significant as the stereochemistry of zirconacycle **320** was tentatively assigned using the NMR of the major deuterated product **406b*R***. The presence of **406b*S*** may have been due to a small amount of this isomer being present in the original zirconacycle mixture.



(i) 1.0 eq CD_3OD, RT, 1 hr; (ii) MeOH, sat. $NaHCO_3$ aq., RT, 16 hr.

Scheme 2-24 Mono-deuteration of simple α-substituted zirconacyclopentanes

Mono-deuteration of the tricyclic zirconacycle **322** and β-substituted zirconacycle **407** resulted in the isolation of single deuterated products **418b** and **412b** respectively (Scheme 2-25). Selectivity for the more sterically hindered carbon zirconium bond was observed in both cases.



(i) 1.0 eq CD_3OD, RT, 1hr; (ii) MeOH, sat. $NaHCO_3$ aq., RT, 16 hr.

Scheme 2-25 Mono-deuteration of tricyclic and β-substituted zirconacyclopentane

In summary mono-deuteration was selective for the more substituted carbon zirconium bond in three out of the four systems studied. The differences observed between the selectivity for deuteration and carbenoid insertion, especially in the simple α-substituted systems **319** and **320** (Scheme 2-24), indicate that the mechanism

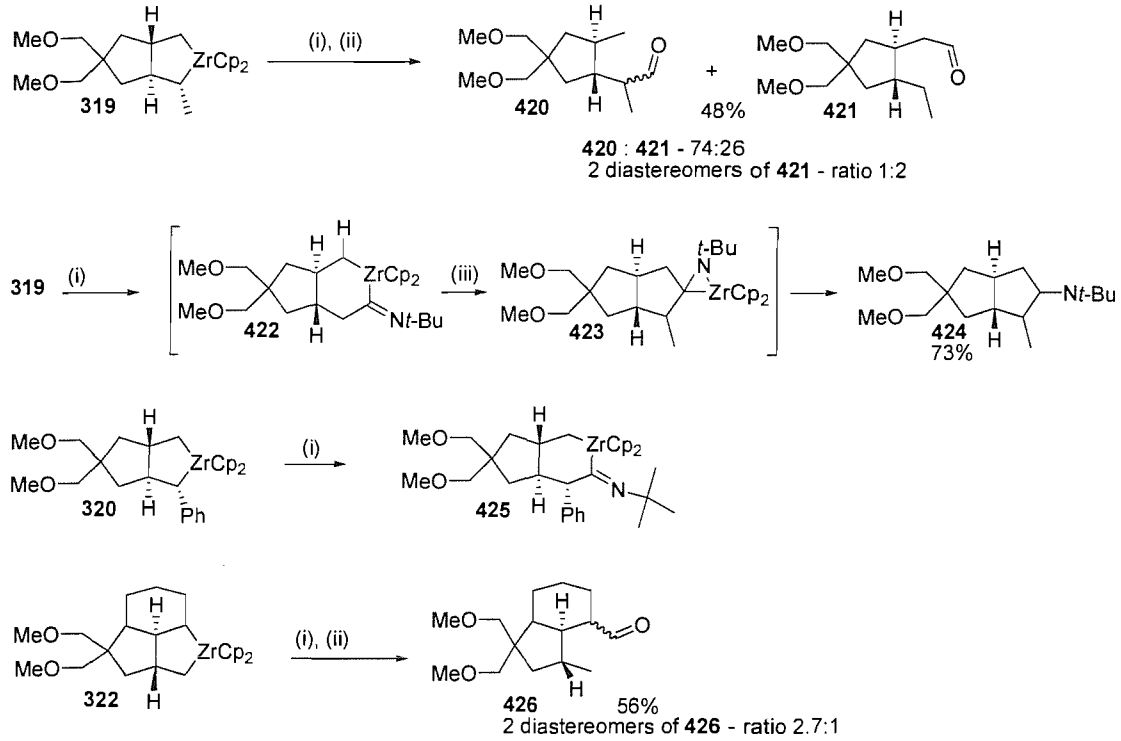
for carbenoid insertion and electrophilic quench are indeed very different. As the electrophilic quench is thought to occur through nucleophilic attack by the carbon zirconium bond these results provide more evidence that carbenoid insertion into zirconacycles does not occur *via* a concerted reaction where the carbenoid acts as an electrophile.

2.2.6 Isonitrile Insertion into Zirconacyclopentanes

Zirconacyclopentanes **319**, **320**, **322** and **407** were treated with *tert*-butyl isocyanide (Scheme 2-26, Scheme 2-27). The type of quench used after isonitrile insertion into α-methyl substituted zirconacyclopentane **319** determined the product observed (Scheme 2-26). A basic quench resulted in the isolation of amine **424**. Unfortunately, as the amine cyclised, information regarding the regiochemistry of insertion was lost. Acidic quench resulted in the isolation of aldehydes **420** and **421** in a 74:26 ratio. The major regioisomer **420** was present as a 2:1 mixture of diastereomers.

Tert-butyl isocyanide insertion into α-phenyl substituted zirconacyclopentane **320** resulted in an unexpectedly stable, 6-member zirconacycle **425** (Scheme 2-26). It was not quenched to the aldehyde upon overnight treatment with aqueous hydrochloric acid solution. Therefore, in order to establish the regiochemistry of isonitrile insertion, the reaction was investigated using NMR. Zirconacycle **320** was synthesised, dissolved in deuterated benzene and NMR data collected. Approximately one equivalent of isonitrile was added, resulting in an instant colour change. Further investigation by NMR revealed isonitrile insertion to have occurred exclusively into the substituted carbon zirconium bond affording zirconacyclohexane **425**.

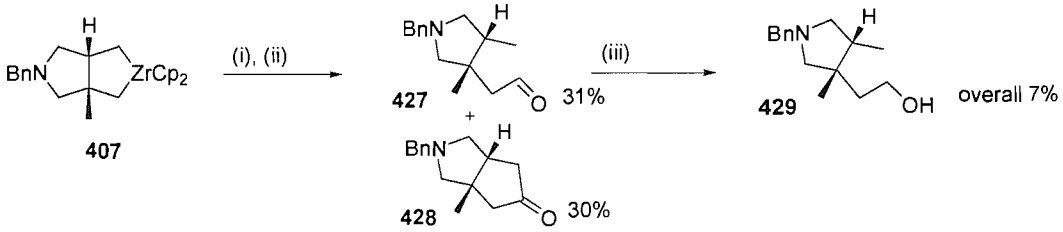
Isonitrile insertion into tricyclic system **322** showed complete selectivity for the substituted carbon zirconium bond affording aldehyde **426**.



(i) 1.0 eq *t*-BuNC, 0°C to RT, 30 min; (ii) 2 M HCl aq., RT, 24 hr; (iii) MeOH, sat. $NaHCO_3$ aq., RT, 16 hr; (iv) 1.0 eq *t*-BuNC, RT.

Scheme 2-26 Isonitrile insertion into α-substituted zirconacyclopentanes

Isonitrile insertion into the β-substituted zirconacyclopentane **407** resulted in an inseparable 1:1 mixture of aldehyde **427** and ketone **428** (Scheme 2-27). The ketone is a known compound.[93] The mixture was separated through reduction followed by isolation of primary alcohol **429**. The partial cyclisation observed means the information gained regarding regioselectivity is limited. Therefore, the reaction was not repeated in order to obtain better conditions for the reduction step.



(i) 1.0eq *t*-BuNC, 0 °C to RT, 30 min; (ii) 2 M HCl aq., RT, 24 hr; (iii) 2.0 eq $NaBH_4$, 0 °C, 2 hr; (iv) 2 M HCl aq., 0 °C.

Scheme 2-27 Isonitrile insertion into β-substituted zirconacyclopentane

Isonitrile insertion into zirconacyclopentanes **319**, **320**, **322** and **407** has revealed significantly different regiochemical behaviour to carbenoid insertion, with selectivity

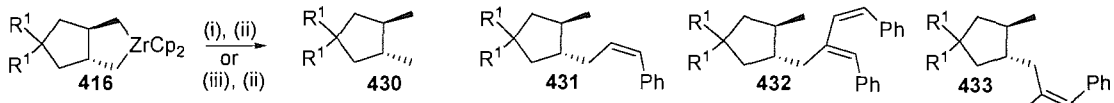
for the α-substituted carbon zirconium bond observed in all cases (Scheme 2-26, Scheme 2-27). The reasons for the differences between the regiochemistry of carbenoid and isonitrile insertion are unclear at this stage.

2.2.7 Co-cyclisation of Allene

This section describes alkyl and alkenyl carbenoid insertion into zirconacyclopentane **435** (Figure 2-6). This zirconacycle is of interest as it contains an exocyclic double bond α- to zirconium. This system is of interest because of work carried out within the group by Norton, which could help explain the regiochemistry of carbenoid insertion into unsymmetrical zirconacycles.[81]

Background

Previous research on the insertion of alkenyl carbenoids into symmetrical zirconacycle **416** provided significant results which help to explain the regiochemistry of carbenoid insertion observed in unsymmetrical cases (Scheme 2-28).[81] Norton showed that the insertion of lithiated (*E*)-β-bromostyrene into zirconacycle **416** resulted in a mixture of non **430**, mono **431**, bis **432** and tris **433** inserted products. Insertion could not be stopped after the first carbenoid insertion had taken place.



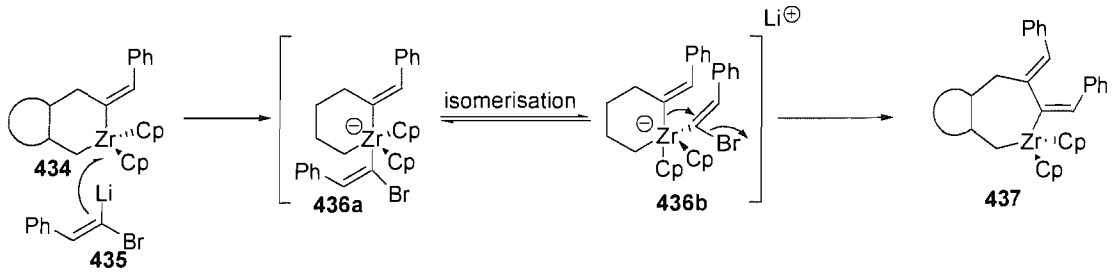
$R^1 = CH_2OCH_3$

1.0 eq carbenoid: **430** = 18%, **431** = 48%, **432** = 11%
2.0 eq carbenoid: **432** = 64%, **433** = 5%

(i) 1.0 eq (*E*)-β–bromostyrene, LDA, -90 °C, 25 min; (ii) MeOH, sat. $NaHCO_3$ aq., RT, 16 hr; (iii) 2.0 eq (*E*)-β–bromostyrene, LDA, -78 °C, 70 min.

Scheme 2-28 Previous results from insertion of lithiated (*E*) –β-bromostyrene

The formation of bis **432** and tris **433** inserted products is particularly significant (Scheme 2-28) due to the proposed intermediate zirconacycle implied through their formation (Scheme 2-29). Carbenoid insertion into intermediate zirconacyclohexane **434** occurs into a very sterically hindered carbon zirconium bond (Scheme 2-29). Since the initial attack of the carbenoid is very unlikely to occur on the hindered side of the zirconacycle, some form of isomerisation, such as Berry pseudorotation, of the intermediate 'ate' complex **436**, followed by migration of the more electron rich carbon zirconium bond must be occurring, resulting in zirconacycloheptane **437**.



Scheme 2-29 Mechanism for bis-insertion of lithiated (*E*)-β-bromostyrene

Probing the regiochemistry of insertion of different types of carbenoid into intermediate zirconacyclohexene **434** would have provided good evidence for the isomerisation mechanism proposed (Scheme 2-29). However, as Norton found it was not possible to limit carbenoid insertion into zirconacyclopentane **434** (Scheme 2-28), a new system with similar properties was sought. Analogous zirconacyclopentane **438** was therefore targeted (Figure 2-6). This system also contained the required exocyclic double bond and could be derived from allene **439**.

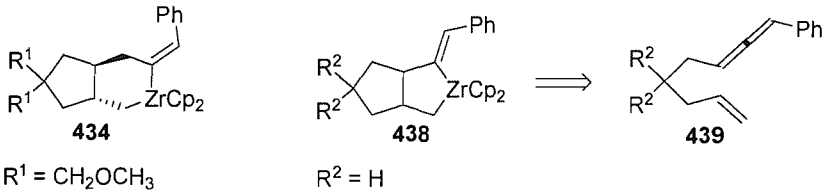
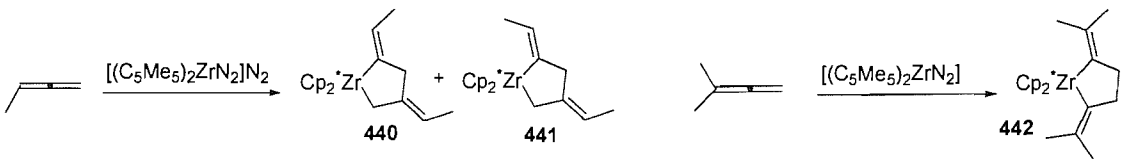


Figure 2-6 Zirconacyclohexane and corresponding zirconacyclopentane

Co-cyclisation of allenes has been previously reported as an intermolecular process. In work by Duggan [94] and Jones [95] allenes reacted quickly, resulting in metallacyclopentanes **440** and **441**, and **442** respectively.

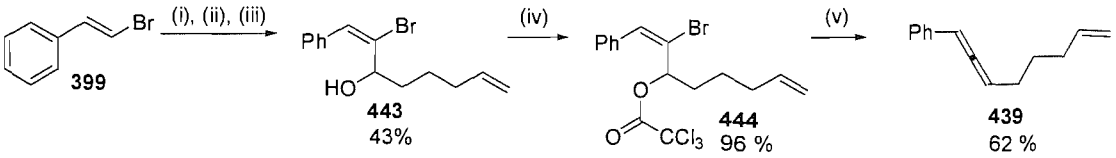


Scheme 2-30 Previous examples of allene cyclisation using zirconium

Allene Synthesis

Allene **439** was made from hex-5-enal and (*E*)-β-bromostyrene. Hex-5-enal was synthesised using a Swern type oxidation from hex-5-en-1-ol according to a procedure by Mukai *et al.* in 65% yield (Scheme 2-31).[96] Problems encountered included residual dichloromethane and dimethyl sulfoxide in the hex-5-enal. Both

these impurities interfered unfavourably in the reaction with lithiated (*E*)-β-bromostyrene, consequently the yield of alcohol **443** was low (33 and 43 %).



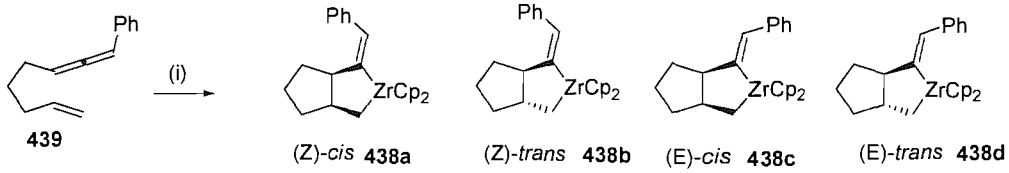
(i) 1.0 eq LDA, -90 °C, 30 min, (ii) $CH_2CH(CH_2)_3CHO$, -90 °C to -30 °C, 3.5 hr; (iii) sat. $NaHCO_3$ aq., (iv) $Cl_3CC(O)Cl$, Et_3N, RT, 30 min; (v) $Pd(PPh_3)_4$, Et_2Zn, RT, 2 hr.

Scheme 2-31 Preparation of octa-1,2,7-trienyl-benzene 436

Following a relevant procedure by Ohno *et al.* [97] alcohol **443** was made into the trichloroacetic acid intermediate **444** (79 to 96%), treatment of **444** with palladium tetrakistriphenylphosphine and diethyl zinc resulted in the allene **439** (48 to 62%) (Scheme 2-31). The best overall yield for the allene was 17% from the commercially available hex-5-en-1-ol.

Allene Cyclisation

The co-cyclisation of allene **439** using zirconocene 1-butene was relatively slow, taking approximately 6 hours to go to completion (Scheme 2-32). Cyclisation resulted in a mixture of the four possible isomers of the zirconacycle **439a-d**. The ratio of these isomers did not stay constant over time.



(i) zirconocene-1-butene, -78 °C to RT.

Scheme 2-32 Co-cyclisation of allene 439 with zirconocene-1-butene

A combination of GC and proton and carbon NMR were used to determine the identity and ratios of the isomers **438a-d** of protonation products of the zirconacycles present at different stages of the reaction (Table 2-1, Table 2-2). The chemical shift and coupling constants for the vinyl protons in **445** were used to determine whether the system was (*E*) or (*Z*). Previous work by Bailey *et al.* determined that the carbon NMR methyl signal from *trans*-1,2-dimethylcyclopentane is at δ 18.78 ppm, whereas the corresponding signal for the *cis* isomer is at δ 15.18 ppm (data recorded by IBM-

200SY spectrometer in deuterated chloroform and referenced to Me_3Si).[98] Hence in cyclopentanes **445a-d** the isomers with methyl signals at δ 16.28 and 16.35 ppm were assigned as *cis* and the isomer with the signal at δ 18.59 ppm was assigned as *trans* (data recorded at 100MHz, in deuterated chloroform, referenced to the central deuterated chloroform peak). The second *trans* isomer was very minor and not observed in ^{13}C NMR.

Table 2-1 GC data for percentage of isomers produced upon cyclisation of allene 439

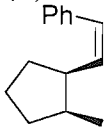
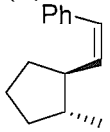
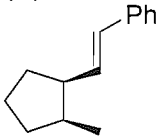
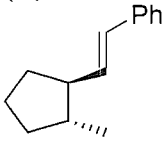
Product Time at room temperature (hr)	(Z)-cis  **445a**	(Z)-trans  **445b**	(E)-cis  **445c**	(E)-trans  **445d**	Ratio *Z:E*	Ratio *cis:trans*
0*	37	36	16	11	73:27	53:47
2.5*	55	7	21	17	62:38	76:24
4.5*	48	4	25	23	52:48	73:27
7.5	55	3	17	25	58:42	72:28
24.0	46	2	15	37	48:52	61:39
48.0	43	1	9	46	45:55	52:48

Table 2-2 NMR data for the percentage of isomers produced upon cyclisation of allene 439

0*	not able to interpret – too much allene remaining					
2.5*	39	5	30	26	44:56	69:31
7.5	52	2	20	26	54:46	72:28
24.0	45	2	16	37	47:52	61:39
48.0	41	Trace	12	47	41:59	53:47

- (%) of each isomer present at time of quench

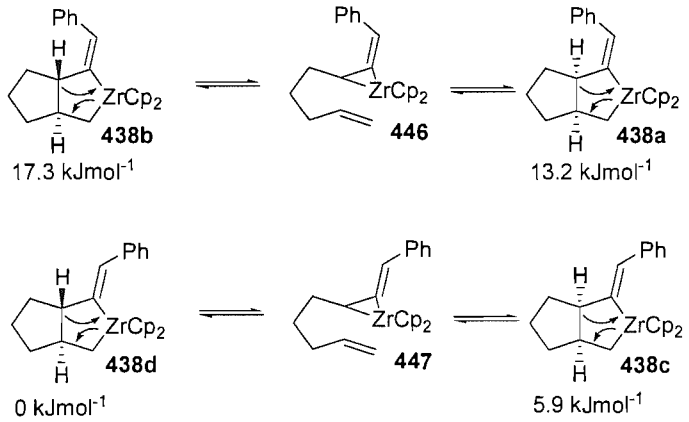
* Still starting allene **439** remaining

^1H NMR data collected at 400 MHz, in $CDCl_3$, referenced to residual $CHCl_3$ peak

^{13}C NMR data collected at 100 MHz, in $CDCl_3$, referenced to the central $CDCl_3$ peak

The data (Table 2-1 and Table 2-2) shows that (*Z*)-*cis* **445a** and (*E*)-*trans* **445d** isomers are the most stable configurations of zirconacyclopentanes **438a-d**. DFT calculations showed that for the (*Z*) alkenes **445a** and **445b**, the parent *cis*-zirconacycle **438a** was 4.1 $kJmol^{-1}$ more stable than the *trans*-zirconacycle **438b** (Scheme 2-33). DFT calculations also showed that for (*E*)-alkenes **445c** and **445d**, the parent *cis*-zirconacycle **438d** was 5.9 $kJmol^{-1}$ more stable than *trans*-zirconacycle **438c**. For both (*Z*) and (*E*) alkenes, the two major products formed **445a** and **445d** correspond to the more stable parent zirconacycles **438a** and **438d** formed under

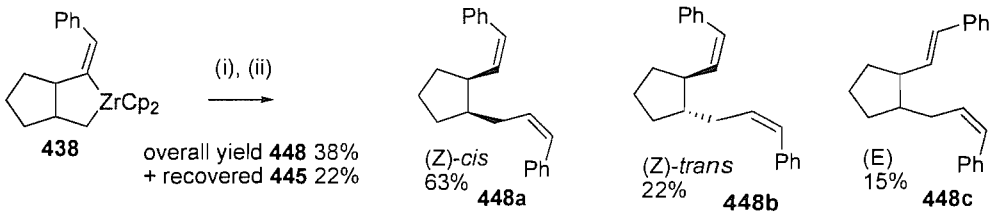
thermodynamic conditions. In the case of the (*Z*)-*cis* **445a** isomer, equilibration to the *cis* isomer occurs at a rate comparable to that of cyclisation. However, this is not the case for the (*E*)-*trans* **445d** isomer where equilibration to the *trans* isomer is slow. The (*E*):(*Z*) ratio does not change as significantly as the *cis* : *trans* ratio over time. The change in *cis*: *trans* (**438a** and **438c** to **438b** and **438d**) ratio can be tentatively explained by the reversibility of the zirconocene co-cyclysation *via* **446** and **447** (Scheme 2-33). Since the zirconium continues complexed to the allene moiety this does not change the (*E*):(*Z*) ratio. The changes observed in these ratios are not understood.



Scheme 2-33 Mechanism for reversibility of allene cyclisation

Carbenoid Insertion

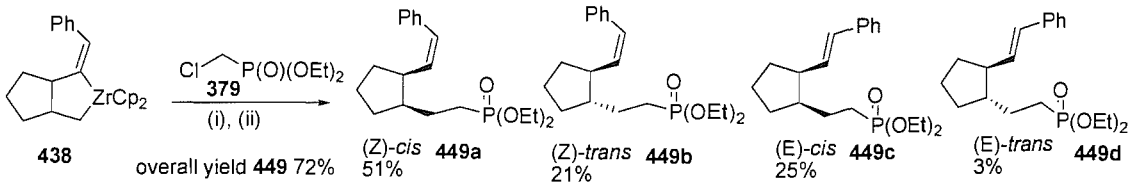
The regiochemistry of vinyl and alkyl carbenoid insertion into zirconacycle **438** was investigated (Scheme 2-34, Scheme 2-35). The insertion of lithiated (*E*)-β-bromostyrene into zirconacycle **438** resulted in the isolation of **448a-c**. Unfortunately the stereochemistry about the ring junction of the minor (*E*) isomer **448c** could not be determined due to inconclusive data (Scheme 2-34).



(i) 1.0 eq (*E*)-β-bromostyrene, LiTMP, -78 to -70°C, 2 hr; (ii) MeOH, sat. $NaHCO_3$ aq., RT, 16 hr.

Scheme 2-34 Vinyl carbenoid insertion into zirconacycle 438

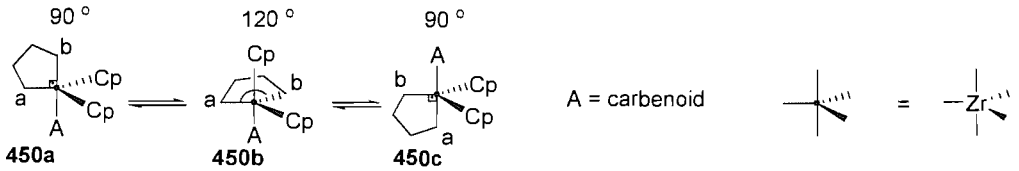
The insertion of the alkyl carbenoid, lithiated diethyl chloromethyl phosphonate, into zirconacycle **438** proved a facile process and resulted in the isolation of phosphonate **449**, as a mixture of 4 diastereomers in 72% yield (Scheme 2-35). Proton NMR was used to determine the ratio and identity of isomers **449a-d**.



(i) 2.0 eq **379**, LiTMP, -90 °C to RT over 16 hr; (ii) MeOH, sat. $NaHCO_3$ aq., RT, 24 hr.

Scheme 2-35 Alkyl carbenoid insertion into zirconacycle 438

Vinyl and alkyl carbenoid insertion into zirconacyclopentane **438** was shown to be regioselective for the least hindered carbon zirconium bond of the zirconacycle (Scheme 2-34, Scheme 2-35). The regioselectivity observed with this 5-member zirconacycle **438** was unexpected and the regiochemistry observed was in direct contrast to Norton's results with the 6-member intermediate zirconacycle **434** (Scheme 2-28),[81] where insertion occurred into the more hindered carbon zirconium bond. The difference between these results can be explained by the lowered conformational flexibility present in the 5-member zirconacycle **438** compared to the 6-member zirconacycle **434**. The 5-member ring system **450** may inhibit the pseudo rotation mechanism for carbenoid site exchange due to this comparatively smaller flexibility (Scheme 2-36). The smaller ring could make isomerisation more energetically unfavourable.

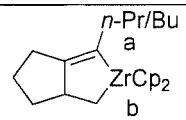
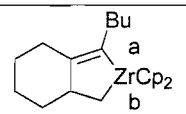
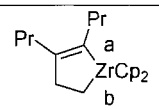
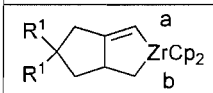
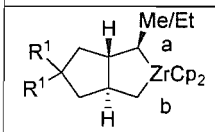
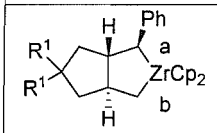
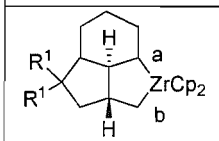
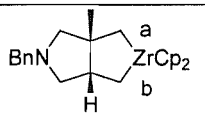
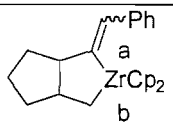


Scheme 2-36 Pseudo-rotation mechanism for carbenoid site exchange in a 5-member zirconacycle

2.3 Conclusions

The results from mono-deuteration, isonitrile insertion, alkyl and alkenyl carbenoid insertion into zirconacyclopentanes and zirconacyclopentenes are summarised in Table 2-3.

Table 2-3 Summary of regiochemistry results

	Carbenoid precursor				Isonitrile	Mono-deuteration
	E poor	E rich	alkenyl			
Zirconacycle	Cl A	Cl SiMe$_3$	Cl Bu	Br Ph	^{t}BuNC	CD_3OD
 **351/304**	b	a:b 13:87[79]	b[54]		b[79]	
 **352**	b					
 **301**	b					
 **378**	b	a:b 3:1	a:b 2.4:1		b	b
 **319/321**	b	a:b 1:39[54]	b[54]	a:b 1:4	a:b 74:26	a:b 36:42
 **320**	b	b	b		a	a:b 74:11
 **322**	a	a:b 8:1[54]	b[54]		a	a
 **407**	a	a:b 63:2	a:b 5:1[54]		a	a
 **438**	b			b		

'a' and/or 'b' represents the carbon zirconium bond into which insertion occurred, or that reacted preferentially

#:# represents the ratio of a:b

A = CN/ SO_2Ph/ $P(O)(OEt)_2$, E = electron, R^1 = $-CH_2OCH_3$

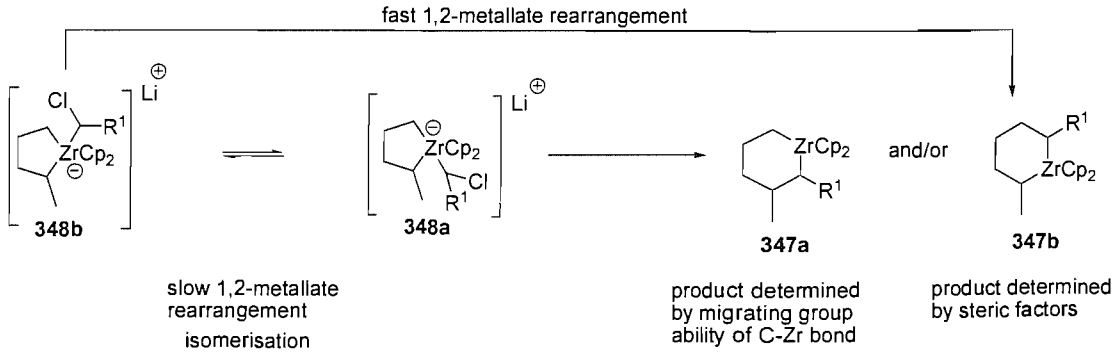
Analysis of these results (Table 2-3) allows some conclusions to be drawn. Mono-deuteration and carbenoid and isonitrile insertion are usually very selective processes. Alkyl carbenoid insertion occurs predominately into the unhindered carbon zirconium bond of an unsymmetrical zirconacycle. This suggests that steric interactions do have an important role in determining regioselectivity. However, the results for zirconacycles **322** and **407** show this is not the only factor influencing regiochemistry. The nature of the carbenoid being inserted also influences the regioselectivity observed. The insertion of electron poor carbenoids are generally more regioselective than electron rich carbenoids.

Isonitrile insertion into zirconacyclopentanes has been shown to be selective for the sterically hindered carbon zirconium bond, whereas the regiochemistry of insertion into zirconacyclopentenes is the opposite. The reasons for the differences between the regiochemistry of carbenoid insertion and isonitrile insertion are not fully understood. However, it can be speculated that they arise due to their different abilities to stabilise the intermediate 'ate' complex.

Mono-deuteration of zirconacyclopentanes does not appear to be influenced by stereochemical issues. In all but one of the cases studied deuteration is selective for the more electron rich and sterically hindered carbon zirconium bond. This indicates that the mechanism for carbenoid insertion and electrophilic quench with methanol are indeed very different. As the electrophilic quench is thought to occur through nucleophilic attack by the carbon zirconium bond, the results in Table 2-3 provide some evidence to show that carbenoid insertion into zirconacycles does not occur *via* a concerted reaction where the carbenoid acts as an electrophile.

These results have provided evidence which points towards the rate of 1,2-metallate rearrangement of rapidly interconverting 'ate' complexes being the determining factor in determining the regiochemistry of carbenoid insertion into zirconacycles and not the regiochemistry of initial carbenoid attack (Section 2.1.3).[37] The evidence comes from the different behaviour displayed by electron poor *versus* electron rich carbenoids as well as the differences in behaviour between zirconacycles.

The model is based on carbenoid insertion being a two-step process. The regiochemistry of the initial 'ate' complex is determined by steric considerations and the carbenoid initially resides on the least hindered side of the zirconacycle (Scheme 2-37). The second step is a 1,2-metalllate rearrangement. If this step is slow then the 'ate' complex **348** may undergo isomerisation. Three mechanisms for this isomerisation were discussed in section 2.1.3. Unfortunately it has not been possible to rule out Berry pseudorotation or loss and re-addition of the carbenoid or the cyclopentadienyl anion as mechanisms through which this isomerisation could be acheived. But independent of the mechanism of isomerisation – when conditions are favourable for isomerisation to occur - the migrating group ability of the carbon zirconium bond determines the product observed.

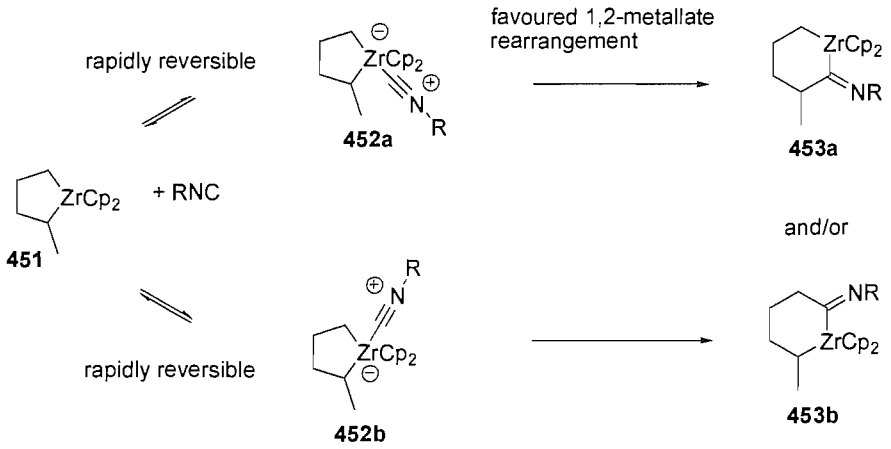


Scheme 2-37 Model to explain the regiochemistry of carbenoid insertion into zirconacycles

This model (Scheme 2-37) is supported by the behaviour of the electron rich silyl carbenoid **381**. Insertion of this carbenoid shows greater regioselectivity for the electron rich carbon zirconium bond when compared to electron poor carbenoids **348**. The β-silicon group could stabilise the intermediate 'ate' complex making 1,2-metallate rearrangement slow. The insertion of alkenyl carbenoids (derived from **387** and **399**) also showed some shift in selectivity towards the migration of the more electron rich carbon zirconium bond (Table 2-3). This insertion process requires the inversion of an sp^2 centre, which due to higher energy requirements also favours slower 1,2-metallate rearrangement, and therefore the migration of the more electron rich carbon zirconium bond.

Isonitrile insertion into unsymmetrical zirconacyclopentanes is regioselective for the more electron rich carbon zirconium bond (Table 2-3). This may be explained by the formation of complex **452** being a rapidly reversible step. If the complex is less stable

than the starting zirconacycle and relatively short lived, the more energetically favourable 1,2-metallate rearrangement of the electron rich carbon zirconium bond will be favoured over that of the electron poor carbon zirconium bond, affording 6-member zirconacycle **453a**.



Scheme 2-38 Isonitrile insertion into non symmetrical zirconacycles

This chapter examined the behaviour of isonitrile, and alkyl and alkenyl carbenoid insertion into unsymmetrical zirconacycles. The results point towards the rate of 1,2-metallate rearrangement being the determining factor in the regiochemistry observed. Further work may be able to provide evidence for the form of isomerisation that may occur in some cases before rearrangement.

Chapter 3 Cyclopropyl Carbenoid Insertion into Organochlorozirconocenes

This chapter presents the results of an investigation into the synthesis of alkenyl- and alkylidene-cyclopropanes using cyclopropyl carbenoid insertion into organochlorozirconocene complexes.

3.1 Introduction

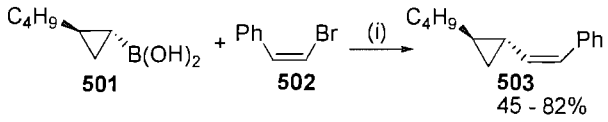
3.1.1 Alkenylcyclopropanes and Alkylidenecyclopropanes

Alkenyl- and alkylidene-cyclopropanes are useful intermediates in organic chemistry as they contain energy stored within their strained structures. They can be made stereoselectively and can be used in variety of different types of chemistry. A few examples of their syntheses are now illustrated.

Synthesis

Methods of synthesising alkenylcyclopropanes include the addition of β-dicarbonyl compounds to *trans*-dihalo but-2-enes[99] and the addition of carbenes to dienes.[100] The synthesis of alkylidenecyclopropanes consists of two main strategies: formation of the cyclopropane ring and formation from preformed cyclopropanes.[101] Formation of the cyclopropane ring can be achieved through carbene (or carbenoid) addition to unsaturated compounds,[102] elimination reactions[103] or in some specific cases rearrangements.[104] Synthesis of alkylidenecyclopropanes from preformed cyclopropanes makes use methods including: elimination reactions,[105] Wittig olefinations[106] and reactions with a double bond shift.[107]

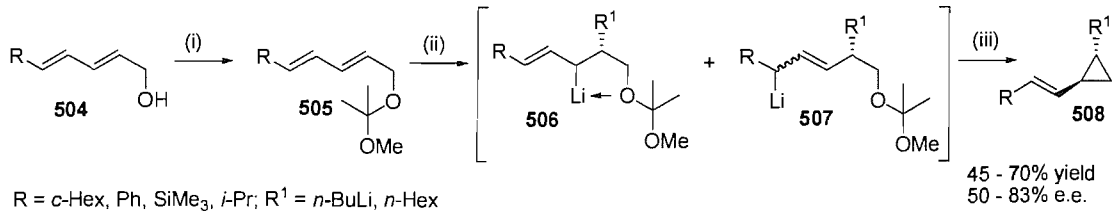
The work discussed in this chapter focuses on 1,2-disubstituted cyclopropyl derivatives. The methodology for synthesis of 1,2-di-alkenylcyclopropanes **503** from the Suzuki coupling[108] of cyclopropyl boronic acids **501** and borate complexes, with alkyl and alkenyl halides **502**, and triflates is a well-established (Scheme 3-1).[109-111]



(i) cat. $Pd(PPh_3)_4$, Ag_2O, KOH.

Scheme 3-1 Synthesis of alkenyl cyclopropanes from boronic acids

In a different approach dienols **504** treated with organolithiums in the presence of (-)-sparteine afford (*E*)- anti disubstituted alkenylcyclopropanes **508** stereoselectively, *via* a 1,3-intramolecular elimination process (Scheme 3-2).[112]

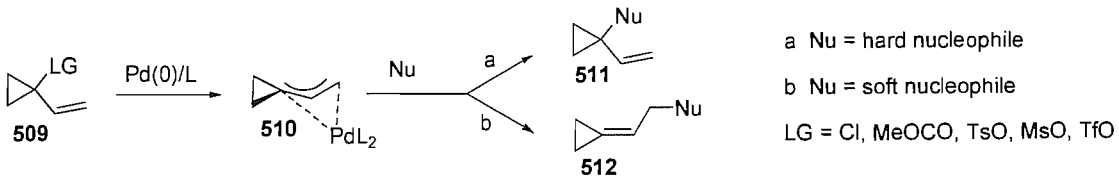


R = *c*-Hex, Ph, $SiMe_3$, *i*-Pr; R^1 = *n*-BuLi, *n*-Hex

(i) $Me_2C(OMe)_2$, 1% $POCl_3$; (ii) R^1Li, 10 mol% (-)-sparteine, -10 °C; (iii) warm to RT

Scheme 3-2 Synthesis of alkenyl cyclopropanes from dieneols

Related work has made use of palladium catalysed chemistry on vinylcyclopropanes **509**, which through intermediate π-allyl palladium complexes **510** have been shown to be a convenient route to alkylidenecyclopropanes **512** (Scheme 3-3).[101] The work discussed in this chapter makes use of preformed cyclopropanes, which after incorporation into vinylzirconocene complexes can be elaborated to alkylidenecyclopropanes.



Scheme 3-3 Synthesis of alkylidenecyclopropanes from vinylcyclopropanes

Novel methodology for the synthesis of alkenylcyclopropanes and alkylidenecyclopropanes are important because they are present in natural products. A review of the biosynthesis and metabolism of cyclopropane rings in natural products contains many examples of alkenylcyclopropanes.[113] Natural products containing alkylidenecyclopropanes are less commonplace than ones that include their alkenyl counterparts. Although other natural products containing alkylidenecyclopropanes

have been isolated[114,115] focus appears to be on the synthesis of naturally occurring amino acids: hypoglycin A **513** and methylenecyclopropylglycine **514** (Figure 3-1).[101] Both exhibit biological activity, the former being responsible for Jamaican vomiting sickness and the latter for hypoglycemia in mice.

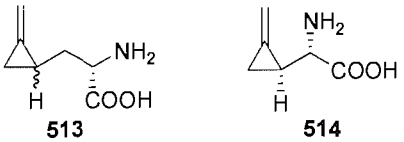
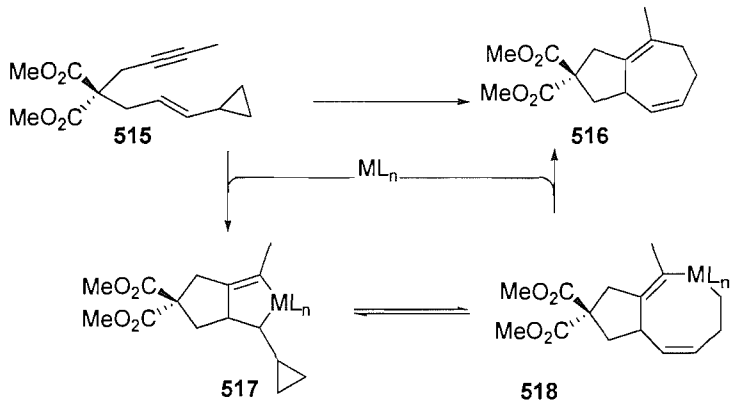


Figure 3-1 Hypoglycin A and methylenecyclopropylglycine – naturally occurring alkylidinecyclopropanes

Useful synthetic intermediates

Alkenylcyclopropanes and alkylidenecyclopropanes are considered useful synthetic intermediates. Not only does their structure hold a lot of strain energy, which can be released though structural rearrangement but in addition they also show good general stability.[116]

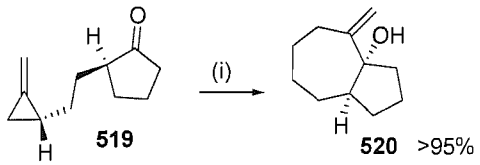
Alkenylcyclopropanes have been widely used in rearrangement reactions. Baldwin has comprehensively reviewed thermal rearrangements of vinylcyclopropanes to cyclopentanes, which have been shown to occur *via* a di-radical mechanism.[117] Alkenylcyclopropanes can also undergo [5+2] cycloadditions resulting in 7-member ring systems. Cycloadditions can occur as thermally driven reactions,[113] or as a result of transition metal catalysis.[118-120] A possible mechanism of such a transition metal mediated cyclisation was provided by Wender *et al* in his work on intramolecular systems (Scheme 3-4).[120]



ML_n = 0.5 mol % $RhCl(PPH_3)_3$, 0.5 mol % AgOTf, 110 °C, 20 min - 83% yield; or ML_n = 10 mol % $RhCl(PPh)_3$, 110 °C, 48 hr - 84% yield

Scheme 3-4 Proposed mechanism for transition metal catalysed [5+2] cycloadditions

Cycloadditions are very typical of alkylidenecyclopropanes.[116,121] Brandi *et al.* has reviewed their part in the formation of heterocycles.[116] Kilburn has shown the Lewis acid mediated cyclisation of silyl-substituted methylene cyclopropyl moieties[122] and the samarium diiodide mediated cyclisation of methylenecyclopropanes (Scheme 3-5)[123] to be efficient processes.



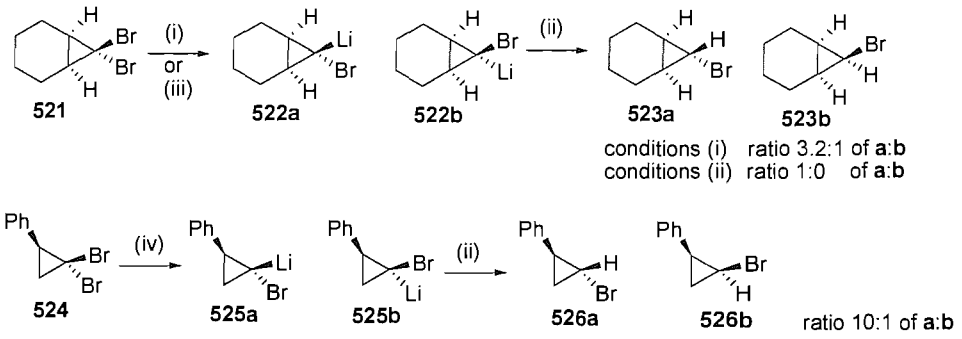
(i) SmI_2, *t*-BuOH, HMPA, THF, 0 °C.

Scheme 3-5 Radical cyclisation of methylenecyclopropane

3.1.2 Cyclopropyl carbenoids

Cyclopropyl carbenoids generated by a single halogen lithium exchange in di-halo species at low temperatures have been the focus of a considerable amount of work due to the selectivity often observed in the process (i.e. Scheme 3-6). Selectivity is influenced by heteroatoms present in the ring system and the difference of stability between the syn and the anti carbenoids.[124] The behaviour observed in these unstable systems is difficult to predict, as the nature of the bonding present is debatable and alkyllithium compounds are known to be oligomeric in solution.[124]

Seyferth *et al.* carried out bromine lithium exchange reactions followed by a protic quench on a series of cyclopropyl dibromides.[125] These experiments revealed the bromine lithium exchange process to be selective for the bromine atom syn to the substituents at the 2-position of the cyclopropane (Scheme 3-6). The carbenoids **522** and **525** highlighted in Scheme 3-6 are used in the work described later in this chapter.

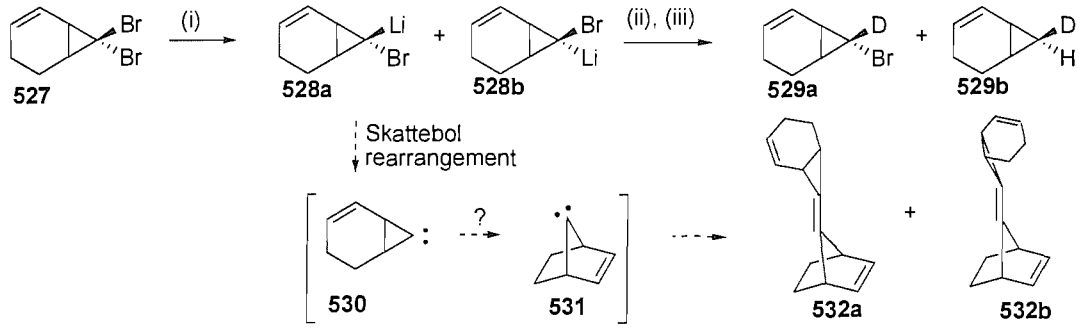


(i) 50 mmol **530**, 56 mmol *n*-BuLi, THF/Diethyl Ether 3:1, -106 °C, 30 min; (ii) HCl aq; (iii) 50 mmol **521**, slight deficiency *n*-BuLi, THF/Ether 3:1, -130 °C to -93 °C, 10 minutes ; (iv) 100 mmol **524**, 106 mmol *n* -BuLi, THF/Ether 3:1, -98 °C, 20 min.

Scheme 3-6 Selective bromine/lithium exchange in substituted di-bromocyclopropanes

The conditions under which bromine lithium exchange is carried out can be altered to achieve completely selective formation of one isomer of the carbenoid (**522a** over **522b**) (Scheme 3-6). Seyferth demonstrated that lithium bromine exchange, with excess dibromide, enables isomerisation of the carbenoid to occur (**522b** to **522a**). The carbenoids studied were not only protonated, as shown in Scheme 3-6, but also trapped with trimethyltin chloride, hexachloroethane and with carbon dioxide followed by acidification.[126]

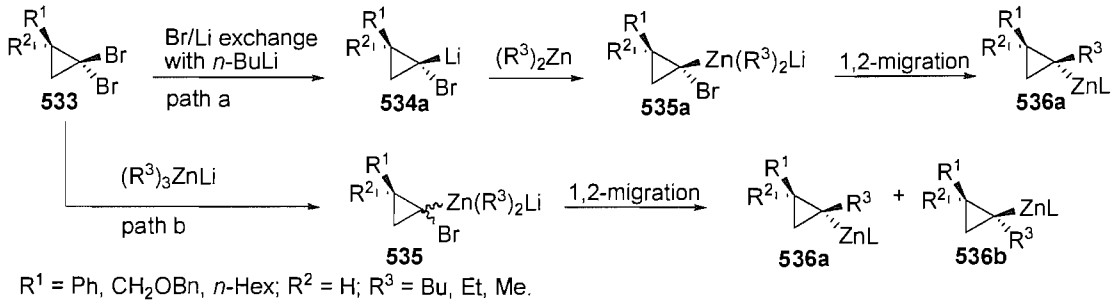
Cyclopropyl carbenoids have also been stereoselectively alkylated and in some systems have been shown to dimerise in the absence of another trap.[127] Unsaturated cyclopropyl carbenoids can also undergo a Skattebol type rearrangement to afford intermediate **531**, which in the example presented in Scheme 3-7 is shown to dimerise affording bicyclic products **532**. [128]



(i) 0.7 eq *n*-BuLi, -100 °C, 5 min; (ii) -78 °C, 5 min; (iii) MeOD, -78 °C to RT.

Scheme 3-7 Dimerisation of carbenoid *via* the Skatebbol rearrangement intermediate

Harada's work on the formation of carbon-carbon bonds *via* 1-halocyclopropyl zincates (**535**) (Scheme 3-8) shows a number of parallels to the work discussed later in this chapter. Cyclopropyl dibromides **533** treated with lithium trialkylzincates react to form zinc carbenoids **535** (path b), which subsequently undergo 1,2-metallate rearrangements to afford alkylated cyclopropyl products **536a** and **536b**.[18]

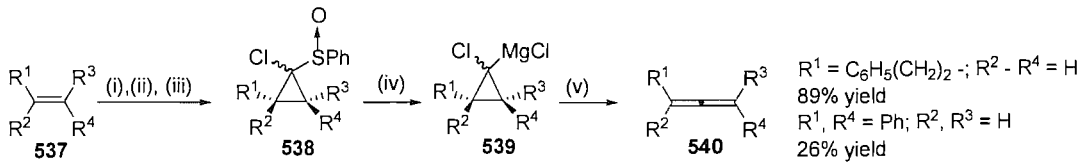


R^1 = Ph, CH_2OBn, *n*-Hex; R^2 = H; R^3 = Bu, Et, Me.

Scheme 3-8 Formation of cyclopropyl zinc carbenoids

Lithium trialkylzincates react with 1,1-dibromocyclopropanes non-specifically. However, if the lithium carbenoid **534a** is initially made stereoselectively (path a), from the respective dibromide **533**, transmetallation of lithium to zinc **535a** retains that stereochemistry and the reaction becomes stereospecific, affording alkylated cyclopropane **536a** (Scheme 3-8).[18] Starting with the appropriate 1-bromo-1-chlorocyclopropane, and taking advantage of faster bromine than chlorine lithium exchange, products with the opposite stereochemistry can also be isolated.[129] The zincate moiety in **536** which is retained in the molecule after the 1,2-rearrangement and can be used in palladium coupling reactions.[129]

Metals including manganese, copper and magnesium have also been incorporated into cyclopropyl carbenoids. Both dialkylcuprates[130] and trialkylmanganates[131] generate carbenoids on reaction with 1,1-dihalocyclopropanes. These then undergo 1,2-metallate rearrangements. However, the overall reaction does not occur with complete selectivity with either metal. The manganate reagent does however, have the advantage of being made and used at 0 °C, whilst the cuprates are unstable at this temperature. Satoh *et al.*[132] developed a route to generate magnesium carbenoids **539** from chlorocyclopropyl phenyl sulphoxides **538** and Grignard reagents. The route lends itself to the synthesis of allenes **540** from olefins **537** (Scheme 3-9).



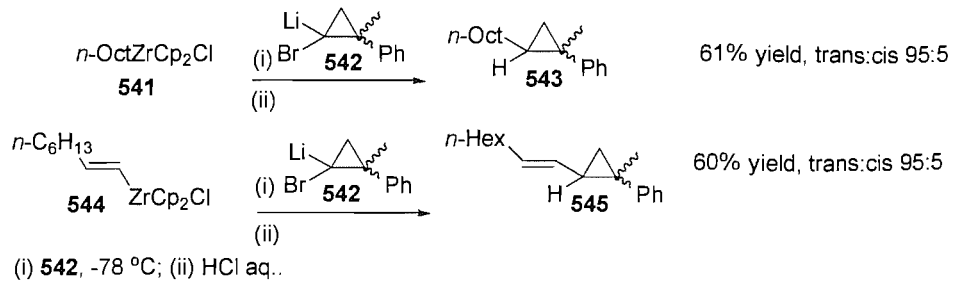
(i) $PhSCH_2Cl$, NaOH aq, benzyltriethylammonium chloride, CH_2Cl_2, RT, 24 hr; (ii) NCS, CCl_4, RT, 20 hr; (iii) mCPBA, -50 to -30 °C, 1.5 hr; (iv) RMgCl, -60 °C, several hours; (v) warming to RT.

Scheme 3-9 Generation of cyclopropyl magnesium carbenoids

In summary, a great deal is known about cyclopropyl carbenoids as they have been studied for many years. Transmetallation and 1,2-metallate rearrangement processes, which are key to the chemistry discussed in this chapter, have previously been observed in a range of cyclopropyl carbenoids.

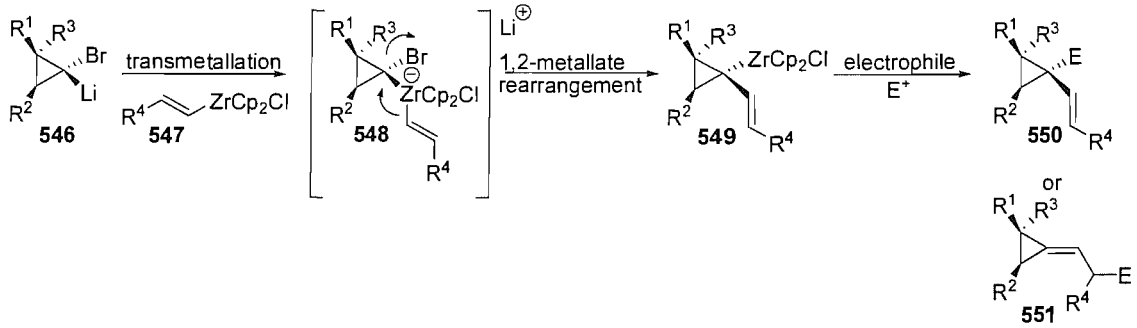
3.1.3 Cyclopropyl Carbenoid Insertion into Organochlorozirconocene Complexes

Negishi *et al* made the first report of cyclopropyl carbenoid **542** insertion into an organochlorozirconocene complexes **541** and **544** (Scheme 3-10).[33] Two examples, which resulted in the isolation of vinylcyclopropane **543** and alkenylcyclopropane **545**, were highlighted as methods for making carbon-carbon bonds utilising migratory insertion chemistry.



Scheme 3-10 First examples of cyclopropyl carbenoid insertion organochlorozirconocene complexes

Previous work within our group showed cyclopropyl carbenoids **546** to insert into organochlorozirconocene complexes **547** (Scheme 3-11).[133] The mechanism was thought to be a two-step process. Firstly the carbenoid **546** and the metal complex **547** formed a 'ate' complex **548** with retention of configuration with respect to lithium. This was followed by a 1,2-metallate rearrangement, with inversion of configuration, which resulted in organozirconocene complex **549**. Quenching with an electrophile could result in the isolation of an alkenyl- **550** or alkylidene-cyclopropane **551**.



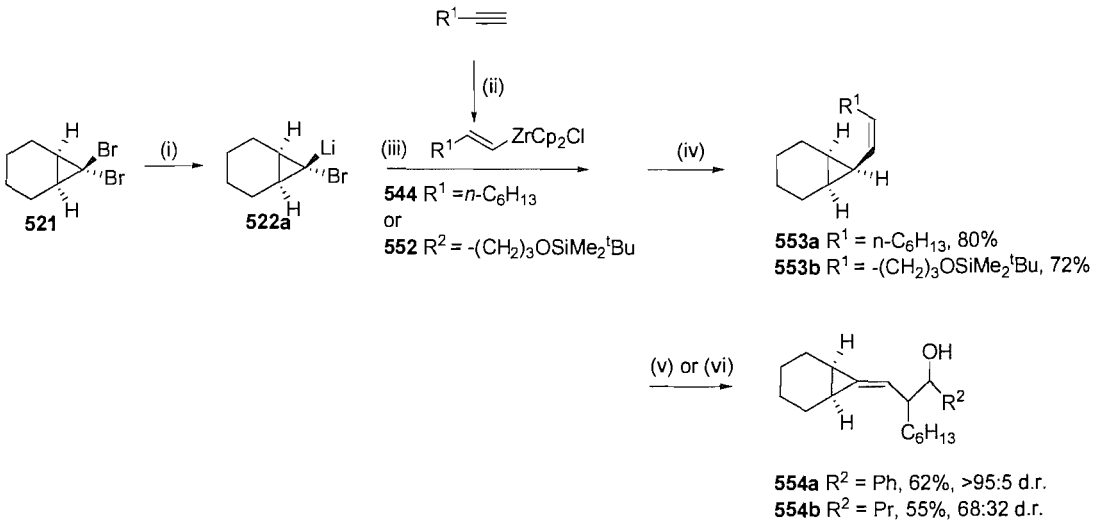
Scheme 3-11 Proposed mechanism for cyclopropyl carbenoid insertion into organochlorozirconocene complexes

3.2 Results and Discussion

The results discussed in the remainder of this chapter have been divided into four areas. Firstly the mechanism of insertion of the 7-bromo-7-lithiobicyclo[4.1.0]heptane carbenoid into organochlorozirconocenes is addressed. This is followed by a very closely related discussion of the behaviour of other cyclopropyl carbenoids. The third section focuses on carbenoids generated *via* deprotonation and the last on the synthesis of di-alkenyl cyclopropanes.

3.2.1 7-Bromo-7-lithio[4.1.0]heptane Carbenoid

Previous work carried out within the group, by Kasatkin,[133] showed the insertion of cyclopropyl carbenoid **522** into organochlorozirconocene **544** and **552** to have resulted in the alkenylcyclopropanes **553a** and **553b**, when quenched with methanol and sat. $NaHCO_3$ solution; and alkylidenecyclopropanes **554a** and **554b**, when quenched with an aldehyde and Lewis acid (Scheme 3-12).[133]



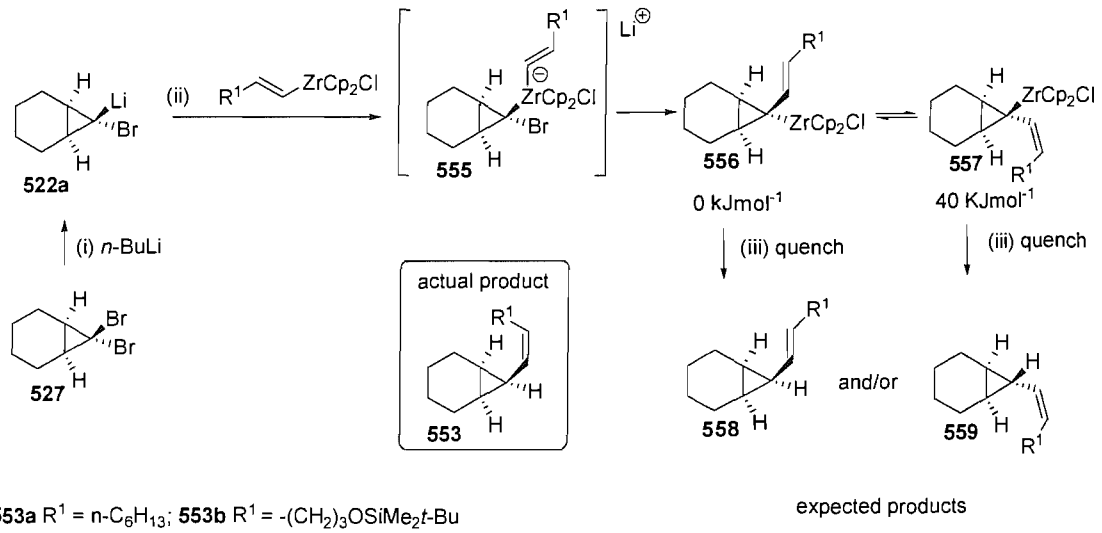
(i) < 1.0 eq *n*-BuLi, -90 °C, 30 min; (ii) 1.0 eq Cp_2ZrHCl, RT, 30 min; (iii) 1.0 eq **544/552**, -90 to -60 °C, 2 hr;
(iv) MeOH, sat. $NaHCO_3$ aq., RT; (v) 1.5 eq $PhCHO/BF_3.Et_2O$, -60 °C to RT, 16 hr at RT;
(vi) 1.5 eq $PrCHO/BF_3.Et_2O$, -60 °C to RT, 16 hr at RT.

Scheme 3-12 Alkylidene or alkenylcyclopropanes from 7-bromo-7-lithio[4.1.0]heptane carbenoid

Synthesis of Alkenylcyclopropane 553 from 7-Bromo-7-lithio[4.1.0]heptane

Although the endo stereochemistry of the $CH=CHR^1$ substituent in **553** was expected from the inversion of configuration on 1,2-metallate rearrangement, the (Z)-stereochemistry of the alkene was not (Scheme 3-12); however, the origin of this anomaly was not investigated at the time.[133] In the predicted mechanism (Scheme 3-13) a single isomer **522a** of 7-bromo-1-lithio[4.1.0]heptane is expected to result from carbenoid formation reaction.[125] This is then incorporated into the 'ate' complex **555** with retention of configuration and undergoes 1,2-metallate rearrangement with inversion of configuration to afford zirconocene species **556**. Isomerisation of the zirconocene species **556** to the (Z)-alkene **557** is possible via 1,3-metal migration, rotation about the carbon-carbon single bond, then reversal of the 1,3-migration, but

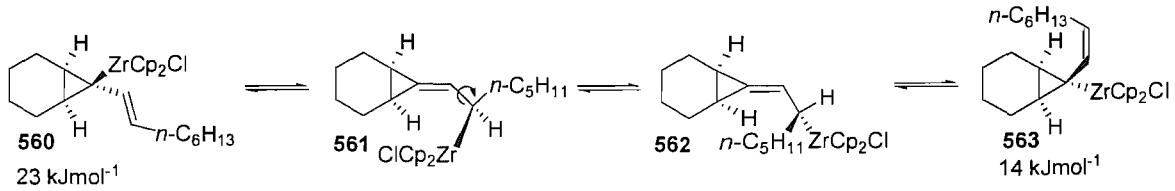
this must be accompanied by a move to the exo face (DFT relative energy calculations indicate isomerisation is energetically unfavourable in this case).



Scheme 3-13 Expected mechanism for formation of alkenylcyclopropanes

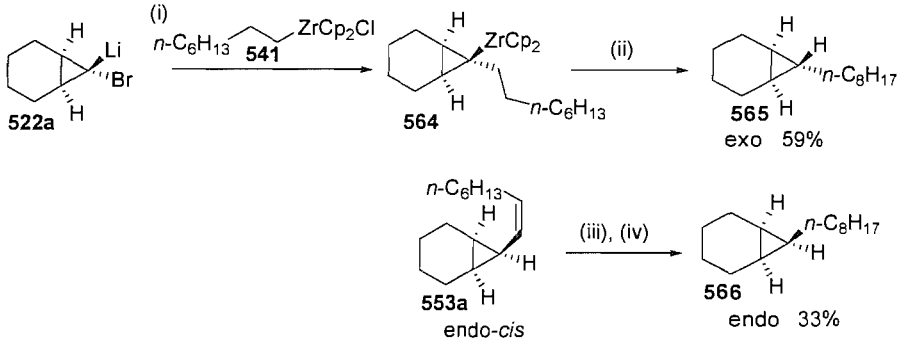
As the observed alkenylcyclopropane product **553** was different to either of those predicted in the expected mechanism, (**558** and/or **559**) (Scheme 3-13) the mechanism was revised through further investigations. Two issues were addressed in this revision: the mechanism for the change of double bond geometry and the relative stereochemistry about the cyclopropane ring. The implication is that the observed (Z)-endo-product **553** must be derived by isomerisation from the (E)-alkene-endo-organozirconium species **560** (Scheme 3-14).

The isomerisation from the (*E*) to the (*Z*) double bond geometry observed in alkenylcyclopropane **553** can be rationalised using the stability of the intermediate zirconocene species **560** and **563** (Scheme 3-14) (DFT relative energy calculations indicate isomerisation is favourable in this case). Due to its steric bulk the zirconocene moiety is more stable in the exo position **563.**



Scheme 3-14 Proposed mechanism for isomerisation from *trans* to *cis* alkenylcyclopropane

Evidence to support the explanation for isomerisation of the double bond came from carbenoid insertion into a chlorozirconocenealkane complex **541** (Scheme 3-15). The resulting cyclopropyl alkane complex **564** cannot isomerise *via* the same mechanism as the cyclopropyl alkene complex **560** (Scheme 3-14). Exo-cyclopropane product **565** was therefore expected, and subsequently isolated. The stereochemistry was crosschecked by reduction of alkenylcyclopropane **553a** which afforded cyclopropane **566**.[134,129]

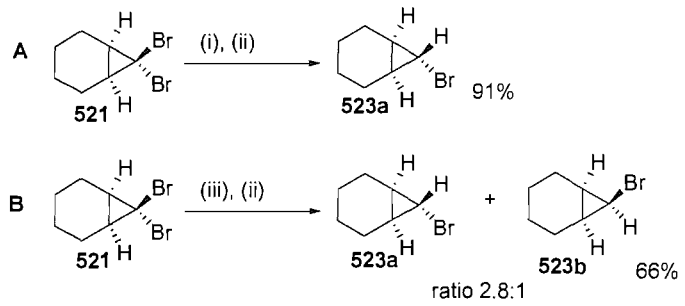


(i) 0.81 eq **541**, -95 to -60 °C, 1 hr; (ii) MeOH, sat. $NaHCO_3$ aq., RT, 16 hr; (iii) 10.0 eq TsNNH, DME, reflux; (iv) 20 eq NaAc aq., addition over 3.5 hr at reflux.

Scheme 3-15 Evidence to support isomerisation mechanism

The investigation into the isomerisation of the double bond highlighted the fact that intermediate endo zirconocene species **560** has the opposite relative stereochemistry about the cyclopropane than would be predicted from the expected mechanism (Scheme 3-13 and Scheme 3-14). Carbenoid **522a** insertion into the organozirconocene complex **544/552** appears to proceed with overall retention of configuration from the carbenoid. This was not anticipated as transmetallation was thought to occur with retention of configuration and 1,2-metallate rearrangement was thought to occur with inversion of configuration (Section 3.1.2 and 3.1.3).

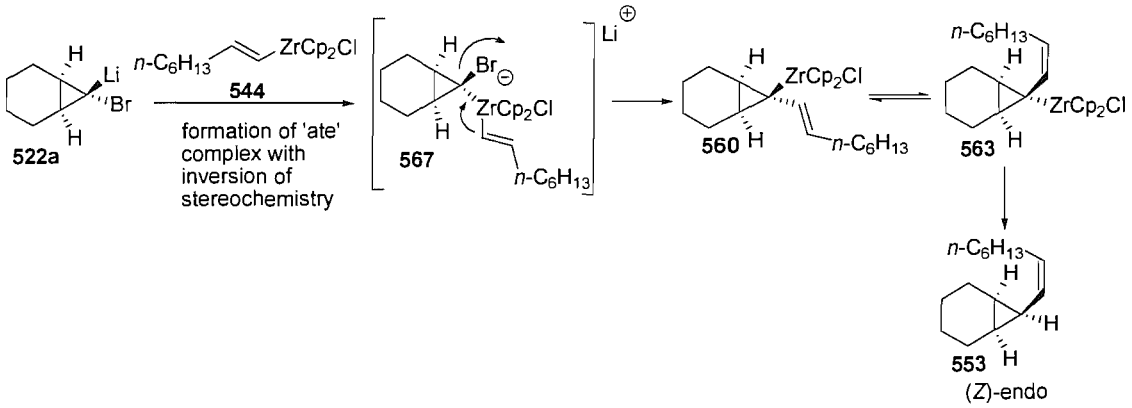
In order to investigate this observation the relative stereochemistry of the carbenoid **522** was confirmed as **522a** through isolation of monobromide **523a** (Scheme 3-16). It had been hoped that a mixture of the two isomers **522** could have been made and subsequently used in the insertion reaction (Scheme 3-16-B). Unfortunately this was not possible as reaction with the organochlorozirconocene complex **544a** did not proceed at –108 °C, and carbenoid **523b** was not stable at higher temperatures.



(i) 0.91 eq *n*-BuLi, -108 to -93 °C over 15 min, -93 °C, 10 min ; (ii) H_2O, RT; (iii) 1.12 eq *n*-BuLi, 108 °C, 30 min.

Scheme 3-16 Investigation into stereochemistry of carbenoid

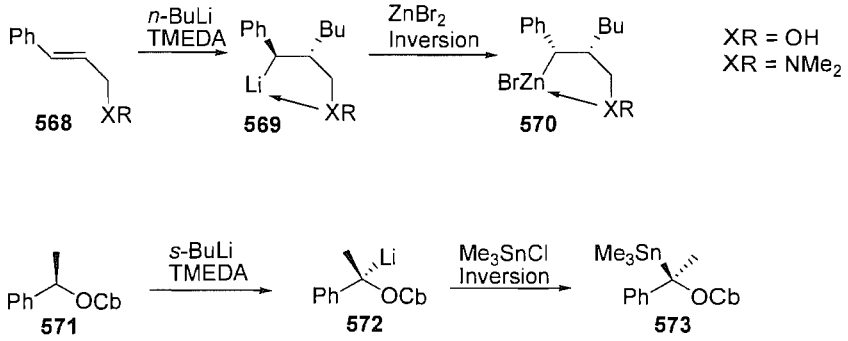
There are two possible explanations for the retention in configuration observed in the reaction towards alkenylcyclopropane **553**. Insertion of the minor carbenoid isomer **522b** into the organochlorozirconocene could be favoured over the insertion of the major carbenoid isomer **522a** as the lithium is on the more accessible exo face. So if **522a** and **522b** were interconverting faster than trapping by zirconium, then **560** could form preferentially. Alternatively, lithium/zirconium transmetallation in the formation of the 'ate' complex **567** could occur with inversion of configuration (Scheme 3-17) to afford **560**. This appears to be the more likely explanation, as it is unlikely that interconversion of **522a** and **522b** would be fast enough.



Scheme 3-17 Mechanism for carbenoid insertion with overall retention of configuration

If the formation of the 'ate' complex **567** occurred with inversion, followed by a second inversion with the 1,2-metallate rearrangement, overall retention of configuration would be observed resulting in complex **560** (Scheme 3-17). Subsequent isomerisation of the double bond to **563** *via* 1,3-shift and exo/endo exchange satisfies the observation of the (*Z*)-endo alkenylcyclopropane **553**, as the isolated product.

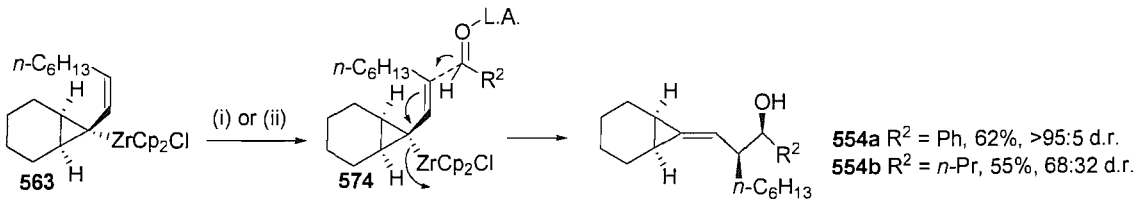
Though transmetallation is generally considered to result in retention of configuration (Section 3.1.2). There has been some precedent for transmetallation occurring with inversion of stereochemistry (Scheme 3-18). In work carried out on the configurational stability of benzylic organozinc halides **570**, the transmetallation of lithium to zinc (**569** to **570**) was shown to occur with inversion of stereochemistry.[135] Transmetallation with inversion of stereochemistry was also observed when a tertiary lithium intermediate **572** derived from a benzyl carbamate **571** was reacted with chlorotrimethylstannane resulting in stannane **573**.[136]



Scheme 3-18 Precedent for transmetallation with inversion of configuration

Synthesis of alkylidenecyclopropane 554 from 7-Bromo-7-lithio[4.1.0]heptane

The relative stereochemistry of alkylidene cyclopropane **554** was not investigated by Kasatkin.[133] The prediction is that the substituents should be in a syn arrangement assuming an open transition state **574** for the aldehyde addition to the organochlorozirconocene complex **554** (Scheme 3-19).

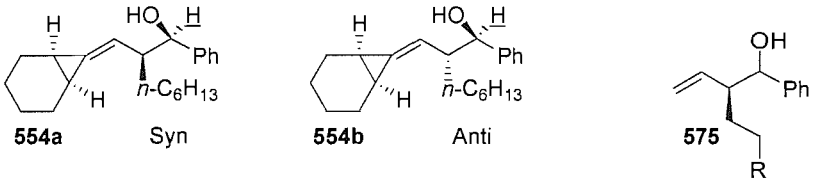


(i) 1.5 eq $PhCHO/BF_3.Et_2O$, -60 °C to RT, 16 hr at RT; (ii) 1.5 eq n-$PrCHO/BF_3.Et_2O$, -60 °C to RT, 16 hr at RT.

Scheme 3-19 Mechanism for formation of alkylidene cyclopropane

NMR data from the literature provides some limited evidence to support the assignment of the major isomer of alkylidenecyclopropane **554** as syn. The proton α- to the hydroxy group in **554** displays a characteristic doublet splitting pattern, similar

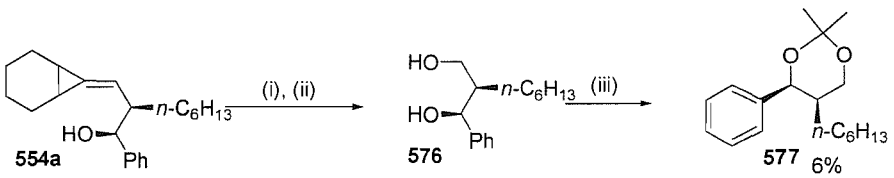
to that found in other unsaturated alcohols **575**.[137,66,138-141] Review of the literature suggested that the syn isomers of **575** have a chemical shift 0.2 ppm higher in ^{1}H NMR (4.6 rather than 4.4) and has a lower coupling constant (5-6 Hz rather than 7-8 Hz) than the anti isomers. However, as the shifts and couplings for the proton α- to the hydroxy group in **554** do not fall into these non-overlapping categories no firm conclusions can be drawn.



ratio >95:5
syn (?) major H δ = 4.65 ppm, d, *J* = 6.6 Hz
anti (?) minor H δ = 4.52 ppm, d, *J* = 7.7 Hz

Figure 3-2 Relative stereochemistry of alkylidenecyclopropane

Independent confirmation of the relative stereochemistry of **554** was sought through synthesis of acetal **577**, derived from alkylidenecyclopropane **554**. The requisite diol **576** was originally going to synthesised through ozonolysis of alkylidenecyclopropane **554**. Unfortunately it was found that ozonolysis of alkylidenecyclopropanes is not possible.[142] Treatment of alkylidenecyclopropanes with ozone causes the ring opening of the cyclopropane through a number of proposed pathways resulting in a complex mixture of products. An alternative method consisted of a Lemieux cleavage of the double bond in **554**, reduction of the resulting aldehyde using $NaBH_4$ and formation of the acetal **577** from the resulting 1,3-diol **576**.



(i) 0.5 eq OsO_4, 50.0 eq $NaIO_4$, H_2O, MeCN, pH 7 - buffer; RT, 3 hr; (ii) 4.0 eq, $NaBH_4$, MeOH, 0 °C, then RT 16 hr; (iii) $(CH_3)_2C(OCH_3)_2$, PPTS, benzene, RT, 16 hr.

Scheme 3-20 Formation of acetal – for determination of relative stereochemistry

Precedent was not found for oxidative cleavage of methylene cyclopropane. However, it was found for the oxidative cleavage of β,γ-unsaturated alcohol in a different system. It is not a facile process and requires stoichiometric OsO_4.[143] This procedure

was followed and resulted in the isolation of the 1,3-diol **576** in 11% yield. The subsequent formation of the acetal using 2,2-dimethoxypropane resulted in an overall yield of the acetal **577** of 6% (Scheme 3-20). As alternatives the alkylidenecyclopropane **554** was submitted to standard Lemieux conditions[144] and simple Sharpless asymmetric dihydroxylation [145] conditions; however, no reaction was observed.

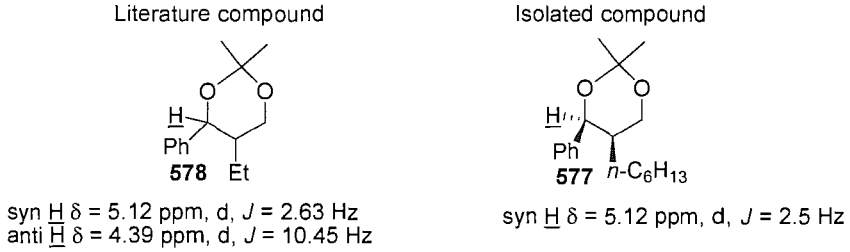
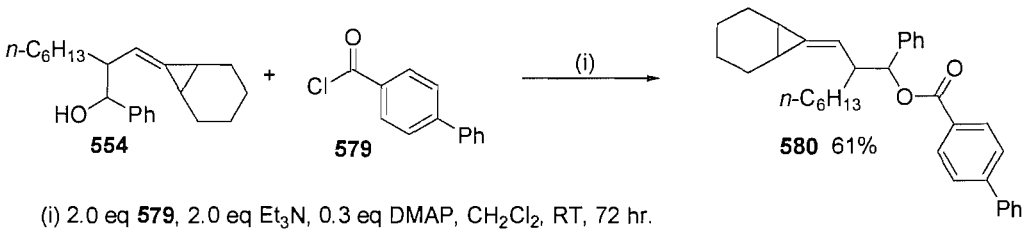


Figure 3-3 Acetal isolated from alkylidenecyclopropane 554 and reference literature compound

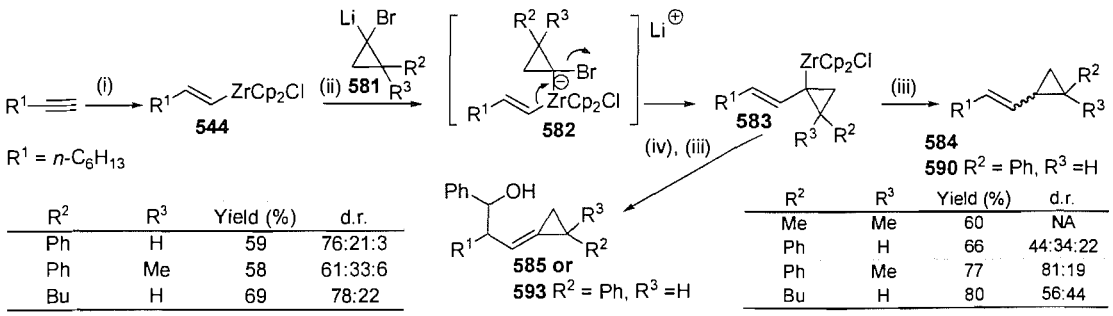
Comparison between the acetal **574** and a very similar acetal **575** found in the literature[146] indicates that the two chiral centres in the acetal are in a syn relationship to one another. This stereochemical relationship translates back to the starting alkylidenecyclopropane **554a**. However, due to low yield (the mass balance was not accounted for), it can only still tentatively be assigned as syn **554a**. Further evidence was sought regarding the overall stereochemistry of the product by derivitisation of the hydroxy group in alkylidenecyclopropane **554a**, unfortunately ester **580** was isolated as an oil (Scheme 3-21).



Scheme 3-21 Derivitisation of alkylidenecyclopropane

3.2.2 Other Cyclopropyl Carbenoids

Work carried out by Kasatkin[133] provided interesting results regarding the insertion of other cyclopropyl carbenoids **581** into organochlorozirconocene **544** (Scheme 3-22).



R^2	R^3	Yield (%)	d.r.
Ph	H	59	76:21:3
Ph	Me	58	61:33:6
Bu	H	69	78:22

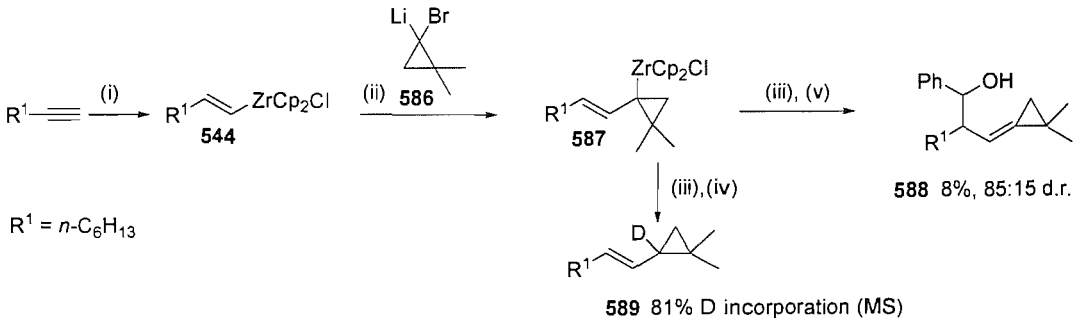
R^2	R^3	Yield (%)	d.r.
Me	Me	60	NA
Ph	H	66	44:34:22
Ph	Me	77	81:19
Bu	H	80	56:44

(i) 1.0 eq Cp_2ZrHCl, RT, 30 min; (ii) 1.5 eq **581**, -90 to -60 °C, 2 hr; (iii) MeOH, sat. $NaHCO_3$ aq., RT, 16 hr; (iv) 1.5 eq PhCHO, $BF_3.Et_2O$, -60 °C to RT, then RT 16 hr.

Scheme 3-22 Previous results from cyclopropyl carbenoid insertion

1-Bromo-1-lithio-2,2-dimethyl Cyclopropane Carbenoid

Kasatkin[133] did not isolate the alkylidenecyclopropane, in the **585** series, where R^2 and R^3 were both methyl groups **588**. Isolation **588** (Scheme 3-22) was achieved in consistently low yields (7 and 8%). The first steps, hydrozirconation of 1-octyne and insertion of the cyclopropyl carbenoid **586**, were found to work well.



(i) 1.0 eq Cp_2ZrHCl, RT, 1 hr; (ii) 1.1 eq **586**, -90 °C to -40 °C, 4hr; (iii) 1.3 eq PhCHO, $BF_3.Et_2O$, -70 °C to RT, 16 hr; (iv) D_2O, RT, 16 hr; (v) MeOH, sat. $NaHCO_3$ aq, RT, 24 hr.

Scheme 3-23 Synthesis of alkylidenecyclopropane 588

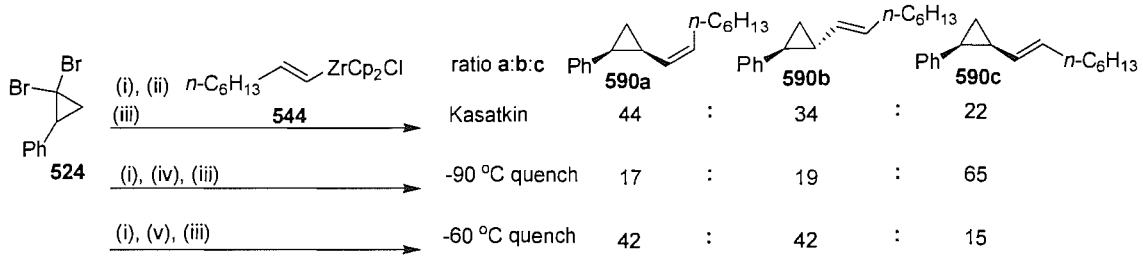
Having established that the electrophilic quench of the zirconocene species **587** with benzaldehyde was the low yielding step, attempts were made at optimisation. The first check showed the active organometallic **583** was still present *via* a deuterium oxide quench affording alkenylcyclopropane **589** (Scheme 3-23).

It was therefore proposed that the zirconocene species **583** might be coordinating to the Lewis acid preventing it from being effective in activating the aldehyde. However, addition of two equivalents of boron trifluoride-diethyl-etherate, test reactions with

alternative Lewis acids (magnesium triflate, zinc chloride and titanium tetrachloride) and longer reaction times did not result in any improvement in yield. A possible explanation for the low-yielding nature of the reaction in Scheme 3-23 is steric encumbrance.

1-Bromo-1-lithio-2-phenylcyclopropane carbenoid

As part of the review of Kasatkin's work[133] it was decided that the behaviour of 1-bromo-1-lithio-2-phenyl cyclopropyl carbenoid **525**, which is derived from cyclopropyl dibromide **524** (Scheme 3-6), warranted more investigation. Previously insertion into the organochlorozirconocene **544** resulted in the isolation of 1-(2-(oct-1-enyl)cyclopropyl)benzene **590** as a mixture of three isomers in a ratio of 44:34:24 (Scheme 3-22). A better understanding of the reaction was subsequently gained by the determination of the ratio of carbenoid isomers present at the time of the reaction and by quenching the reaction at different temperatures. With reaction quenched at –90 °C (Scheme 3-24) poor conversion of starting moieties to product **590** was observed (1-octene was still present), whereas the reaction quenched at –60 °C displayed good conversion (no 1-octyne was present). The samples of **590** were analysed as mixtures with residual mono- and di-bromides **524** and **526** therefore the yields were not obtained.

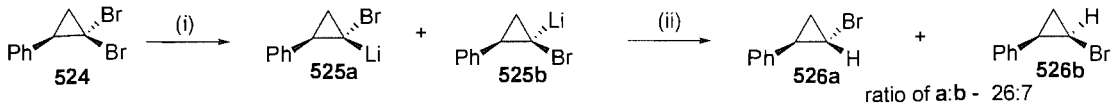


(i) 1.0 eq *n*-BuLi, -95 to -90 °C; (ii) 1.0 eq **544**, - 90 to -60 °C, 3 hr; (iii) MeOH, sat. $NaHCO_3$ aq, RT, 16 hr; (iv)1.0 eq **544**, - 90 °C, 10 min; (v)1.0 eq **544**, -90 to -60 °C, 1 hr.

Scheme 3-24 Reaction to afford alkenylcyclopropane 590 quenched at different temperatures

Carbenoid **525** was quenched with water at –90 °C (Scheme 3-25). In accordance with precedent[125] bromine syn to the 2-substituent was shown to have preferentially undergone bromine lithium exchange. The mono bromide **526** was recovered as a mixture of isomers **a**:**b** in an 85% yield in the ratio of 26:7. The two isomers were

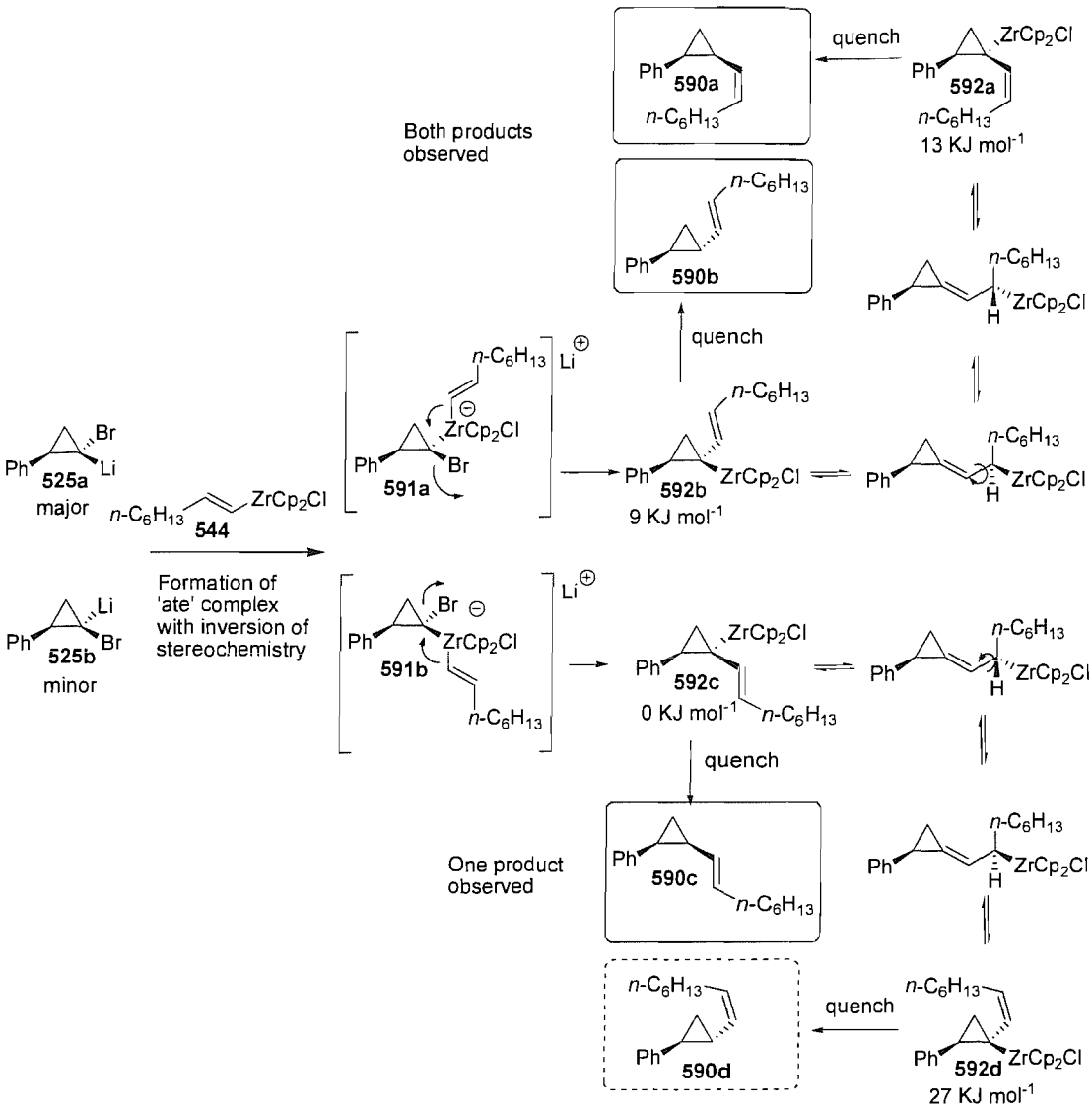
identified using ^{1}H and ^{13}C NMR data compared with literature data for 2 compounds.[147-149]



(i) 1.0 eq *n*-BuLi, -95 °C to -90 °C over 15 min, -90 °C 10 min; (ii) H_2O, -90 °C to RT.

Scheme 3-25 Ratio of isomers from the 1-bromo-1-lithio-2-phenylcyclopropane carbenoid

The information provided by quenching the reaction at different temperatures (Scheme 3-24) and the ratio of carbenoid isomers present at the time of reaction (Scheme 3-25) provided the basis to explain the isolation of three isomers of alkenylcyclopropane product **590 a-c**.

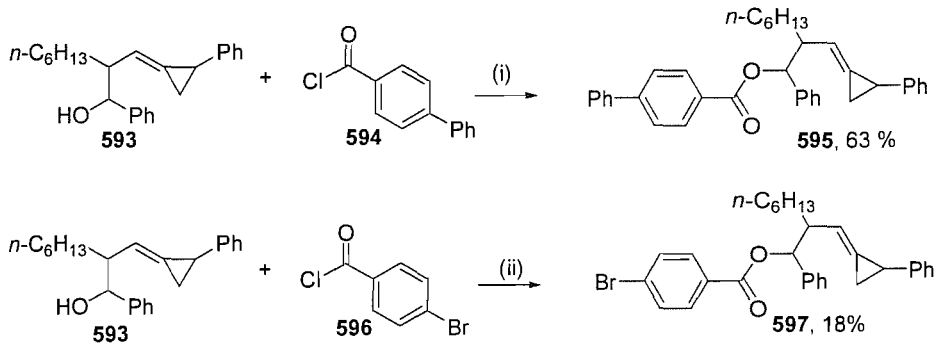


Scheme 3-26 Proposed mechanism for 1-bromo-1-lithio-2-phenylcyclopropane carbenoid insertion into organochlorozirconocene complex

Information from DFT calculations and the ratio of carbenoid isomers **525** present at the start of the reaction were used to propose a mechanism for the formation of alkenylcyclopropanes **590a-c** (Scheme 3-26). Minor carbenoid isomer **525b** was responsible for the formation of the minor alkenylcyclopropane **590c**. This was formed quickly (high concentrations in reaction quenched at –90 °C). The zirconocene intermediate **592c** did not isomerise to form the (*Z*)- anti alkenylcyclopropane **592d** due to unfavourable energies. Major carbenoid isomer **525a** was responsible for the formation of alkenylcyclopropanes **590a** and **590b**. These were formed more slowly than **590c** (present in small amounts in reaction quenched at –90 °C). Intermediate **592b** is in equilibrium with complex **592a**, due to

the small energy difference between them (within the error bounds for these DFT calculations). Hence, due to equilibriation, products **590a** and **590b** are observed in a 1:1 ratio (reaction quenched at –60 °C) (Scheme 3-24).

Kasatkin (Scheme 3-22) previously synthesised alkylidenecyclopropane **593**.[133] However, more information was sought regarding the stereochemistry of the major adduct. The reaction was repeated as part of this work and resulted in the isolation of the alkylidenecyclopropane **593** in 73% yield as a mixture of two isomers in a ratio of approximately 1:1 (different ratio accounted for by longer exposure to aldehyde and Lewis acid). The isomer, isolated as the major product by Kasatkin was derivitised by reaction with acid chlorides **594** and **596**, and the products unfortunately isolated as oils **595** and **597** (Scheme 3-27).



(i) 2.0 eq **594**, 2.0 eq Et_3N, 0.3 eq DMAP in CH_2Cl_2, RT, 72 hr; (ii) 2.0 eq **596**, 0.3 eq DMAP in pyridine, RT, 96 hr.

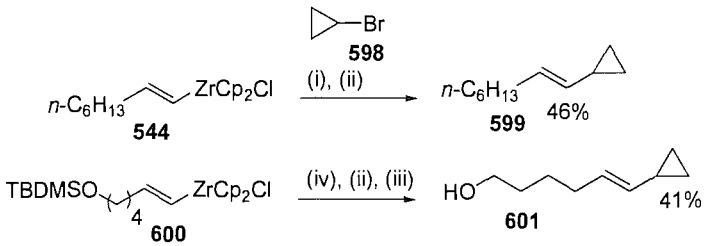
Scheme 3-27 Derivitisation of alkylidenecyclopropane

The study of carbenoid **525** has shown that its insertion into organochlorozirconocenes either occurs preferentially into the carbenoid's minor isomer **525b** or that initial transmetallation of lithium to zirconium is occurring with inversion of configuration (as is depicted in Scheme 3-26).

3.2.3 Cyclopropyl Carbenoids Generated *via* Deprotonation

In-situ carbenoid generation *via* deprotonation would simplify the procedure for the synthesis of alkenylcyclopropanes and alkylidenecyclopropanes, whilst making use of the methodology discussed previously in this chapter. The first step was to try out the idea using a simple cyclopropyl bromide. Cyclopropyl bromide **598** is commercially available and proved to be a suitable cyclopropyl carbenoid precursor (Scheme 3-28).

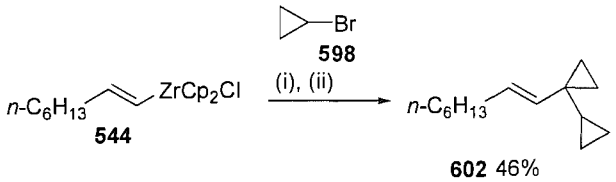
The carbenoid was generated *in-situ via* deprotonation using LiTMP. Insertion into organochlorozirconocenes **544** and **600** was facile and afforded of alkenylcyclopropanes **599** and **601** in moderate yield.



(i) 2.0 eq **598** and LiTMP, -90 °C, 10 min; (ii) MeOH, $NaHCO_3$ aq, RT, 16 hr; (iii) 2.0 eq TBAF, RT, 18 hr; (iv) 2.0 eq **598** and LiTMP, -90 °C, 15 min.

Scheme 3-28 Cyclopropyl carbenoid insertion into zirconocene alkenes.

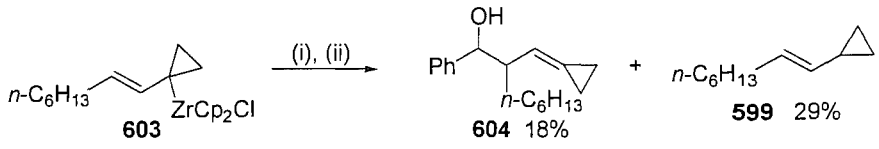
The moderate yields observed for these reactions (Scheme 3-28) were due to problems with double carbenoid insertion into the organochlorozirconocenes **544** and **600**. Conditions which would have favoured a higher conversion of **544** into **599**, (e.g. higher concentrations of the carbenoid and higher reaction temperatures), unfortunately also favoured the formation of the double insertion product **602**.



(i) 4.0 eq **598** and LiTMP, -40 to -30 °C; (ii) MeOH, $NaHCO_3$ aq.

Scheme 3-29 Formation of bis inserted product

Further elaboration of the allyl zirconium system **603** using a benzaldehyde/Lewis acid quench was shown to be possible and resulted in the isolation of alkylidenecyclopropane **604** (Scheme 3-30). Due to the consistently disappointing yields it was not further investigated.



(i) 1.5 eq PhCHO and $BF_3.Et_2O$, -90 °C to RT, 8 hr then RT for 14 hr; (ii) MeOH, sat. $NaHCO_3$ aq, RT, 6 hr.

Scheme 3-30 Elaboration of allyl zirconocene intermediate

Having established that cyclopropyl carbenoids generated *in-situ* successfully inserted into organochlorozirconocenes (**544**, **600**), a method to introduce diversity within the carbenoid was sought. Ethers such as carbamates have been used in the past to generate carbenoids *via* deprotonation.[79] Tosylate was also considered to be a good leaving group and a suitable carbenoid precursor, unfortunately cyclopropyl tosylate **605** was found not to be useful as a carbenoid precursor, as it did not deprotonate in the presence of LiTMP (Figure 3-4). Carbamate **606** could not be made despite some precedent. [150,151]

605 **606**

did not generate carbenoid

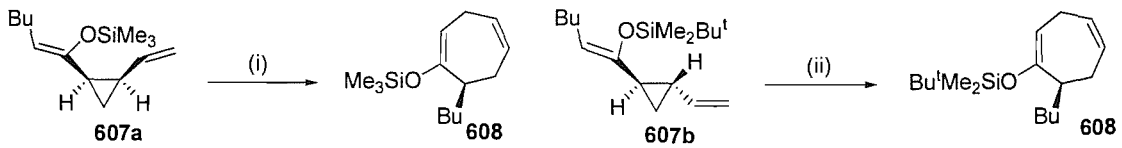
not made

Figure 3-4 Unsuccessful precursors to cyclopropyl carbenoids

The difficulties encountered in synthesising cyclopropanes **605** and **606** (Figure 3-4), outweighed the potential benefits though their ease of use and were therefore not pursued further.

3.2.4 Synthesis of di-alkenyl cyclopropanes

The synthesis of 1,2-di-alkenylcyclopropanes, from alkenyl cyclopropane carbenoids and organochlorozirconocene complexes was considered as an application of the methodology discussed previously. Di-alkenylcyclopropanes are interesting targets as they have been shown to undergo thermal [5+2] cycloadditions resulting in cycloheptadienes. Singh *et al* have shown both syn and anti di-alkenyl cyclopropanes **607a-b** to cyclise to cycloheptadiene **608** under thermal conditions (Scheme 3-31).[152]



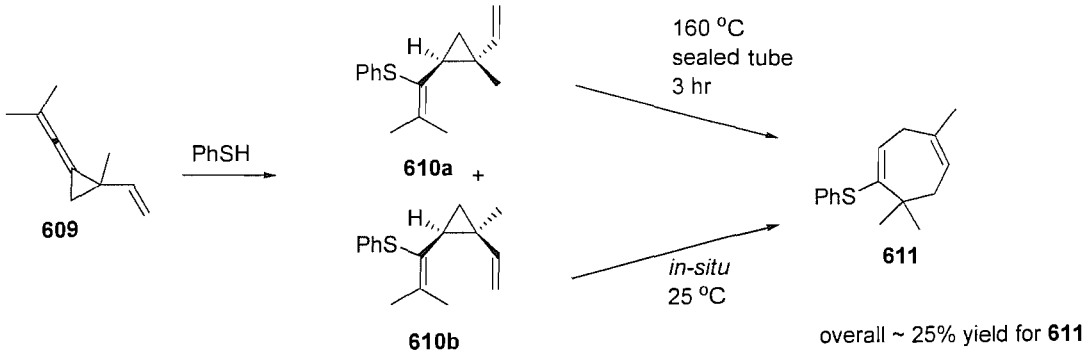
607a **608** **607b** **608**

(i) 100 -110 °C, neat, 30 min; (ii) 230 °C, neat, 30 - 60 min.

Scheme 3-31 Precedent for cyclisation of di-alkenyl cyclopropanes

Work by Cairns *et al.* described the cyclisation of divinysulfides to gain cycloheptadiene **611**.[153] The syn isomer of the di-alkenylsulfide **610b** underwent

Cope rearrangement instantaneously at room temperature to afford cycloheptadiene **611**. The mixture of **611** and **610a** were separated by chromatography. The anti isomer **610a** had to be heated in a sealed tube to undergo cyclisation (Scheme 3-32). Similar kinds of cycloaddition have also been achieved using transition metal catalysis (Section 3.1.1).

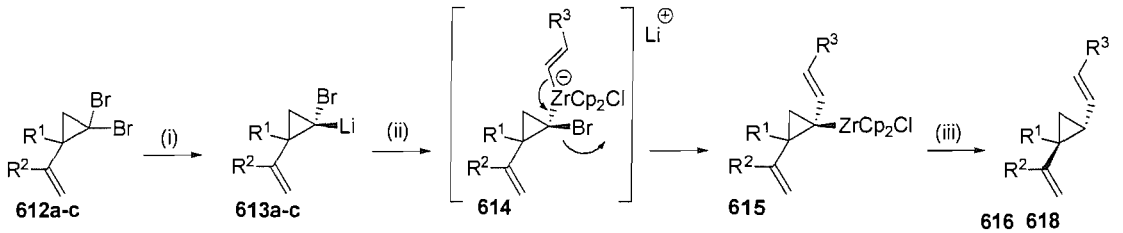


Scheme 3-32 Precedent for cyclisation of di-alkenylcyclopropanes

Di-bromo vinylcyclopropanes **613 a-c** (carbenoid starting materials) were synthesised from commercially available dienes.[100] It had been anticipated that syn di-alkenylcyclopropanes would result from vinyl carbenoid insertion into organochlorozirconocene complexes. However, results obtained since, and discussed in previous sections have shown this is not the case. Anti di-alkenylcyclopropanes **618**, **619**, **623** and **624** were isolated in reasonable yields from reactions with organochlorozirconocene complexes **544** and **620** (Scheme 3-33) (Table 3-1).

Some cyclisation of di-alkenylcyclopropanes **616** and **621** (Table 3-1) was observed upon work-up, suggesting the syn and anti products were formed in the reactions. However, as the cyclised and non-cyclised products were inseparable, the isolated mixtures were heated completing cyclisation and products isolated as the cyclohepatadienes **617** and **622** (Table 3-1). The low yields observed were due to problems with poly carbenoid insertion. The addition of organochlorozirconocene solutions **544** and **620**, dropwise at room temperature, to a solution of the carbenoid **613a** resulted in numerous products, due to the instability of the carbenoid at higher temperatures. In order to combat this problem a flask with two interconnected wells was designed, allowing quick addition of the organochlorozirconocene solution to the

carbenoid **613a**, while maintaining the low temperature. Fast reaction times and low temperatures (Scheme 3-33) resulted in very low conversion rate, and consequently low yields of di-alkenylcyclopropanes **617** and **621**.

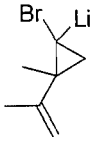
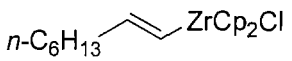
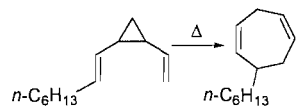
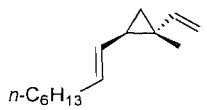
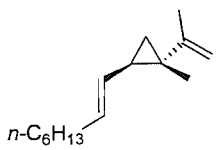
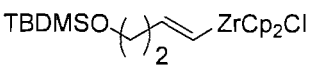
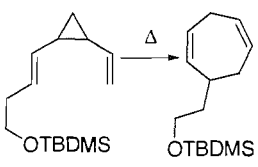
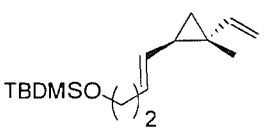
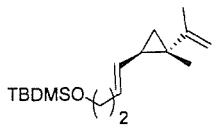


R^1 = H or CH_3; R^2 = H or CH_3; R^3 = n-C_6H_{13} or -$(CH_2)_2$OTBDMS.

(i) >2.0 eq **612a-c** and n-BuLi, -90 °C, 10 to 15 min; For **616**, **621** (ii) 1.0 eq $R^3CHCH(ZrCp_2Cl)$, -90 °C, 20 min; For **618** (ii)1.0 eq $R^3CHCH(ZrCp_2Cl)$, -90 to -40 °C, over 6 hr; For **619** (ii) 1.0 eq $R^3CHCH(ZrCp_2Cl)$, -90 °C to RT, over 5.5 hr; For **623** (ii)1.0 eq $R^3CHCH(ZrCp_2Cl)$, -90 to -70 °C, over 4.5 hr; For **624** (ii) 1.0 eq $R^3CHCH(ZrCp_2Cl)$, -90 to 10 °C, 3 hr; (iii) MeOH, sat. $NaHCO_3$aq, RT, 16 hr.

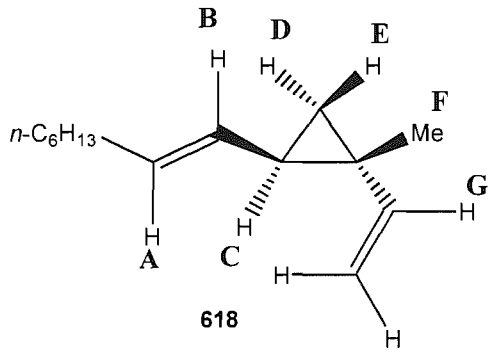
Scheme 3-33 Proposed mechanism for formation of di-alkenylcyclopropanes

Table 3-1 alkenyl carbenoid insertion into zirconocene alkenes

Carbenoid / Organozirconocene	 **613a**	 **613b**	 **613c**
 **544**	 **616** to **617** overall 5%	 **618** 57%	 **619** 65%
 **620**	 **621** to **622** overall 25%	 **623** 52 %	 **624** 50%

The stereochemistry of the di-alkenylcyclopropane **618** was further investigated using NOE studies and found to be anti about the cyclopropane (Figure 3-5). As di-

alkenylcyclopropanes **619**, **623** and **624** displayed the same properties upon attempted cyclisation (Scheme 3-34), they were also assigned as anti.

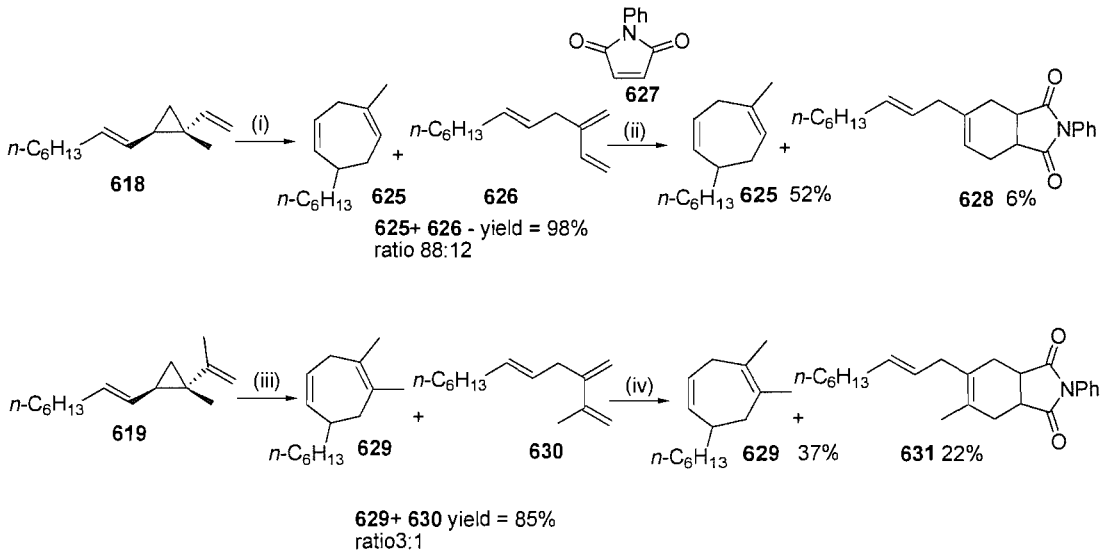


Significant NOE intereactions

Proton	A	B	C	D	E	F	G
A					x		
B					x	x	
C							x
D							x
E	x	x				x	
F		x			x		
G			x	x			

Figure 3-5 Key NOE interactions which helped to determine stereochemistry about cyclopropane

Gas chromatographic analysis of di-alkenyl cyclopropane samples **618** and **619** displayed two product peaks. Samples were found to be cyclising upon injection into the high temperature vaporisation chamber of the gas chromatographer. This was confirmed by changing the temperature in the chamber. More or less of the cyclised product was observed with an increase or decrease of the temperature, respectively. Heating di-alkenyl cyclopropanes **618** and **619** resulted in cycloheptadienes **625** and **629** in good yields (Scheme 3-34).



(i) 170 °C, mW, DMF; (ii) 0.12 eq **627**, Tol, 115 °C; (iii) 180 °C, mW, DMF; (ii) 0.5eq **627**, Tol, 115 °C.

Scheme 3-34 Cyclisation of di-alkenyl cyclopropanes

Unfortunately the conditions required to achieve cyclisation also resulted in the formation of triene by-products **626** and **630** (Scheme 3-34). The inseparable mixture

of diene and triene were treated with a dieneophile **627**, allowing the two products to be separated. The mechanism for the formation of the trienes **626** and **630** is unknown.

3.3 Conclusions

Reaction of cyclopropyl carbenoids with organochlorozirconocene complexes has shown good potential for synthesis of 2-substituted alkylidene and alkenylcyclopropanes. Interesting mechanistical aspects of this reaction have been investigated. The most pertinent observation to emerge from these investigations is the proposal that transmetallation of the lithium present in the carbenoid and zirconium occurs with inversion of configuration. Further work in this area may include providing evidence for the inversion of stereochemistry on transmetallation by using chiral cyclopropyl carbenoids.

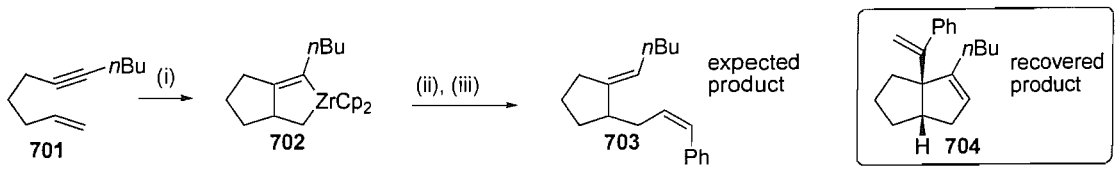
Chapter 4 Rearrangement to a Zirconium Alkenylidene Complex through a 3-Component Coupling of Zirconacycles, Dihalocarbenoids and Acetylides

This chapter presents the results of sequential addition of 1,1-dihalo-1-lithioalkanes and acetylides to zirconacyclopentenes and zirconacyclopentanes. This process results in highly elaborated bicyclo[3.3.0]-octenes and -octanes which are thought to be generated *via* the rearrangement of an alkynyl-zirconium to a zirconocene alkenylidene complex.

4.1 Introduction

4.1.1 Background

The insertion of (*E*)-β-fluoro-β-lithiostyrene into a zirconacyclopentene **702** was attempted by a former group member.[54] This was expected to result in the isolation of diene **703**; however, diene **704** was isolated instead (Scheme 4-1). Previous insertion of (*E*)-β-bromo-β-lithiostyrene generated *in situ* through addition of LDA to a mixture of **702** and (*E*)-β-bromostyrene had resulted in diene **703**, on protonation.[79]

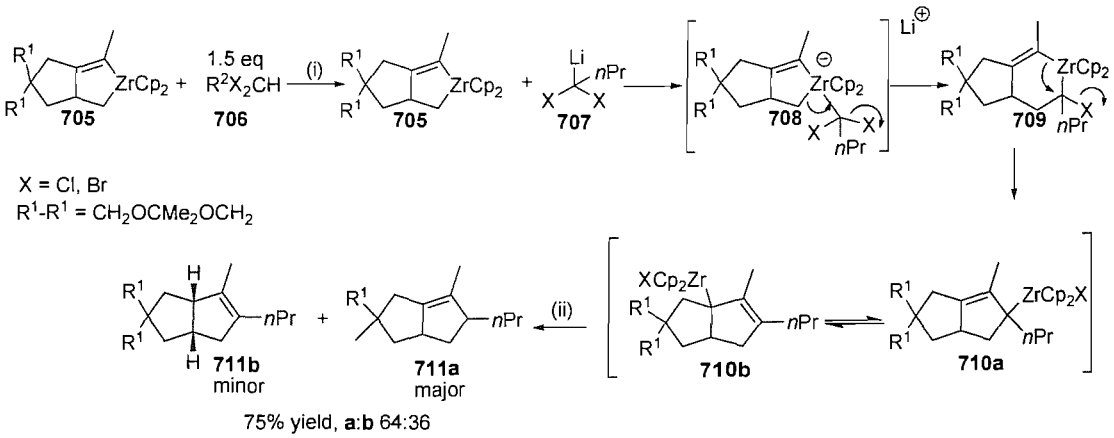


(i) zirconocene(but-1-ene), -78 °C to RT over 2hr; (ii) 1.0 eq β-fluorostyrene (+ CH_2Cl_2 contaminant), 1.5 eq LiTMP, -78 °C to -65 °C, over 45 min, then RT, 3 hr; (iii) MeOH, sat. $NaHCO_3$ aq., RT, 12 hr.

Scheme 4-1 Previous results – isolation of unexpected diene 704

Diene **704** contained one more carbon than would have been expected if it had arisen from coupling of the styrene and the zirconacycle **702**. This was traced to the presence of residual dichloromethane in the very volatile β-fluorostyrene starting material (Scheme 4-1). Dichloromethane is known to undergo deprotonation in the presence of lithiated amide bases, resulting in a carbenoid which could be trapped by zirconacycle **702**.[154]

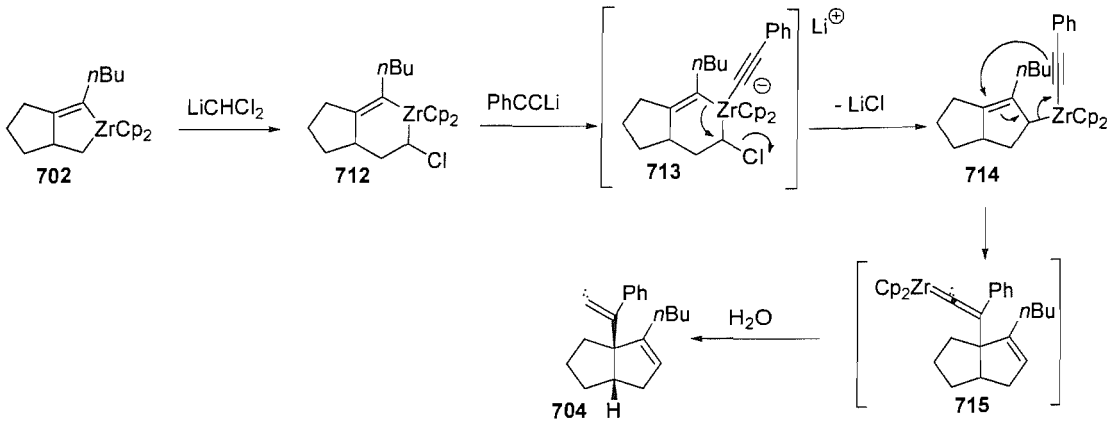
Generation of 1,1-dihalo-1-lithio species **707** is not restricted to dichloromethane; other 1,1-dihaloalkanes also form carbenoids upon treatment with amide bases. These have been trapped by saturated and unsaturated zirconacycles resulting, after hydrolysis, in bicyclo[3.3.0]-octanes and -octenes respectively.[154] In the unsaturated case a mixture of products **711a** and **711b** was observed (Scheme 4-2). In a comparison between the insertion of dichloromethane and other 1,1-dihaloalkanes, dichloromethane was found to be low yielding. The use of dichloromethane can result in multiple carbenoid insertions, whereas the other more sterically hindered carbenoids do not.



(i) 1.7 eq LDA, -78 °C to -55 °C, over 2hr; (ii) AcOH, -78 °C.

Scheme 4-2 Reaction of 1,1-dihalo-1-lithioalkane with zirconacyclopentenes

It was subsequently established that fluoro styrene undergoes hydrogen fluoride elimination in the presence of base.[54] This results in the formation of a terminal alkyne, which is then deprotonated. Hence it was proposed that diene **704** was the result of the reaction between the zirconacycle **702**, a 1,1-dihalocarbenoid **707** and phenyl acetylide. This gave rise to a proposed mechanism for the formation of **704** (Scheme 4-3).

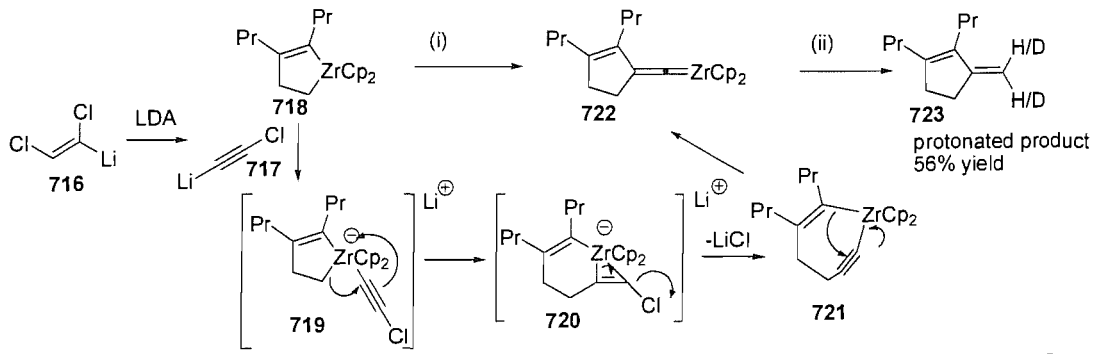


Scheme 4-3 Proposed mechanism for the formation of diene 704

Carbenoid insertion results in the formation of bicyclo[3.3.0]octene **714** (Scheme 4-3). This occurs *via* two 1,2-metallate rearrangements, the first results in zirconacyclohexene **712**. The second 1,2-metallate rearrangement could occur with or without the coordination of phenyl acetylide **713** to form bicyclo[3.3.0]octene **714**. It is thought that the coordination of phenyl acetylide may make this a more favourable process at –78 °C. This is followed by the key step, a 3,3-sigmatropic Cope-type rearrangement of **714** resulting in the formation of zirconocene alkenylidene complex **715**.

4.1.2 Zirconocene Carbene Complexes

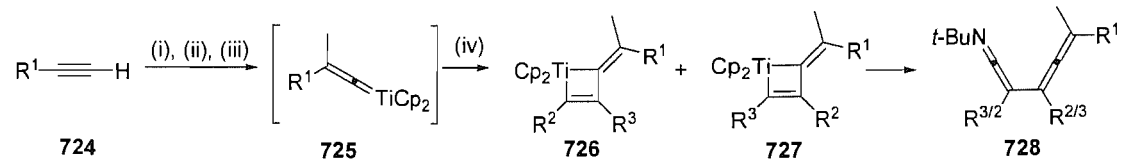
Zirconocene alkenylidenes are very unusual intermediates. They have previously been proposed as the intermediate in a different reaction undertaken within group (Scheme 4-4).[80] The mechanism for the formation of diene **723** suggests 1-lithio-2-chloroethyne **717** adds to zirconacycle **718** and upon loss of lithium chloride and rearrangement of intermediate **721**, gives the zirconocene alkenylidene complex **722**.



(i) 1.0 eq *Z*-1,2-dichloroethene, 2.0 eq LDA, -78 °C, 15 min; (ii) MeOH and sat. $NaHCO_3$ aq. or MeOD and D_2O, RT, 20 hr.

Scheme 4-4 Precedent for key zirconocene alkenylidene intermediate

Zirconocene alkenylidene complexes are not otherwise known. An attempt to generate them through a protocol used for titanocene alkenylidene complexes was not successful.[155] Titanocene alkenylidenes **725** have been implied as the intermediates in the formation of ketenimines **728** (Scheme 4-5).[156]

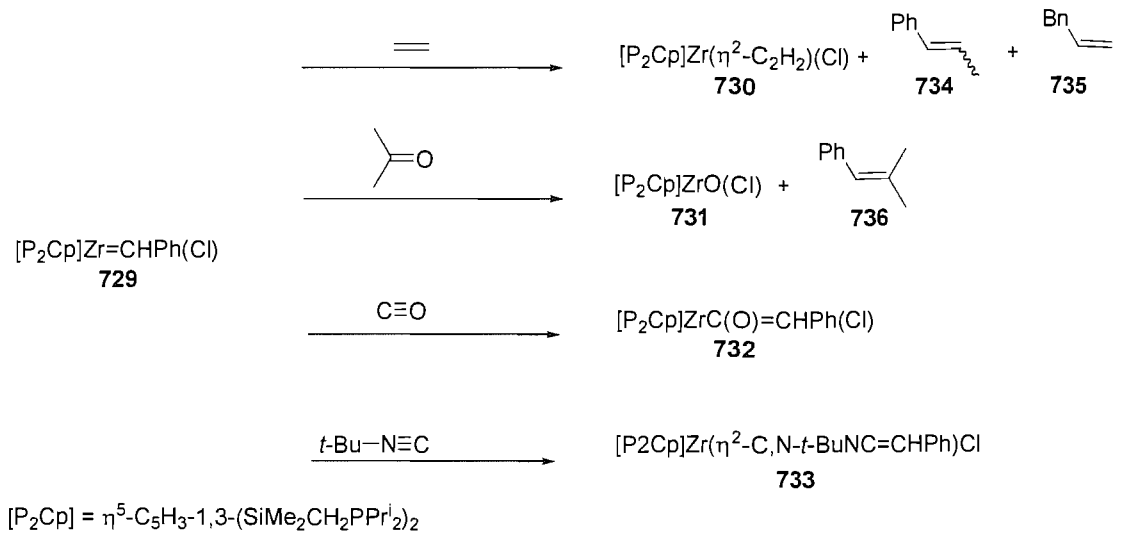


R^1 = *n*-Pr, *n*-Pent, Ph; R^2 = H, *n*-Pr, *n*-Pent; R^3 = *n*-Pr, Ph, $SiMe_3$.

(i) *n*-BuLi, 20 °C, 15 min; (ii) $Cp_2TiMeCl$, Me_2AlCl, Tol, 20 °C, 2 hr; (iii) HMPA, 20 °C, 15 min; (iv) *t*-BuNC, hexane, RT, 16hr.

Scheme 4-5 Titanocene alkenylidene intermediate

Zirconocene alkylidene complexes, however, are better established. Zirconocene alkylidene complexes have been shown to react with esters to afford vinyl ethers and with ketones, imines and imidates to afford olefins of defined stereochemistry.[157,158] Work by Fryzuk *et al.* resulted in the isolation of the zirconocene alkylidene complex $[P_2Cp]Zr{=}CHPh(Cl)$ as a crystalline solid.[159] Fryzuk *et al.* have also shown zirconocene alkylidene complexes to react with alkenes, ketones, carbon monoxide and isonitriles (Scheme 4-6).[160] This resulted in the recovery of novel complexes **730-733** and in some cases, new organic products **734-736**.



Scheme 4-6 Reactions of zirconocene alkylidenes

There were two aspects of the formation of diene **704** that made it an interesting target for research. The proposed mechanism for its formation included an unusual 3,3-sigmatropic rearrangement involving a metal complex. Zirconocene alkenylidene complexes are unknown and a new method for their synthesis could allow further investigation of their chemistry.

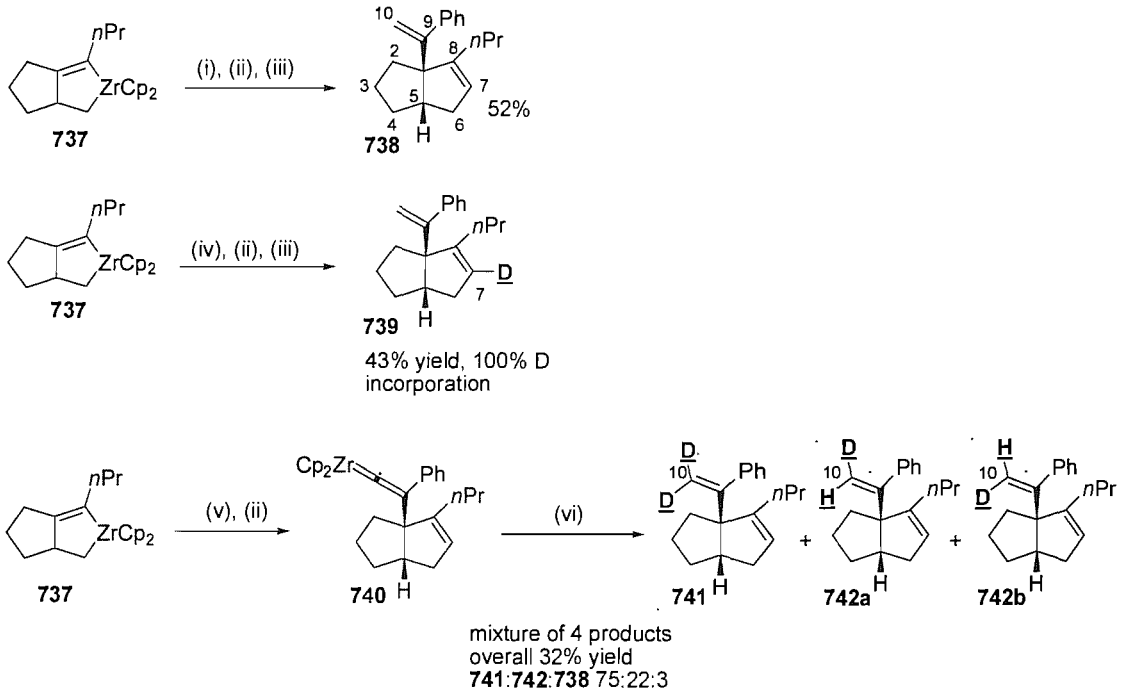
4.2 Results and Discussion

4.2.1 Mechanism for the Formation of Diene 704

An investigation into the mechanism of this unusual reaction was undertaken. Initial aims included provision of evidence for dichloromethane as the source of the additional carbon observed in diene **704** and for the resulting zirconocene alkenylidene complex **715**. It was also important to show that the reaction with phenyl acetylide afforded the same product **704** as that isolated from β-fluorostyrene.

The procedure for making diene **704** was modified to include the addition of phenyl acetylide to a solution of the zirconacycle **737**, dichloromethane and LiTMP (Scheme 4-7) (starting zirconacyclopentene was changed from the α-butyl substituted system **702** to the α-propyl substituted system **737**, due to the ready availability of the starting material). This resulted in the isolation of diene **738** in a modest 52% yield. Repetition of the reaction with deuterated dichloromethane resulted in deuterium incorporation at

carbon C7 of **739**, confirming dichloromethane as source of the additional carbon observed in diene **704**.



(i) 1.5 eq CH_2Cl_2, LiTMP, -78 °C; (ii) 1.1eq LiCCPh, -78 °C, 20 min; (iii) MeOH, sat. $NaHCO_3$ aq., RT, 16 hr; (iv) 1.1eq CD_2Cl_2, LiTMP, -78 °C; (v) 1.1eq LiCCPh, -78 °C to -50 °C over 2 hr; (vi) 1.1 eq CH_2Cl_2, LiTMP, -78 °C; (vii) 1.1eq LiCCPh, -78 °C to -45 °C over 2 hr; (vi) CD_3OD, D_2O, RT, 16hr.

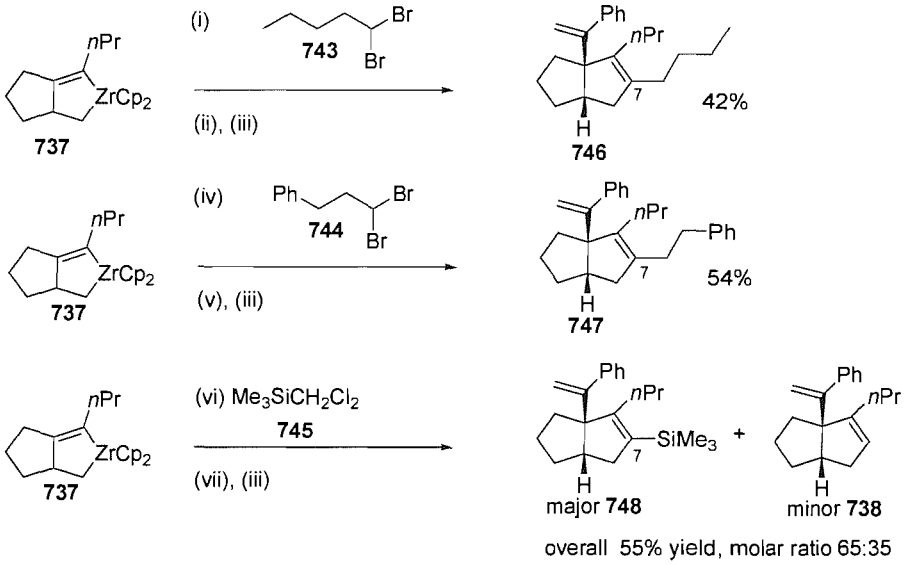
Scheme 4-7 Results from experiments used to probe the reaction mechanism

Evidence for the intermediacy of the zirconocene alkenylidene complex **740** was obtained by quenching the reaction with D_4-methanol and deuterium oxide (Scheme 4-7). Double deuterium incorporation was observed at carbon C10 of diene **741**. Attempts to trap the proposed zirconocene alkenylidene intermediate with benzaldehyde were unsuccessful.

4.2.2 Scope

The scope of the reaction was investigated through variation of the starting materials. Following precedent for the formation of bicyclo[3.3.0]octenes (Scheme 4-2)[154] variation at C7 was achieved through substitution of dichloromethane for alkyl, alkenyl and silyl substituted gem-dihalides (Scheme 4-8). Dibromides **743** and **744** were synthesised from commercially available starting materials using literature

methods.[3,161] Pleasingly their use in the reaction resulted in the isolation of dienes **746** and **747** in modest yields.

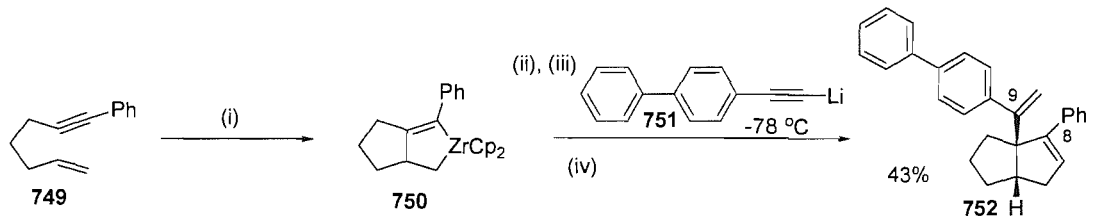


(i) 1.5 eq **743**, 1.5 eq LiTMP, -78 °C; (ii) 1.1 eq LiCCPh, -78 °C to -50 °C, 2 hr; (iii) MeOH, sat. $NaHCO_3$ aq., RT, 16 hr; (iv) 1.5 eq **744**, 1.5 eq LiTMP, -78 °C; (v) 1.1 eq LiCCPh, -78 °C, 50 min; (vi) 1.5 eq **745**, 1.5 eq LiTMP, -78 °C; (vii) 1.1 eq LiCCPh, -78 °C to -60 °C, 2 hr.

Scheme 4-8 Introduction of variation at C7 of diene 738

The (dichloromethyl)trimethylsilane **745** also proved to be a suitable carbenoid precursor; however, the conditions used for the reaction resulted in some de-silylation (Scheme 4-8). The silylated **748** and desilylated diene **738** were inseparable and therefore isolated as a mixture. Different quench conditions may have prevented de-silylation from occurring, however these were not tried. The reactions were monitored by gas chromatography and quenched when they were shown no longer to be changing composition. This accounts for the slightly different conditions used for each reaction.

Variation at carbon C8 of diene **738** was achieved using a different enyne, 1-(hept-6-en-1-ynyl)benzene **749**, to make the initial zirconacycle **750** (Scheme 4-9). Substitution of the propyl group for a phenyl group still resulted in the isolation of the diene **752** despite the increased steric bulk.



(i) 1.0 eq zirconocen(but-1-ene), -78 °C to RT, 2 hr; (ii) 1.1eq CH_2Cl_2, LiTMP, -78 °C; (iii) 1.1 eq **751**, -78 °C to -15 °C, 1.5 hr; (iv) MeOH, sat. $NaHCO_3$ aq., RT, 16 hr.

Scheme 4-9 Introduction of variation at C8 and C9 of diene

It must be noted that in this example **752** variation at C9 was achieved by 4-phenyl substitution of phenyl acetylene (Scheme 4-9) (synthesised according to literature procedures from the corresponding aldehyde).[162,163] It had been hoped that the presence of a high density of aromatic character in diene **752** would make it crystalline, however, a crystalline sample was never obtained. Crystallisation was attempted through slow evaporation of benzene, hexane and methanol. Scratching and storage of the small samples in the different solvents was also unsuccessful.

Pleasingly greater variation at carbon C9 of diene **738** was subsequently achieved. The introduction of butyl acetylene proved to be comparable, in terms of yield, to the aromatic acetylenes previously used and resulted in the isolation of diene **754** (Scheme 4-10).

(i)1.5eq CH_2Cl_2, LiTMP, -78 °C; (ii) 1.1 eq **753**, -78 °C, 1.5 hr; (iii) MeOH, sat. $NaHCO_3$ aq., RT, 16 hr.

Scheme 4-10 Introduction of variation at C9 of diene 738

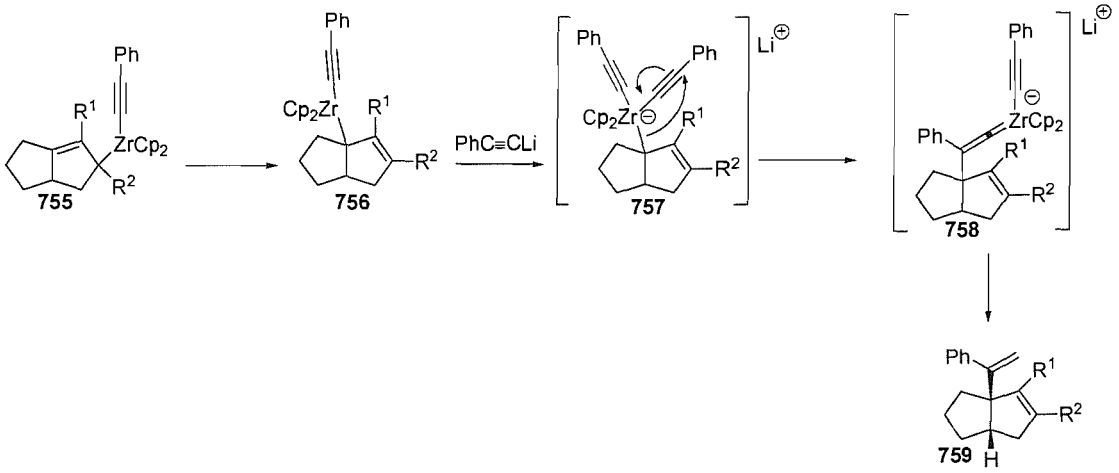
Further variation was sought in the size of the ring system present in the diene **738**. Co-cyclisation of the homologous enyne, undec-1-en-7-yne, resulted in a bicyclo[4.3.0]zirconacycle. Unfortunately many unidentifiable products emerged when it was subjected to conditions used in the isolation of diene **738**. The isolation of a crystalline product derived from diene **738** was sought through the oxidation of its di-substituted double bond. However, reactions with both borane methyl sulfide and

borane-THF complex proved unfruitful. This is now thought to be due to steric encumbrance about the double bond.

4.2.3 Improvements

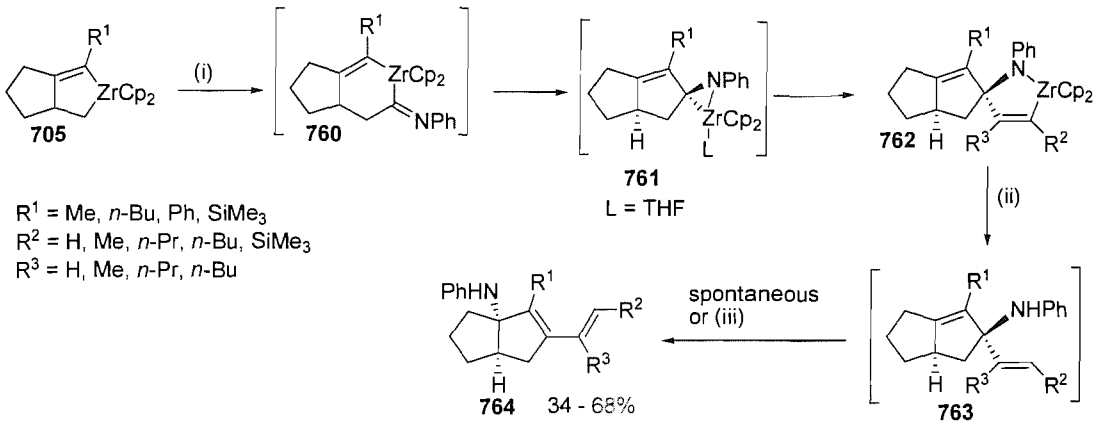
Theoretical calculations for the proposed mechanism for the formation of diene **704/738** failed to find a viable transition state for the key 3,3-sigmatropic Cope-type rearrangement (Scheme 4-3). Indications were that it might be energetically unfavourable.

A new mechanism was therefore proposed based on a 1,3-metal shift in **755** followed by a 1,3-alkyl shift in 'ate' complex **757** to afford the zirconocene alkenylidene complex **758**. (Scheme 4-11). DFT calculations suggested that the 1,3-alkyl shift would only be favoured for a charged zirconate complex **757**, rather than in a neutral intermediate **756**. This means that two equivalents of acetylide were needed for one equivalent of diene **759** obtained. This would help account for the modest yields observed when 1.1 equivalents of acetylide were used.



Scheme 4-11 Revised mechanism for the formation of diene 759

The driving force for the 1,3-metal shift in **755** is the release of strain energy. A similar 1,3-nitrogen shift was previously observed in the strained **763** system and is responsible for the synthesis of diene **764** (Scheme 4-12).[64]

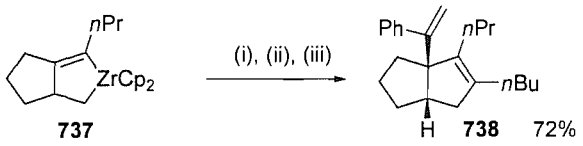


(i) 1.0 eq PhNC, 4.0 eq R^2CCR^3, -35 °C to RT over 30 min, then 67 °C, 1 hr; (ii) MeOH, $NaHCO_3$ aq.; (iii) SiO_2 chromatography.

Scheme 4-12 Precedent – 1,3-amine shift[64]

The revised mechanism (Scheme 4-11) for the formation of zirconocene alkenylidene **758** is based on a 1,3-alkyl shift. There is limited precedent available for this transformation. A 1,3-carbon shift was used to explain the formation of zirconocene alkenylidene **722** (Scheme 4-4), in work by Norton.[80] Theoretical calculations on a 1,3-methyl shift in a rhodium alkene complex resulting in an alkenylidene complex have shown it to be energetically favourable.[164] Corresponding 1,3-hydrogen shifts are better known and have been used in the synthesis of metal alkenylidene complexes.[165,166]

In light of the new proposed mechanism (Scheme 4-11) a sample reaction was repeated with two or more equivalents of phenyl acetylide (Scheme 4-13). It was found that a reaction carried out with two equivalents of phenyl acetylide followed by quench at –78 °C still resulted in a modest 44% yield of diene **738**. However, the combination of three equivalents of phenyl acetylide and warming the reaction before quench resulted in an improved 72% yield of diene **738** (Scheme 4-13). (It should be noted that warming the reaction to room temperature in the presence of only 1.1 equivalents of phenyl acetylide did not result in any improvement in yield). This result provided some evidence for the charged bis-alkyne complex **757** being responsible for the formation of the zirconocene alkenylidene complex **758**.

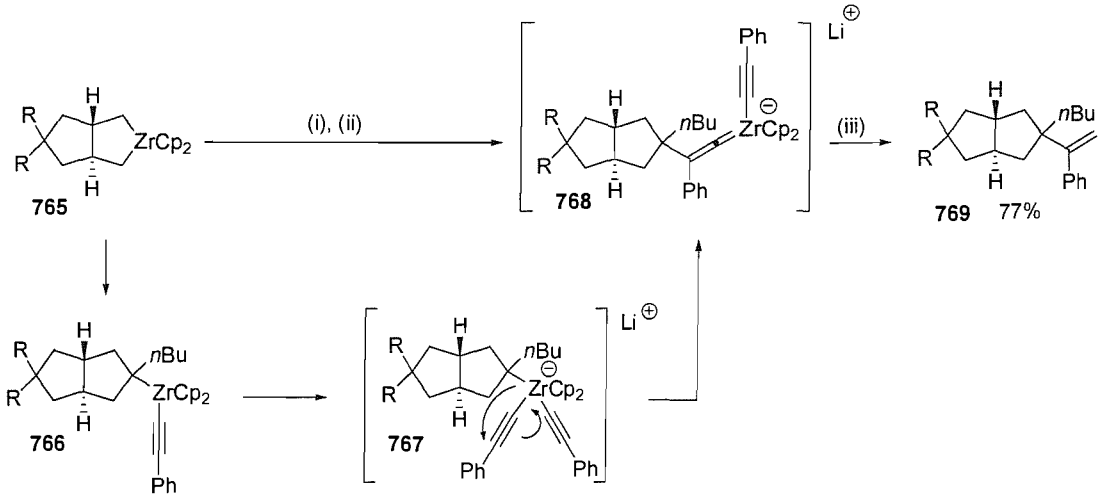


737 738 72%

(i) 1.5 eq $CH_3(CH_2)_3CHBr_2$, 1.5 eq LiTMP, -78 °C; (ii) 3.0 eq PhCCLi, -78 °C to -10 °C, 4 hr; (iii) MeOH, sat. $NaHCO_3$ aq., RT, 16 hr.

Scheme 4-13 Improved protocol for the formation of diene

In the revised mechanism (Scheme 4-11), formation of the zirconocene alkenylidene is independent of the 1,3-metal shift. This provided new scope for the reaction as the protocol could be extended to bicyclo[3.3.0]octanes. A sample reaction using zirconacyclopentane **765** and the revised protocol resulted in alkene **769** in good yield (Scheme 4-14).

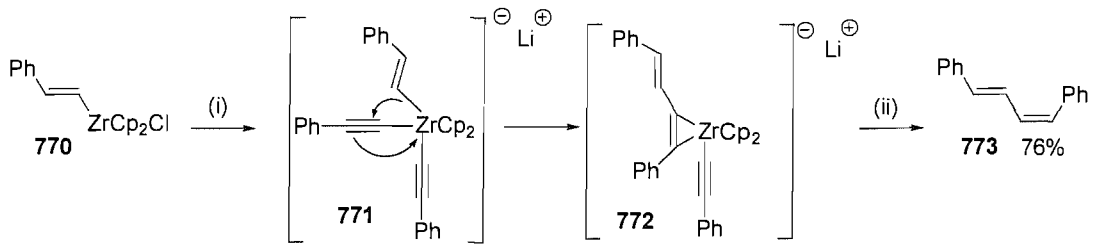


R = $-CH_2OCH_3$

(i) 1.5 eq $CH_3(CH_2)_3CHBr_2$, 1.5 eq LiTMP, -78 °C; (ii) 3.0 eq PhCCLi, -78 °C to RT, 4 hr; (iii) MeOH, sat. $NaHCO_3$ aq., RT, 16 hr

Scheme 4-14 Extension of alkenylidene protocol to unsaturated zirconacycles

Thoughts then turned to the possibility of carrying out the same reaction with acyclic organochlorozirconocene complexes **770**. However, the addition of the phenyl acetylide to the organochlorozirconocene complex **770** is a known reaction and does not result in a 1,3-alkyl migration (Scheme 4-15).[167] The product **773** results from a zirconocene promoted 1,2-migration reaction *via* the zirconate complex **771**.[168]



(i) 2.0 eq PhCCLi, -78 °C to RT, 1 hr; (ii) HCl aq., -78 °C to RT, 10 min.

Scheme 4-15 Reaction of organochlorozirconocene complex 772 with lithiated acetylene[167]

The 1,2-alkyl shift in zirconate complex **771** observed by Negishi[168] (Scheme 4-15) is in direct contrast to the 1,3-alkyl shift thought to occur in the synthesis of **759** (Scheme 4-11). The difference is thought to be the result of the difference steric encumbrance present parent systems **755** and **770** respectively.

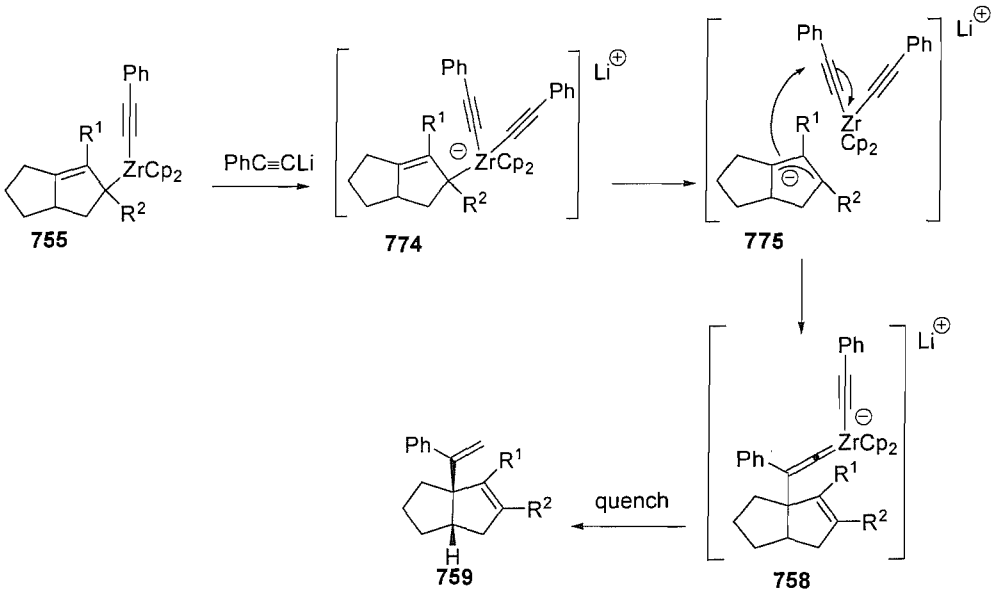
4.3 Conclusions

The isolation of the serendipitous diene product **704** was investigated. A combination of experimental procedures and theoretical calculations has been used to propose a mechanism for its formation. The key steps involve: insertion of a 1,1-dihalogen-1-lithioalkane carbenoid species, 1,3-metal migration to relieve ring strain and a 1,3-alkyl shift of a bis-alkyne zirconate complex to afford a zirconocene alkenylidene intermediate. The scope of the reaction was also investigated through variation of the three components used in the reaction.

4.4 Further work

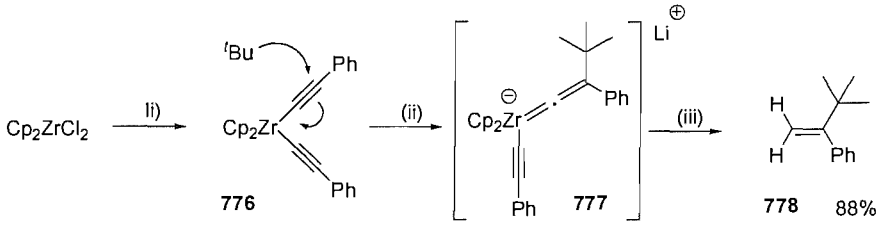
Due to time constraints the improved conditions that resulted in the isolation of diene **738**, in 72% yield were not refined and applied to the other systems studied. Further investigations carried out by a group member[169] provided evidence that the conversion of **755** into the zirconocene alkenylidene complex **758** occurs via

formation of 'ate' complex **774**, heterolysis to afford the allyl anion / dialkynylzirconocene **775**, and β-addition of the allyl anion to a zirconium-alkyne to afford the alkenylidenezirconate complex **758** (Scheme 4-16). This is in contrast to the mechanism proposed in Scheme 4-11 where formation of alkenylidenezirconate complex was arrived at *via* two 1,3-shifts.



Scheme 4-16 Revised mechanism for the formation of the alkenylidene zirconate complex

Supporting evidence for this latest mechanism is that treatment of zirconocene bis-alkyne **776** with *tert*-BuLi resulted in β-addition to afford upon quench the terminal diene **778** in excellent yield, presumably via the alkenylidene- zirconate complex **777** (Scheme 4-17).[169]



(i) 2.0 eq lithiated phenyl acetylene (pre-formed from phenyl acetylene + 1.0 eq *n*-BuLi in THF at 0 °C for 1 hr) -78 °C to RTover 5 hr; (ii) *t*-BuLi (1.0 eq), -78 °C, 20 min; (iii) MeOH, sat. $NaHCO_3$ aq., -78 °C to RTover 2 hr then RT for 16 hr.

Scheme 4-17 Evidence for proposed loss and re-addition mechanism

Chapter 5 Experimental

5.1 General

All the 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 °C, for at least 12 hours) and cooled in a sealed desiccator over silica gel before assembly.

Unless otherwise stated, reagents were obtained from commercial suppliers and if necessary dried and distilled before use. THF and diethyl ether used in air-sensitive reactions were freshly distilled from sodium benzophenone ketal under argon. Pentane and dichloromethane were dried over CaH_2 and degassed before use. *n*-Butyllithium (*n*-BuLi) was used as a 2.5 mol dm^3 solution in hexanes, stored in stock bottles under argon. Lithium diisopropylamide (LDA) was made from diisopropylamine (distilled, stored over KOH) in THF by addition of 1 equivalent of *n*-BuLi at 0 °C. Lithium 2,2,6,6-tetramethylpiperidide (LiTMP) 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 °C and stirring for 20 minutes. Petroleum ether (petrol) refers to the fraction that boils between 40 and 60 °C.

NMR spectra were recorded on Bruker AV300, AM300 or DPX400 spectrometers. The chemical shifts, δ, were recorded as values in ppm referenced to chloroform peaks at 7.26 ppm for ^1H spectra and 77.16 ppm for ^{13}C spectra and benzene 7.16 ppm for ^1H spectra and 128.06 ppm for ^{13}C spectra.[170] The following abbreviations were used to denote multiplicity and may be compounded: s = singlet, d = doublet, t = triplet, q = quartet, fs = fine splitting. Coupling constants, *J*, are measured in Hertz (Hz). ^{13}C spectra were proton decoupled. DEPT, COSY and ^1H-^{13}C correlation experiments were used to aid assignment of spectra.

Accurate mass spectra were recorded on a VG analytical 70-250-SE double focussing mass spectrometer using Chemical Ionisation (CI) (NH_3 reagent gas) or an Electron Impact Ionisation (EI) at 70eV. LRMS (EI) and (CI) (NH_3 reagent gas) were recorded on a ThermoQuest TraceMS GCMS. Electrospray mass spectra were recorded using a

VG platform quodrupole spectrometer. Values of *m/z* are reported in atomic mass units and the peak intensity relative to the base peak is reported in parenthesis.

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. Absoptions are given in wavenumbers (cm^{-1}) and the following abbreviations used to denote peak intensities: s = strong, m = medium, w = weak.

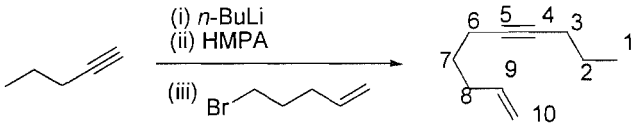
Thin layer chromatography was carried out on aluminium backed silica plates and spots visualized by UV (254 nm lamp), phosphomolybdic acid, sulphuric acid or permanganate stains. Flash column chromatography on silica gel was performed on Kieselgel 60 (230-400 mesh) silica gel. Columns were packed and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

Gas chromatography was performed on a Hewlett Packard HP 6890 series GC system, using an HP-5 (cross-linked 5% PH ME siloxane) 30 m column, with a film thickness of 0.25μm and phase ratio 320. The carrier gas was helium and the flow rate 2.7 mL min^{-1}.

A few compounds were prepared by literature methods and had spectral properties consistent with those included in the thesis of former group members. These include: 4,4-bis-methoxymethyl-octa-1,6-diene, 3-(1,1-bis-methoxymethyl-but-3-enyl)-cyclohexene, 5,5-diallyl-2,2-dimethyl-[1,3]-dioxane, 4,4-bis-methoxymethyl-hept-1-en-6-yne, 4,4-bis-methoxymethyl-hepta-1,6-diene, (4,4-bis-methoxymethyl-hepta-1,6-dienyl)-benzene, hept-6-en-ynyl-benzene, dec-1-en-6-yne, dodec-1-en-6-yne and dodec-1-en-7-yne. Dibrominated cyclopropanes 1,1-dibromo-2-vinylcyclopropane, 1,1-dibromo-2-methyl-2-vinylcyclopropane, 1,1-dibromo-2-methyl-(prop-1-en-2-yl)cyclopropane and 7,7-dibromocyclopropane[4.1.0]heptane were synthesised *via* cyclopropanation using bromoform.[100]

5.2 Experimental from Chapter 2

5.2.1 Preparation of Dec-1-en-6-yne



$C_{10}H_{16}$

A solution of 1-pentyne (14.6 mL, 2.00 eq, 148.0 mmol) in THF (60 mL) was cooled to –78 °C, *n*-BuLi (59.2 mL, 2.00 eq, 148.0 mmol) was added and the reaction mixture was stirred for 30 minutes. There followed the addition of HMPA (25.7 mL, 2.00 eq, 148.0 mmol). The reaction was kept at –78 °C for 30 min before it was warmed to –40 °C. Neat 5-bromo-1-pentene (8.0 mL, 0.90 eq, 67.0 mmol) was added to the reaction mixture which was kept at –40 °C for 1 hour then warmed to 0 °C in an ice bath and allowed thereon to warm gradually to room temperature for 16 hours. The reaction mixture was quenched with sat. NH_4Cl aqueous solution (60 mL) and stirred for 1 hour. The aqueous layer was removed and the organic phases were washed repeatedly with water to remove THF. The organic phase was distilled at water pump pressure using a tall distillation apparatus (distillation temperature approx. 100 °C) to remove the excess 1-pentyne. The final product was purified further by Kugelrohr distillation (60-80 °C/ 1.0 mm Hg) to give a clear oil (8.1 g, 89%)

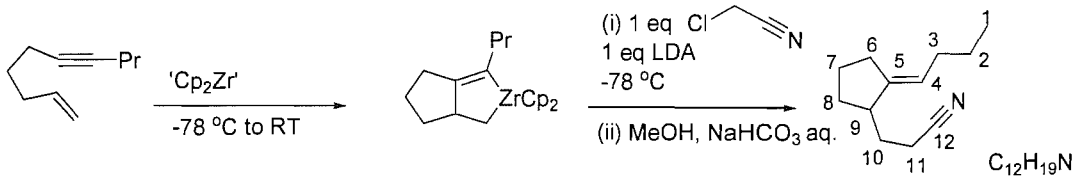
^{1}H NMR (300 MHz, $CDCl_3$): δ 5.80 (1H, ddt, J = 17.0, 10.2, 6.8 Hz, H_9), 5.03 (1H, ddt, J = 17.0, 3.5, 1.7 Hz, H_{10}), 4.99 (1H, ddt, J = 10.2, 3.5, 1.1 Hz, H_{10}), 2.21 –2.10 (6H, m), 1.63–1.43 (4H, m), 0.97 (3H, t, J = 7.4 Hz, H_1) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 138.28 (CH, C_9), 115.07 (CH_2, C_{10}), 80.54 (C, C_4 or C_5), 80.05 (C, C_4 or C_5), 32.97 (CH_2, C_8), 28.47 (CH_2, C_7), 22.66 (CH_2, C_2), 20.90 (CH_2, C_3), 18.31 (CH_2, C_6), 13.63 (CH_3, C_1) ppm.

GCMS (EI) *m/z* (%): 136 ($(M)^+$, 4), 121 ($(M\text{-}CH_3)^+$, 50), 107 ($(M\text{-}C_2H_5)^+$, 80), 93 ($(M\text{-}C_3H_7)^+$, 97).

HRMS (EI) for $C_{10}H_{16}$ $(M)^+$ calculated 136.1252, found 136.1242.

5.2.2 Preparation of 3-((*E*)-2-butylidene-cyclopentyl)-propanenitrile 353



A solution of *n*-BuLi (0.80 mL, 2.00 eq, 2.00 mmol) (2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) in THF (5 mL) at –78 °C. This was stirred for 10 minutes before the addition of dec-1-en-6-yne (0.136 g, 1.00 eq, 1.00 mmol) as a solution in THF (1 mL). The cool bath was then removed and the reaction mixture was allowed to warm to room temperature over 2 hours.

The reaction mixture was cooled to –78 °C before the addition of chloroacetonitrile (0.075 g, 1.00 eq, 1.00 mmol) as a solution in THF (1 mL) followed by the dropwise addition of LDA (0.85 mL, 1.00 eq, 1.00 mmol in THF). The reaction mixture was kept at –78 °C for 30 minutes before it was quenched with MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (5 mL). The cold bath was then removed and the reaction mixture was stirred vigorously for 16 hours. The product was extracted into diethyl ether (3 x 30 mL), the combined organic phases were washed with sat $NaHCO_3$ aqueous solution (30 mL), water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash silica column chromatography (petrol/diethyl ether 95:5) to yield a clear colourless oil, the title compound (0.100 g, 56%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.17 (1H, tq, J = 7.4, 2.2 Hz, H_4), 2.43 (1H, dt, J = 8.1, 6.6 Hz, H_{11}), 2.40–2.27 (3H, m, H_{11} and others), 2.20 (1H, broad sextet J = 8.1 Hz, H_9), 1.99–1.84 (4H, m, H_3 and others), 1.75 (1H, m), 1.65–1.50 (2H, m), 1.37 (2H, sextet, J = 7.4 Hz, H_2), 1.24 (1H, m), 0.89 (3H, t, J = 7.4 Hz, H_1) ppm.

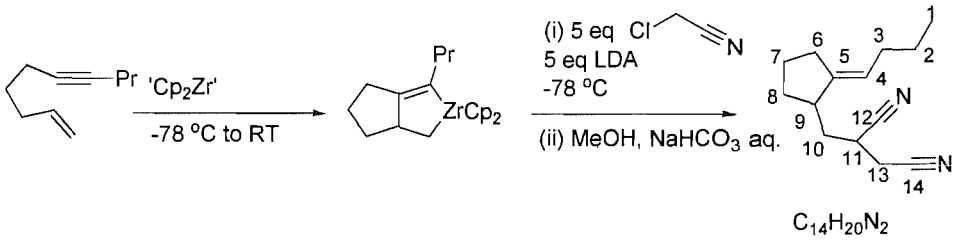
^{13}C NMR (75 MHz, $CDCl_3$,): δ 144.58 (C, C_5), 121.62 (CH, C_4), 120.29 (C, C_{12}), 43.28 (CH, C_9), 32.25 (CH_2), 31.65 (CH_2), 30.01 (CH_2), 28.93 (CH_2), 24.05 (CH_2), 22.89 (CH_2), 15.48 (CH_2), 14.02 (CH_3, C_1) ppm.

IR (film): 2954 (s), 2930 (s), 2868 (s), 2245 (m), 1451 (w), 1429 (w), 890 (w) cm^{-1}.

GCMS (CI) *m/z* (%): 195 ($(M+NH_4)^+$, 20), 178 ($(M+H)^+$, 75), 148 ($(M-CH_3N)^+$, 80).

HRMS (EI) for $C_{12}H_{19}N$ $(M)^+$ calculated 177.1518, found 177.1518.

5.2.3 Preparation of 2-((*E*)-2-butylidene-cyclopentylmethyl)-succinonitrile 354



$C_{14}H_{20}N_2$

A solution of *n*-BuLi (0.80 mL, 2.00 eq, 2.00 mmol) (2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) in THF (5 mL) at –78 °C. This was stirred for 10 minutes before the addition of dec-1-en-6-yne (0.136 g, 1.00 eq, 1.00 mmol) as a solution in THF (1 mL). The cool bath was then removed and the reaction mixture was allowed to warm to room temperature over 2 hours.

The reaction mixture was cooled to –78 °C before the addition of chloroacetonitrile (0.31 mL, 5.00 eq, 5.00 mmol) and followed by the dropwise addition of LDA (4.0 mL, 5.00 eq, 5.00 mmol in THF). The reaction mixture was kept at –78 °C for 30 minutes before it was quenched with MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (5 mL). The cold bath was removed and the reaction mixture was stirred vigorously for 16 hours. The products were extracted into diethyl ether (3 x 30 mL), the combined organic phases were washed with sat. $NaHCO_3$ aqueous solution (30 mL), water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash silica column chromatography (petrol/diethyl ether 9:1 to 1:1) to yield a clear oil (mono-inserted product 24 mg, 13% - see 5.2.2) and a yellow oil, the title compound (34 mg, 16%). The ratio of diastereomers was 1:2.2 (isomer 1: isomer 2). These were separated to give analytical samples of the diastereomers.

Isomer 1

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.27 (1H, tq, J = 7.0, 2.5 Hz, H_4), 3.00 (1H, dq, J = 9.5, 6.5 Hz, H_{11}), 2.73 (2H, d, J = 6.5 Hz, H_{13}), 2.56 (1H, pentet, J = 6.7 Hz, H_9), 2.34–2.17 (2H, m, H_6 or H_7 or H_8), 2.02–1.90 (3H, m, H_3, and H_6 or H_7 or H_8), 1.85–1.59 (4H, m, H_{10}, and H_6 or H_7 or H_8), 1.46–1.35 (3H, m, H_2, and H_6 or H_7 or H_8), 0.91 (3H, t, J = 7.3 Hz, H_1) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.94 (C, C_5), 122.77 (CH, C_4), 119.27 (C, C_{12}), 115.54 (C, C_{14}), 42.15 (CH, C_9), 36.44 (CH_2, C_{10}), 32.63 (CH_2, C_3), 31.52 (CH_2, C_6 or C_7 or C_8), 27.93 (CH_2, C_6 or C_7 or C_8), 27.06 (CH, C_{11}), 24.00 (CH_2, C_2), 23.59 (CH_2, C_6 or C_7 or C_8), 22.65 (CH_2, C_{13}), 13.83 (CH_3, C_1) ppm.

IR (film): 2956 (s), 2930 (s), 2870 (m), 2360 (w), 2246 (w), 1637 (w), 1450 (m), 1429 (m), 890 (w), 879 (w) cm^{-1}.

GCMS (CI) *m/z* (%): 234 ($(M+NH_4)^+$, 16), 217 ($(M+H)^+$, 32), 201 ($(M-CH_3)^+$, 8), 187 ($(M-C_2H_5)^+$, 45), 81 ($(C_6H_9)^+$, 100).

HRMS: (EI) for $C_{14}H_{20}N_2$ $(M)^+$ calculated 216.16265, found 216.16326.

Isomer 2

^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.19 (1H, tq, J = 7.0, 2.5 Hz, H_4), 2.99–2.92 (1H, m, H_{11}), 2.81–2.70 (2H, m, H_{13}), 2.61 (1H, m, H_9), 2.35 (1H, m, H_6), 2.21 (1H, dt, J = 16.8, 8.5 Hz, H_6), 2.07 (1H, ddd, J = 14.1, 11.0, 4.5 Hz, H_{10}), 2.01–1.94 (3H, m, H_3 and H_7), 1.80 (1H, m, H_8), 1.65–1.57 (2H, m, H_8 and H_{10}), 1.38 (2H, pentet, J = 7.3 Hz, H_2), 1.24 (1H, m, H_7), 0.91 (3H, t, J = 7.3 Hz, H_1) ppm.

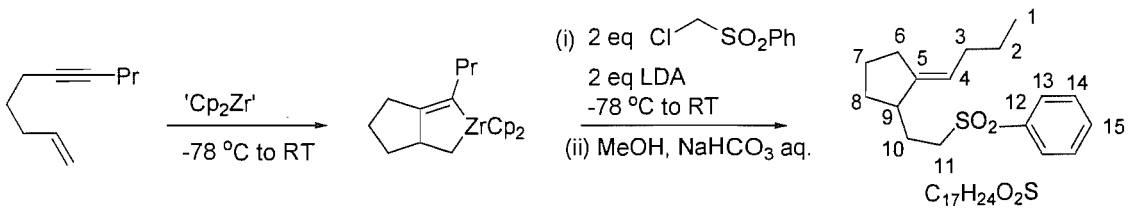
^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.53 (C, C_5), 122.06 (CH, C_4), 119.27 (C, C_{12}), 115.97 (C, C_{14}), 41.84 (CH, C_9), 37.07 (CH_2, C_{10}), 32.65 (CH_2, C_8), 31.91 (CH_2, C_3), 29.31 (CH_2, C_6), 27.59 (CH, C_{11}), 24.42 (CH_2, C_7), 23.06 (CH_2, C_2), 22.01 (CH_2, C_{13}), 14.24 (CH_3, C_1) ppm.

IR (film): 2957 (s), 2926 (s), 2858 (m), 2250 (w), 1445 (m), 1231 (m), 872 (m) cm^{-1}.

GCMS (CI) *m/z* (%): 234 ($(M+NH_4)^+$, 100), 217 ($(M+H)^+$, 35), 187 ($(M-C_2H_5)^+$, 30).

HRMS (EI) for $C_{14}H_{20}N_2$ $(M)^+$ calculated 216.1627, found 216.1631.

5.2.4 Preparation of 1-[2-((*E*)-2-butylidene-cyclopentyl)-ethylsulfonyl]-benzene 355



$C_{17}H_{24}O_2S$

A solution of *n*-BuLi (0.80 mL, 2.00 eq, 2.00 mmol) (2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) in THF (5 mL) at –78 °C. This was stirred for 10 minutes before the addition of dec-1-en-6-yne (0.136 g, 1.00 eq, 1.00 mmol) as a solution in THF (1 mL). The cool bath was then removed and the reaction mixture was allowed to warm to room temperature over 2 hours.

The reaction mixture was cooled to –78 °C before the addition of chloromethyl phenyl sulfone (0.381 g, 2.00 eq, 2.00 mmol) as a solution in THF (1.5 mL) and subsequently the dropwise addition of LDA (2 mL, 2.00 eq, 2.00 mmol). The reaction mixture was warmed to –20 °C over 1 hour, kept at –20 °C for 4 hours then 0 °C for 2 hours before it was quenched with MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (5 mL) and stirred vigorously for 16 hours. The product was extracted into diethyl ether (3 x 30 mL), the combined organic phases were washed with sat $NaHCO_3$ aqueous solution (30 mL), water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash silica column chromatography (petrol/diethyl ether 7:3) to yield a clear colourless oil, the title compound (0.245 g, 84%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (2H, d, J = 7.4 Hz, H_{13}), 7.66 (1H, t, J = 7.4 Hz, H_{15}), 7.57 (2H, t, J = 7.4 Hz, H_{14}), 5.06 (1H, tq, J = 7.0, 2.5 Hz, H_4), 3.17–3.06 (2H, m, H_{11}), 2.35 (1H, m, H_9), 2.24 (1H, m, H_6), 2.11 (1H, dt, J = 16.2, 8.0 Hz, H_6), 2.00–1.89 (3H, m, H_3 and H_{10}), 1.78 (1H, td, J = 11.5, 6.8 Hz, H_8), 1.72–1.63 (2H, m, H_7

and H_{10}), 1.52 (1H, m, H_7), 1.33 (2H, pentet, J = 7.3 Hz, H_2), 1.18 (1H, m, H_8), 0.87 (3H, t, J = 7.3 Hz, H_1) ppm.

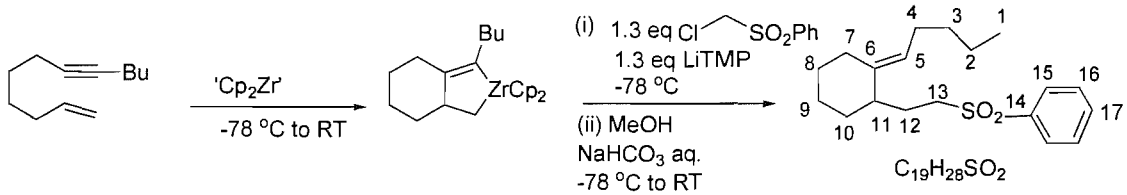
^{13}C NMR (100 MHz, $CDCl_3$): δ 144.66 (C, C_5), 139.71 (C, C_{12}), 133.98 (CH, C_{15}), 129.65 (2CH, C_{13}), 128.45 (2CH, C_{14}), 121.85 (CH, C_4), 54.93 (CH_2, C_{11}), 43.03 (CH, C_9), 32.58 (CH_2, C_8), 31.87 (CH_2, C_3), 29.21 (CH_2, C_6), 26.98 (CH_2, C_{10}), 24.27 (CH_2, C_7), 23.09 (CH_2, C_2), 14.22 (CH_3, C_1) ppm.

IR (film): 2954 (s), 2930 (s), 2869 (s), 1738 (w), 1304 (s), 1143 (s) cm^{-1}.

GCMS (CI) *m/z* (%): 310 ($(M+NH_4)^+$, 20), 293 ($(M+H)^+$, 15), 150 ($(C_{11}H_{18})^+$, 100).

HRMS (CI) for $C_{17}H_{24}O_2S$ $(M+H)^+$ calculated 293.15753, found 293.15838.

5.2.5 Preparation of 1-(2-((*E*)-2-pentylidenecyclohexyl)ethylsulfonyl)-benzene 356



A solution of *n*-BuLi (0.80 mL, 2.00 eq, 2.00 mmol) (2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) in THF (5 mL) at –78 °C. This was stirred for 10 minutes before the addition of dodec-1-en-7-yne (0.164 g, 1.00 eq, 1.00 mmol) as a solution in THF (1 mL). The cool bath was then removed and the reaction mixture was allowed to warm to room temperature over 2 hours.

The reaction mixture was cooled to –78 °C, followed by the slow addition of a solution of chloromethyl phenyl sulfone (0.248 g, 1.30 eq, 1.30 mmol) in THF (1.5 mL) and subsequently the drop wise addition of LiTMP (1.5 mL, 1.30 eq, 1.30 mmol) over 10 minutes. The reaction mixture was kept at –78 °C for 2 hours before it was quenched with MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (6 mL). The cold bath was then removed and the reaction mixture was allowed to stir vigorously for 16 hours. The product was extracted into diethyl ether (3 x 30 mL), the combined organic phases were washed with sat. $NaHCO_3$ aqueous solution (30 mL), water (30 mL) and

brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash silica column chromatography (petrol/diethyl ether 7:3) to yield the title compound, a yellow oil (0.191g, 60%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92 (2H, d, J = 6.6 Hz, H_{15}), 7.66 (1H, t, J = 6.6 Hz, H_{17}), 7.57 (2H, t, J = 6.6 Hz, H_{16}), 4.95 (1H, t, J = 7.1 Hz, H_5), 3.15–2.94 (2H, m, H_{13}), 2.13–1.84 (6H, m), 1.72–1.19 (11H, m), 0.87 (3H, t, J = 6.9 Hz, H_1) ppm.

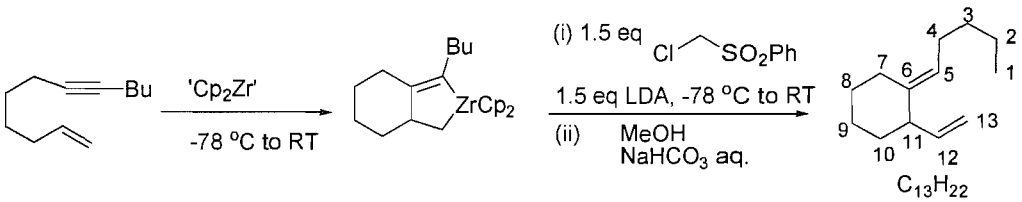
^{13}C NMR (75 MHz, $CDCl_3$): δ 139.52 (C, C_6 or C_{14}), 139.42 (C, C_6 or C_{14}), 133.73 (CH, C_{17}), 129.40 (2CH, C_{15} or C_{16}), 128.17 (2CH, C_{15} or C_{16}), 123.10 (CH, C_5), 55.11 (CH_2, C_{13}), 43.57 (CH, C_{11}), 33.83 (CH_2), 32.44 (CH_2), 27.96 (CH_2), 26.85 (CH_2), 25.95 (CH_2), 24.62 (CH_2), 23.20 (CH_2), 22.45 (CH_2), 14.16 (CH_3, C_1) ppm.

IR (film): 2953 (m), 2954 (m), 2854 (m), 2359 (w), 2331 (w), 1446 (m), 1305 (m), 1146 (m), 1086 (m), 733 (m) cm^{-1}.

GCMS (CI) *m/z* (%): 338 ($(M+NH_4)^+$, 100), 321 ($(M+H)^+$, 30).

HRMS (EI) for $C_{19}H_{28}SO_2$ $(M)^+$ calculated 320.1810, found 320.1812.

5.2.6 Preparation of (*E*)-1-pentylidine-2-vinyl-cyclohexane 357



A solution of *n*-BuLi (0.80 mL, 2.00 eq, 2.00 mmol) (2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) in THF (5 mL) at –78 °C. This was stirred for 10 minutes before the addition of dodec-1-en-7-yne (0.164 g, 1.00 eq, 1.00 mmol) as a solution in THF (1 mL). The cool bath was then removed and the reaction mixture was allowed to warm to room temperature over 2 hours.

The reaction mixture was cooled to –78 °C, followed by the slow addition of a solution of chloromethyl phenyl sulfone (0.286 g, 1.50 eq, 1.50 mmol) in THF (1.5

mL) and subsequently, the dropwise addition of LDA (1.8 mL, 1.50 mmol, 1.50 eq) over 10 minutes. The reaction mixture was kept at –78 °C for 1 hour then warmed to room temperature over 16 hours. The reaction was subsequently quenched with MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (6 mL) and stirred vigorously over 2 days. The product was extracted into diethyl ether (3 x 30 mL), the combined organic phases washed with sat. $NaHCO_3$ aqueous solution (30 mL), water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*, to yield a dark oil. The crude product was purified by flash silica column chromatography (petrol) and Kugelrohr distillation (120–130 °C / 1 mm Hg) to yield a clear oil. The product was 84% pure (determined by NMR) as it contained some quenched zirconacycle and another unidentified impurity (total mass 69 mg, 39%).

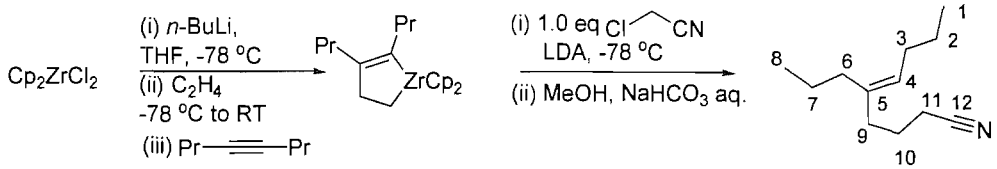
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.91 (1H, ddd, J = 16.7, 10.2, 6.7 Hz, H_{12}), 5.09 (1H, t, J = 7.2 Hz, H_5), 5.04–4.98 (2H, m, H_{13}), 2.71 (1H, m, H_{11}), 2.39 (1H, m, H_4 or H_7), 2.07–1.91 (3H, m, H_4 and H_7), 1.75–1.70 (2H, m), 1.58 (1H, m), 1.51–1.7 (7H, m), 0.91 (3H, t, J = 6.0 Hz, H_1) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 142.16 (CH, C_{12}), 140.89 (C, C_6), 122.31 (CH, C_5), 114.43 (CH_2, C_{13}), 48.85 (CH, C_{11}), 34.62 (CH_2), 32.70 (CH_2), 28.42 (CH_2), 28.16 (CH_2), 27.25 (CH_2), 25.24 (CH_2), 22.74 (CH_2), 14.44 (CH_3, C_1) ppm.

IR (film): 2955 (s), 2924 (s), 2854 (s), 1639 (w), 1446 (m), 1377 (w), 998 (w), 910 (s), 841 (w) cm^{-1}.

GCMS (EI): Retention time - 9.21 minutes *m/z* (%): 166 ($(M)^+$, 45), 137 ($(M-C_2H_5)^+$, 5), 95 ($(C_7H_{11})^+$, 100) (quenched zirconocycle).
Retention time - 9.82 minutes *m/z* (%): 178 ($(M)^+$, 50), 163 ($(M-CH_3)^+$, 10), 149 ($(M-C_2H_5)^+$, 45), 135 ($(M-C_3H_7)^+$, 70), 121 ($(M-Bu)^+$, 100) (title product).
Retention time - 13.33 and 13.40 minutes *m/z* (%): 304 ($(M)^+$, 10), 275 (5), 261 (10), 247 (60) (unidentified impurity).

5.2.7 Preparation of (*E*)-5-propyl-non-5-ene-nitrile 370



$C_{12}H_{21}N$

A solution of *n*-BuLi (0.80 mL, 2.00 eq, 2.00 mmol) (2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) in THF (5 mL) at –78 °C. This reaction mixture was warmed to room temperature under an atmosphere of ethene. A solution of 4-octyne (0.110 g, 1.00 eq, 1.00 mmol) in THF (1 mL) was then added to the reaction mixture and stirred for 2 hours.

The reaction mixture was cooled to –78 °C before the addition of chloroacetonitrile (0.075 g, 1.00 eq, 1.00 mmol) in THF (1 mL) and subsequently the dropwise addition of LDA (1.1 mL, 1.00 eq, 1.00 mmol). The reaction mixture was stirred at –78 °C for 10 minutes before it was quenched by the addition of MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (5 mL) and stirred vigorously at room temperature for 16 hours. The product was extracted into diethyl ether (3 x 30 mL), the organic phases washed with sat. $NaHCO_3$ aqueous solution (30 mL), water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by flash silica column chromatography (petrol/diethyl ether 95:5) to yield a clear colourless oil, the title product (0.103 g, 56%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.17 (1H, t, J = 7.1 Hz, H_4), 2.29 (2H, t, J = 7.2 Hz, H_{11}), 2.11 (2H, t, J = 7.2 Hz, H_9), 2.01–1.93 (4H, m, H_3 and H_6), 1.74 (2H, pentet, J = 7.2, H_{10}), 1.43–1.28 (4H, m, H_2 and H_7), 0.88 (6H, t, J = 7.4 Hz, H_1 and H_8) ppm.

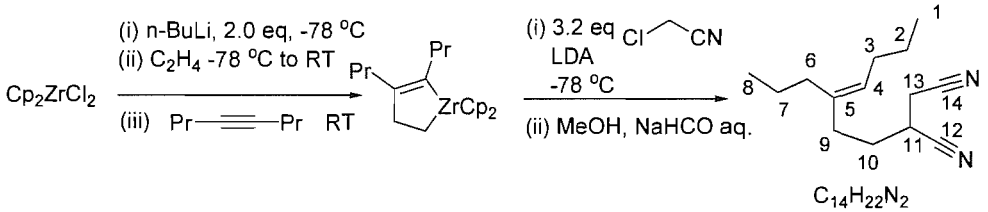
^{13}C NMR (75 MHz, $CDCl_3$): δ 136.71 (C, C_5), 127.29 (CH, C_4), 119.98 (C, C_{12}), 35.55 (CH_2, C_9), 31.77 (CH_2, C_3 or C_6), 29.90 (CH_2, C_3 or C_6), 23.84 (CH_2, C_{10}), 23.20 (CH_2, C_2 or C_7), 21.66 (CH_2, C_2 or C_7), 16.50 (CH_2, C_{11}), 14.21 (CH_3, C_1 or C_8), 13.97 (CH_3, C_1 or C_8) ppm.

IR (film): 2957 (s), 2931 (s), 2870 (m), 2245 (w), 1456 (m), 1427 (w), 1377 (w), 1085 (w), 893 (w), 738 (w) cm^{-1}.

GCMS (EI) *m/z* (%): 179 ($(M)^+$, 6), 164 ($(M\text{-}CH_3)^+$, 8), 150 ($(M\text{-}C_2H_5)^+$, 48), 136 ($(M\text{-}C_3H_7)^+$, 100), 122 ($(M\text{-}C_3H_7N)^+$, 75).

HRMS (EI) for $C_{12}H_{21}N$ $(M)^+$ calculated 179.1674, found 179.1669.

5.2.8 Preparation of 2-((*E*)-3-propyl-hept-3-enyl)-succionitrile 371



A solution of *n*-BuLi (0.80 mL, 2.00 eq, 2.00 mmol) (2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) in THF (5 mL) at –78 °C. This reaction mixture was warmed to room temperature under an atmosphere of ethene. A solution of 4-octyne (0.110 g, 1.00 eq, 1.00 mmol) in THF (1 mL) was then added to the reaction mixture and stirred for 2 hours.

The reaction mixture was cooled to –78 °C before the addition of chloroacetonitrile (0.151 g, 2.20 eq, 2.20 mmol) as a solution in THF (1 mL) followed by the dropwise addition of LDA (2.0 mL, 2.20 eq, 2.20 mmol) over 10 minutes. The reaction mixture was stirred at –78 °C for 2 hours. The reaction did not go to completion therefore further chloroacetonitrile (0.075 g, 1.00 eq, 1.00 mmol) was added as a solution in THF (1 mL) followed by LDA (1.0 mL, 1.00 eq, 1.00 mmol). The reaction mixture was stirred for 10 minutes before quenching by addition of MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (5 mL) and stirring for 16 hours at room temperature. The product was extracted into diethyl ether (3 x 30 mL), the combined organic phases were washed with sat. $NaHCO_3$ aqueous solution (30 mL), water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by flash silica column chromatography (petrol/ethyl acetate 3:1) followed by Kugelrohr distillation (130-150 °C / <1 mm Hg) to yield a clear colourless oil (0.050 g, 23%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.24 (1H, t, J= 7.0 Hz, H_4), 2.89 (1H, apparent pentet, J = 7.0 Hz, H_{11}), 2.76 (1H, dd, J = 16.9, 5.9 Hz, H_{13}), 2.70 (1H, dd, J = 16.9, 7.4 Hz,

H_{13}), 2.34–2.08 (2H, m, H_9), 2.05–1.93 (4H, m, H_3 and H_6), 1.90–1.83 (2H, m, H_{10}), 1.45–1.29 (4H, m, H_2 and H_7), 0.91 (3H, t, J = 7.3 Hz, H_1 or H_8), 0.90 (3H, t, J = 7.4 Hz, H_1 or H_8) ppm.

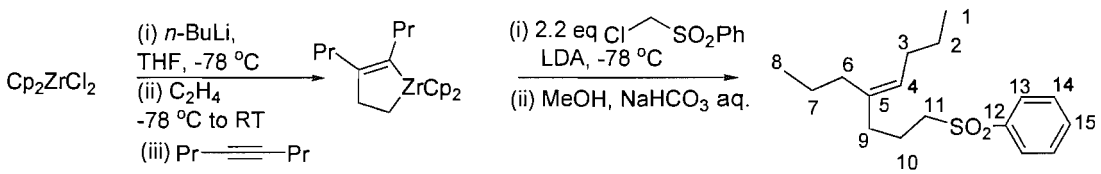
^{13}C NMR (75 MHz, $CDCl_3$): δ 136.06 (C, C_5), 128.09 (CH, C_4), 119.04 (C, C_{14}), 115.77 (C, C_{12}), 33.80 (CH_2, C_9), 31.75 (CH_2, C_3 or C_6), 30.66 (CH_2, C_{10}), 29.96 (CH_2, C_3 or C_6), 27.87 (CH, C_{11}), 23.18 (CH_2, C_2 or C_7), 21.69 (CH_2, C_2 or C_7), 21.13 (CH_2, C_{13}), 14.23 (CH_3, C_1 or C_8), 14.05 (CH_3, C_1 or C_8) ppm.

IR (film): 2957 (s), 2931 (s), 2869 (m), 2247 (w), 1650 (w), 1456 (m), 1377 (w), 893 (m) cm^{-1}.

GCMS (EI) *m/z* (%): 218 ($(M)^+$, 6), 203 ($(M\text{-}CH_3)^+$, 10), 189 ($(M\text{-}C_2H_5)^+$, 48), 175 ($(M\text{-}C_3H_7)^+$, 100) 161 ($(M\text{-}C_4H_9)^+$, 50).

HRMS (EI) for $C_{14}H_{22}N_2$ $(M)^+$ calculated 218.1783, found 218.1782.

5.2.9 Preparation of ((*E*)-4-propyl-oct-4-ene-1-sulfonyl)-benzene 372



$C_{17}H_{26}SO_2$

A solution of *n*-BuLi (0.80 mL, 2.00 eq, 2.00 mmol) (2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) in THF (5 mL) at –78 °C. This reaction mixture was warmed to room temperature under an atmosphere of ethene. A solution of 4-octyne (0.110 g, 1.00 eq, 1.00 mmol) in THF (1 mL) was then added to the reaction mixture and stirred for 2 hours.

The reaction mixture was cooled to –78 °C before the addition of chloromethyl phenyl sulfone (0.419 g, 2.20 eq, 2.20 mmol) in THF (2 mL) and subsequently the dropwise addition of LDA (2.0 mL, 2.20 eq, 2.20 mmol). The reaction mixture was stirred at –

78 °C for 2.5 hours. It was quenched with MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (5 mL) and stirred vigorously at room temperature for 16 hours. The product was extracted into diethyl ether (3 x 30 mL), the organic phases were washed with sat. $NaHCO_3$ aqueous solution (30 mL), water (30 mL) and brine (30mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by flash silica column chromatography (petrol/diethyl ether 7:3) to yield a clear colourless oil, the title product (0.214 g, 73%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (2H, d, J = 7.4 Hz, H_{13}), 7.66 (1H, t, J = 7.4 Hz, H_{15}), 7.57 (2H, t, J = 7.4 Hz, H_{14}), 5.07 (1H, t, J = 7.0 Hz, H_4), 3.07–3.02 (2H, m, H_{11}), 2.03 (2H, t, J = 7.2 Hz, H_9), 1.97–1.85 (4H, m, H_3 and H_6), 1.81 (2H, m, H_{10}), 1.31 (4H, m, H_2 and H_7), 0.87 (3H, t, J = 7.3 Hz, H_1 or H_8), 0.85 (3H, t, J = 7.4 Hz, H_1 or H_8) ppm.

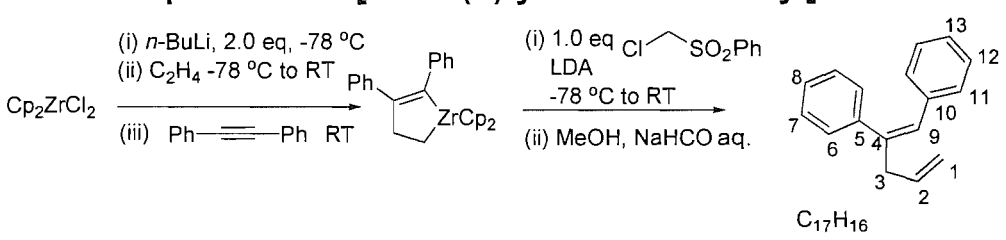
^{13}C NMR (100 MHz, $CDCl_3$): δ 139.47 (C, C_{12}), 136.97 (C, C_5), 133.74 (CH, C_{15}), 129.40 (2CH, C_{14}), 128.23 (2CH, C_{13}), 127.24 (CH, C_4), 55.86 (CH_2, C_{11}), 35.25 (CH_2, C_9), 31.77 (CH_2, C_3 or C_6), 29.94 (CH_2, C_3 or C_6), 23.25 (CH_2, C_2 or C_7), 21.63 (CH_2, C_2 or C_7), 21.12 (CH_2, C_{10}), 14.23 (CH_3, C_1 or C_8), 14.02 (CH_3, C_1 or C_8) ppm.

IR (film): 2965 (m), 2929 (w), 2870 (w), 1446 (m), 1305 (s), 1148 (s), 1086 (s), 788 (m), 730 (s), 688 (s) cm^{-1}.

GCMS (CI) *m/z* (%): 312 ($(M+NH_4)^+$, 80), 295 ($(M+H)^+$, 45), 152 ($(M-SO_2Ph)^+$, 100), 123 ($(M-C_2H_4SO_2Ph)^+$, 40).

HRMS (EI) for $C_{17}H_{26}O_2S$ $(M)^+$ calculated 294.1654, found 294.1652.

5.2.10 Preparation of [1-eth-(*Z*)-ylidine-but-3-enyl]-benzene 374



A solution of *n*-BuLi (0.80 mL, 2.00 eq, 2.00 mmol) (2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) in THF (5 mL) at –78 °C. The reaction mixture was warmed to room temperature under an atmosphere of ethene. A solution of diphenylacetylene (0.178 g, 1.00 eq, 1.00 mmol) in THF (1 mL) was then added to the reaction mixture and stirred for 2 hours.

The reaction mixture was cooled to –78 °C before the addition of chloromethyl phenyl sulfone (0.190 g, 1.00 eq, 1.00 mmol) as a solution in THF (1.5 mL) followed by the dropwise addition of LDA (1.5 mL, 1.00 eq, 1.00 mmol) over 10 minutes. The reaction was kept at –78 °C for 3 hours the warmed to room temperature over 16 hours. The reaction was quenched with MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (5 mL) and stirred for 24 hours. The product was extracted into diethyl ether (3 x 30 mL), the combined organic phases were washed with sat. $NaHCO_3$ aqueous solution (30 mL), water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by flash silica column chromatography (pentane) followed by Kugelrohr distillation (110-160 °C / 0.4 mm Hg) and radial chromatography (pentane) to yield a clear oil, which was still only 80-90% pure (0.092 g, 42%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25–7.15 (3H, m), 7.10–7.07 (2H, m), 7.03–6.96 (3H, m), 6.86–6.84 (2H, dd, J = 7.8, 1.8 Hz, H_6 or H_{11}), 6.38 (1H, s, H_9), 5.81 (1H, ddt, J = 16.8, 10.0, 6.8 Hz, H_2), 5.02 (1H, d+fs, J = 16.8 Hz, H_1 *trans*), 4.98 (1H, d+fs, J = 10.0 Hz, H_1 *cis*), 3.15 (2H, dd, J = 6.8, 1.2 Hz, H_3) ppm.

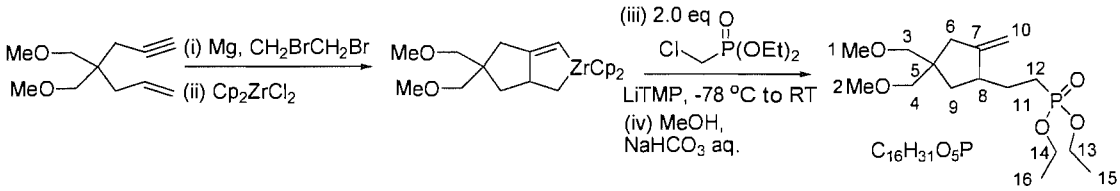
^{13}C NMR (100 MHz, $CDCl_3$): δ 141.43 (C, C_5 or C_{10}), 141.37(C, C_5 or C_{10}), 137.51 (C, C_4), 136.04 (CH, C_9), 129.21 (2CH), 128.75 (2CH), 128.62 (2CH), 128.00 (2CH), 127.25 (CH, C_8 or C_{13}), 127.13 (CH, C_8 or C_{13}), 126.44 (CH, C_2), 116.80 (CH, C_1), 44.87 (CH_2, C_3) ppm.

IR (film): 3077 (w), 3055 (w), 3023 (w), 1636 (w), 1492 (w), 1443 (w), 994 (w), 914 (m), 758 (m), 694 (s) cm^{-1}.

GCMS (CI) *m/z* (%): 238 ($(M+NH_4)^+$, 20), 220 ($(M)^+$, 100), 205 ($(M-CH_3)^+$, 85), 191 ($(M-C_2H_5)^+$, 25).

HRMS (EI) for $C_{17}H_{16}$ $(M)^+$ calculated 220.1252, found 220.1255.

5.2.11 Preparation of diethyl{2-[4,4-di(methoxymethyl)-2-methylenecyclopentyl]ethyl}phosphonate 382



Magnesium (39 mg, 1.50 eq, 1.50 mmol) was weighed into a 3 neck schlenk flask fitted with an in-line cinter and dry stirred whilst being put under argon. It was suspended in THF (3 mL) and 1,2-dibromoethane (13 μL, 0.15 eq, 0.15 mmol) was added neat. After stirring at room temperature for 1 hour. The solvent was removed by vacuum transfer. The 4,4-bis(methoxymethyl)hept-1-en-6-yne (0.182 g, 1.00 eq, 1.00 mmol) was added to the magnesium as a solution in THF (3 mL). After stirring for 30 minutes the reaction was cooled to 0 °C and Cp_2ZrCl_2 (0.322 g, 1.10 eq, 1.10 mmol) was added as a solution in THF (4 mL). The cold bath was removed and the reaction mixture was stirred at room temperature for 3 hours.

The reaction mixture was filtered to remove the magnesium and the filtrate cooled to –78 °C. A solution of diethylchloromethyl phosphonate (0.373 g, 2.00 eq, 2.00 mmol) in THF (1 mL) was added to the zirconacycle followed by the dropwise addition of LiTMP (2.2 mL, 2.00 eq. 2.00 mmol) (freshly prepared) over 20 minutes. The reaction mixture was allowed to warm to room temperature over 14 hours and quenched with MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (5 mL) and stirred vigorously for 24 hours. The product was extracted into diethyl ether (3 x 50 mL), the combined organic phases washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified using flash silica column chromatography (diethyl ether/ethyl acetate 1:1) to yield the title compound, a clear oil (120 mg, 36%), also recovered was protonated zirconacycle 5.2.14 (100 mg, 54%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.87 (1H, s, H_{10}), 4.78 (1H, s, H_{10}), 4.07 (4H, q+fs, J = 7.2 Hz, H_{13} and H_{14}), 3.32 (6H, s, H_1 and H_2), 3.23 (2H, s, H_3 or H_4), 3.19 (2H, s, H_3 or H_4), 2.49 (1H, m, H_8), 2.24 (1H, d, (AB quartet), J = 17.8 Hz, H_6), 2.20 (1H, d,

(AB quartet), J = 17.8 Hz, H_6), 1.91 (1H, m, H_{11}), 1.86 (1H, dd, J= 12.9, 8.4 Hz, H_9), 1.79–1.65 (2H, m, H_{12}), 1.52 (1H, m, H_{11}), 1.31 (6H, t, J = 7.2 Hz, H_{15} and H_{16}), 1.14 (1H, dd, J = 12.9, 9.6 Hz, H_9) ppm.

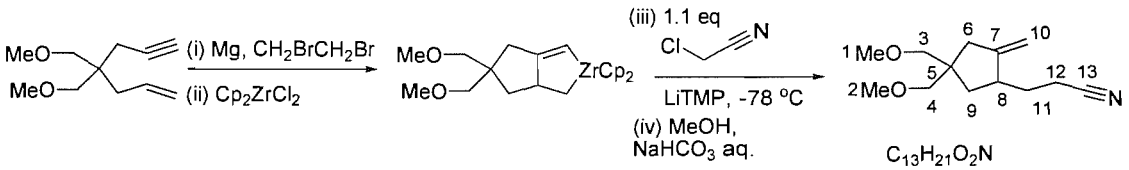
^{13}C NMR (100 MHz, $CDCl_3$): δ 153.97 (C, C_7), 106.16 (CH_2, C_{10}), 77.29 (CH_2, C_3 or C_4), 75.51 (CH_2, C_3 or C_4), 61.57 (CH_2, d, J = 2.9 Hz, C_{13} or C_{14}), 61.50 (CH_2, d, J = 3.4 Hz, C_{13} or C_{14}), 59.38 (CH_3, C_1 or C_2), 59.36 (CH_3, C_1 or C_2), 45.78 (C, C_5), 42.47 (CH, d, J = 17.5 Hz, C_8), 39.81 (CH_2, C_6), 37.41 (CH_2, C_9), 27.05 (CH_2, d, J = 4.4 Hz, C_{11}), 23.83 (CH_2, d, J = 140.1 Hz, C_{12}), 16.62 (CH_3, C_{15} or C_{16}), 16.56 (CH_3, C_{15} or C_{16}) ppm.

IR (film): 2980 (w), 2926 (w), 2874 (w), 2826 (w), 1655 (w), 1449 (w), 1391 (w), 1242 (m), 1199 (m), 1163 (w), 1103 (s), 1055 (s), 1023 (s), 956 (s), 879 (m), 787 (m) cm^{-1}.

GCMS (CI) *m/z* (%): 335 ($(M+H)^+$, 100), 303 ($(M-CH_3O)^+$, 4), 271 (128), 257 (35), 119 (24).

HRMS (EI) for $C_{16}H_{32}O_5P$ $(M)^+$ calculated 335.1982, found 335.1987.

5.2.12 Preparation of 2-[4,4-di(methoxymethyl)-2-methylenecyclopentyl]ethyl cyanide 383



$C_{13}H_{21}O_2N$

Magnesium (39 mg, 1.50 eq, 1.50 mmol) was weighed into a 3 neck schlenk flask fitted with an in-line cinter and dry stirred whilst being put under argon. It was suspended in THF (3 mL) and 1,2-dibromoethane (13 μL, 0.15 eq, 0.15 mmol) was added neat. After stirring at room temperature for 1 hour. The solvent was removed by vacuum transfer. The 4,4-bis(methoxymethyl)hept-1-en-6-yne (0.182 g, 1.00 eq, 1.00 mmol) was added to the magnesium as a solution in THF (3 mL). After stirring for 30 minutes the reaction was cooled to 0 °C and Cp_2ZrCl_2 (0.322 g, 1.10 eq, 1.10

mmol) was added as a solution in THF (4 mL). The cold bath was removed and the reaction mixture was stirred at room temperature for 3 hours.

The reaction mixture was filtered to remove the magnesium and the filtrate cooled to –78 °C. A solution of chloroacetonitrile (70 μL, 1.10 eq, 1.10 mmol) in THF (1 mL) was added to the zirconacycle and was followed by the dropwise addition of LiTMP (1.4 mL, 1.10 eq. 1.10 mmol) over 20 minutes. The reaction mixture was stirred at –78 °C for 15 minutes and quenched with HCl (6 mL, 2M aqueous solution) and stirred vigorously for 16 hours at room temperature. The product was extracted into diethyl ether (3 x 50 mL), the combined organic phases washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified using flash silica column chromatography (petrol/diethyl ether 1:1) to yield the title compound, a clear oil (45 mg, 20%). Protonated zirconacycle 5.2.14 (53 mg, 29%) was also recovered.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.85 (1H, d, J = 1.8 Hz, H_{10}), 4.72 (1H, d, J = 1.8 Hz, H_{10}), 3.26 (6H, s, H_1 and H_2), 3.17 (2H, s, H_3 or H_4), 3.13 (2H, s, H_3 or H_4), 2.53 (1H, m, H_8), 2.40–2.22 (2H, m, H_{12}), 2.18 (2H, m, H_6), 1.93 (1H, m, H_{11}), 1.84 (1H, dd, J = 13.1, 8.3 Hz, H_9), 1.54 (1H, m, H_{11}), 1.10 (1H, dd, J = 13.1, 9.5 Hz, H_9) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.39 (C, C_7), 119.87 (C, C_{13}), 106.69 (CH_2, C_{10}), 77.12 (CH_2, C_3 or C_4), 75.61 (CH_2, C_3 or C_4), 59.46 (CH_3, C_1 or C_2), 59.42 (CH_3, C_1 or C_2), 46.01 (C, C_5), 41.12 (CH, C_8), 39.48 (CH_2, C_6), 37.24 (CH_2, C_9), 30.36 (CH_2, C_{11}), 15.55 (CH_2, C_{12}) ppm.

IR (film): 2980 (m), 2926 (m), 2877 (m), 2828 (m), 2359 (w), 2246 (w), 1656 (w), 1452 (m), 1198 (m), 1105 (s), 964 (m), 884 (m) cm^{-1}.

GCMS (CI) *m/z* (%): 224 ($(M+H)^+$, 100), 192 ($(M-CH_3O)^+$, 40), 178 ($(M-CH_3OCH_2)^+$, 5), 160 (90), 146 (16).

HRMS (EI) for $C_{13}H_{21}NO_2$ $(M)^+$ calculated 223.1572, found 223.1566.

Minor **B**

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.84 (1H, dt, J = 10.6, 7.3 Hz, H_{12}), 5.48 (1H, d+fs, J = 10.6 Hz, H_{13}), 4.89 (1H, d, J = 2.0 Hz, H_{10}), 4.84 (1H, d, J = 2.0 Hz, H_{10}), 3.34 (3H, s, H_1 or H_2), 3.33 (3H, s, H_1 or H_2), 3.25 (2H, s+fs, H_3 and/or H_4), 3.22 (2H, s+fs, H_3 and/or H_4), 2.69–2.60 (2H, m, H_8 and H_{11}), 2.35 (2H, td, J = 6.8, 2.0 Hz, H_{16}), 2.32–2.19 (3H, m, H_6 and H_{11}), 1.86 (1H, dd, J = 13.1, 12.1 Hz, H_9), 1.58–1.41 (4H, m, H_{17} and H_{18}), 1.22 (1H, dd, J = 13.1, 9.9 Hz, H_9), 0.93 (3H, t, J = 7.2 Hz, H_{19}) ppm.

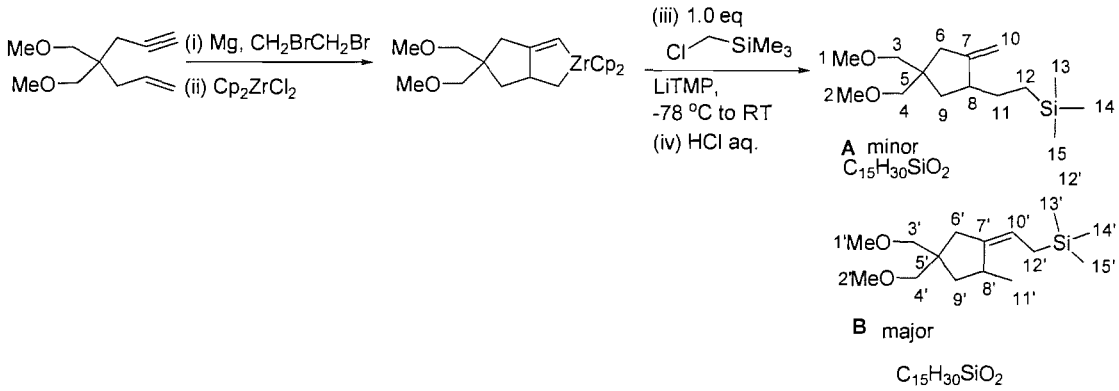
^{13}C NMR (100 MHz, $CDCl_3$): δ 154.58 (C, C_7), 140.56 (CH, C_{12}), 110.54 (CH, C_{13}), 105.64 (CH_2, C_{10}), 94.93 (C, C_{15}), 77.60 (C, C_{14}), 75.60 ($2CH_2$, C_3 and C_4), 59.44 (CH_3, C_1 or C_2), 59.41 (CH_3, C_1 or C_2), 45.78 (C, C_5), 41.70 (CH, C_8), 39.96 (CH_2, C_6), 37.81 (CH_2, C_9), 34.71 (CH_2, C_{11}), 31.11 (CH_2, C_{17}), 22.11 (CH_2, C_{18}), 19.38 (CH_2, C_{16}), 13.74 (CH_3, C_{19}) ppm.

IR (film): 2956 (m), 2925 (m), 2873 (m), 2826 (m), 1655 (w), 1458 (w), 1198 (m), 1107 (s), 964 (m), 879 (m), 737 (m) cm^{-1}.

GCMS (CI) *m/z* (%): 291 ($(M+H)^+$, 5), 259 ($(M-CH_3O)^+$, 42), 245 ($(M-CH_3OCH_2)^+$, 24), 228 ($(M-(CH_3O)_2)^+$, 10), 105 (100).

HRMS (EI) for $C_{19}H_{30}O_2$ $(M+H)^+$ calculated 290.2246, found 290.2241.

5.2.13 Preparation of an inseparable mixture of {2-[4,4-di(methoxymethyl)-2-methylcyclopentyliden]ethyl}(trimethyl)silane (major) 384 and {2-[4,4-di(methoxymethyl)-2-methylenecyclopentyl]ethyl}(trimethyl)silane (minor) 385



Magnesium (39 mg, 1.50 eq, 1.50 mmol) was weighed into a 3 neck schlenk flask fitted with an in-line cinter and dry stirred whilst being put under argon. It was suspended in THF (3 mL) and 1,2-dibromoethane (13 μL, 0.15 eq, 0.15 mmol) was added neat. After stirring at room temperature for 1 hour. The solvent was removed by vacuum transfer. The 4,4-bis(methoxymethyl)hept-1-en-6-yne (0.182 g, 1.00 eq, 1.00 mmol) was added to the magnesium as a solution in THF (3 mL). After stirring for 30 minutes the reaction was cooled to 0 °C and Cp_2ZrCl_2 (0.322 g, 1.10 eq, 1.10 mmol) was added as a solution in THF (4 mL). The cold bath was removed and the reaction mixture was stirred at room temperature for 3 hours.

A solution of chloromethyltrimethylsilane (0.19 mL, 1.39 eq, 1.39 mmol) in THF (10 mL) was cooled to –78 °C before the dropwise addition of *sec*-BuLi (0.99 mL, 1.39 eq, 1.39 mmol) (1.4 M in hexanes) followed by TMEDA (0.21 mL, 1.39 eq, 1.39 mmol). After stirring for 30 minutes at –78 °C, the zirconacycle (≈ 7.0 mL, 1.0 eq, 1.0 mmol) was added dropwise to the carbenoid over 30 minutes. The reaction was quenched with sat. $NaHCO_3$ aqueous solution (5 mL) and MeOH (5 mL), after warming slowly to room temperature in the cold bath over 16 hours. After being stirred vigorously for 6 hours the product was extracted into diethyl ether (3 x 50 mL), the combined organic phases washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The products **A** and **B** were purified using flash silica column chromatography (petrol/diethyl ether 95:5) to yield the title compounds as an inseparable mixture, a clear oil (78 mg, 29%) (ratio of major **A** to

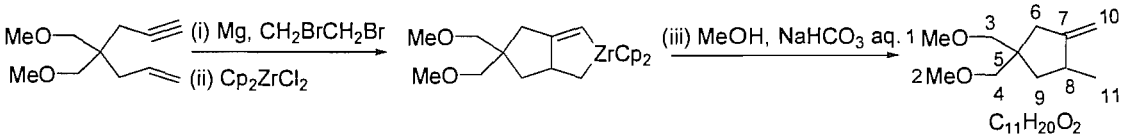
minor **B** was 3:1 determined by NMR), as well as the protonated zirconacycle 5.2.14 (48 mg, 26%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.20 (1H, t, J = 8.5 Hz, $H_{10'}$), 4.86 (1H, s, H_{10}), 4.77 (1H, s, H_{10}), 3.36–3.12 (20H, m, $H_{1\text{-}4}$ and $H_{1'\text{-}4'}$), 2.61 (1H, q, J = 7.2 Hz, H_8), 2.41 (1H, m, $H_{8'}$), 2.40–2.17 (2H, m), 2.07 (1H, d, J = 14.8 Hz), 1.92–1.84 (2H, m), 1.63 (1H, m), 1.45 (1H, dd, J = 13.9, 9.1 Hz), 1.35 (1H, ddd, J = 13.9, 7.3, 2.5 Hz), 1.24 (1H, m), 1.18 (1H, dd, J = 13.4, 6.4 Hz), 1.06 (3H, d, J = 6.8 Hz, $H_{11'}$), 0.94–0.86 (2H, m), 0.59–0.42 (2H, m), 0.01 (9H, s, $H_{13\text{–}15}$ or $H_{13'\text{–}15'}$), -0.01 (9H, s, $H_{13\text{-}15}$ or $H_{13'\text{–}15'}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.43 (C, C_7), 143.93 (C, $C_{7'}$), 117.49 (CH_2, C_{10}), 105.22 (CH, $C_{10'}$), 77.81 (CH_2, $C_{3'}$ or $C_{4'}$), 77.56 (CH_2, C_3 or C_4), 75.59 (CH_2, C_3 or C_4), 74.84 (CH_2, $C_{3'}$ or $C_{4'}$), 59.44 ($2CH_3$, C_1 and C_2, or, $C_{1'}$ and $C_{2'}$), 59.43 ($2CH_3$, C_1 and C_2, or, $C_{1'}$ and $C_{2'}$), 46.66 (C, C_5 or $C_{5'}$), 45.70 (C, C_5 or $C_{5'}$), 44.96 (CH, C_8), 40.96 (CH_2, $C_{6'}$ or $C_{9'}$), 40.22 (CH_2, C_6 or C_9), 40.09 (CH_2, $C_{6'}$ or $C_{9'}$), 37.84 (CH_2, C_6 or C_9), 32.97 (CH, $C_{8'}$), 28.88 (CH_2, C_{11}), 21.74 (CH_3, $C_{11'}$), 19.05 (CH_2, C_{12}), 14.46 (CH_2, $C_{12'}$), -1.47 ($3CH_3$, $C_{13'}$, $C_{14'}$ and $C_{15'}$), -1.58 ($3CH_3$, C_{13}, C_{14} and C_{15}) ppm.

GCMS (CI) *m/z* (%): 271 ($(M+H)^+$, 20), 239 ($(M\text{-}CH_3O)^+$, 100), 225 ($(M\text{-}CH_3\text{-}OCH_2)^+$, 8), 135 (72), 90 (78), 73($(Si(CH_3)_3)^+$, 70).

5.2.14 Preparation of 1,1-di(methoxymethyl)-3-methyl-4-methylenecyclopentane 386a



$C_{11}H_{20}O_2$

Magnesium (39 mg, 1.50 eq, 1.50 mmol) was weighed into a 3 neck schlenk flask fitted with an in-line cinter and dry stirred whilst being put under argon. It was suspended in THF (3 mL) and 1,2-dibromoethane (13 μL, 0.15 eq, 0.15 mmol) was added neat. After stirring at room temperature for 1 hour. The solvent was removed by vacuum transfer. The 4,4-bis(methoxymethyl)hept-1-en-6-yne (0.182 g, 1.00 eq, 1.00 mmol) was added to the magnesium as a solution in THF (3 mL). After stirring for 30 minutes the reaction was cooled to 0 °C and Cp_2ZrCl_2 (0.322 g, 1.10 eq, 1.10

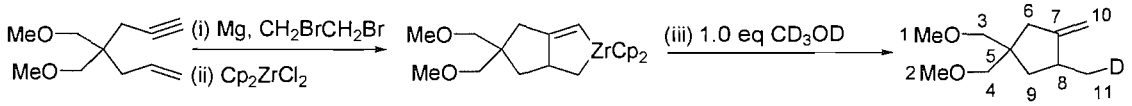
mmol) was added as a solution in THF (4 mL). The cold bath was removed and the reaction mixture was stirred at room temperature for 3 hours.

The reaction mixture was filtered to remove the magnesium, quenched with MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (5 mL) and stirred vigorously for 16 hours. The product was extracted into diethyl ether (3 x 50 mL), the combined organic phases washed with water (50 mL) and brine (50 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The product was purified using flash silica column chromatography (petrol/ether 95:5) to yield the title compound, a yellow oil (103 mg, 56%) (This is a known compound).[171]

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.81 (1H, broad s, H_{10}), 4.74 (1H, broad s, H_{10}), 3.34 (3H, s, H_1 or H_2), 3.33 (3H, s, H_1 or H_2), 3.28–3.18 (4H, m, H_3 and H_4), 2.54 (1H, m, H_8), 2.27–2.23 (2H, m, H_6), 1.89 (1H, dd, J = 13.0, 8.2 Hz, H_9), 1.08 (1H, dd, J = 13.0, 6.0 Hz, H_9), 1.07 (3H, d, J = 6.8 Hz, H_{11}) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 156.67 (C, C_7), 104.54 (CH_2, C_{10}), 77.52 (CH_2, C_3 or C_4), 75.88 (CH_2, C_3 or C_4), 59.40 (CH_3, C_1 or C_2), 59.38 (CH_2, C_1 or C_2), 45.51 (C, C_5), 40.62 (CH_2, C_9), 39.74 (CH_2, C_6), 36.79 (CH, C_8), 18.72 (CH_3, C_{11}) ppm.

5.2.15 Preparation of 3-(duteromethyl)-1,1-di(methoxymethyl)-4-methylenecyclopentane 386b



major $C_{11}H_{19}DO_2$
minor $C_{11}H_{20}O_2$

Magnesium (39 mg, 1.50 eq, 1.50 mmol) was weighed into a 3 neck schlenk flask fitted with an in-line cinter and dry stirred whilst being put under argon. It was suspended in THF (3 mL) and 1,2-dibromoethane (13 μL, 0.15 eq, 0.15 mmol) was added neat. After stirring at room temperature for 1 hour. The solvent was removed by vacuum transfer. The 4,4-bis(methoxymethyl)hept-1-en-6-yne (0.182 g, 1.00 eq, 1.00 mmol) was added to the magnesium as a solution in THF (3 mL). After stirring for 30 minutes the reaction was cooled to 0 °C and Cp_2ZrCl_2 (0.322 g, 1.10 eq, 1.10

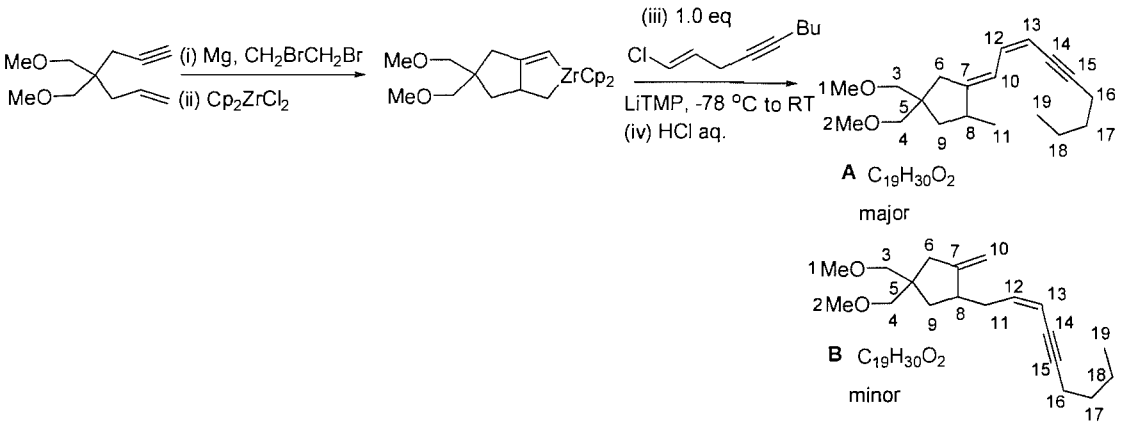
mmol) was added as a solution in THF (4 mL). The cold bath was removed and the reaction mixture was stirred at room temperature for 3 hours.

The reaction mixture was filtered to remove the magnesium, treated with CD_3OD (41μL, 1.00 eq, 1.00 mmol) and stirred at room temperature for 1.5 hours. The reaction was quenched with MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (5 mL) and stirred vigorously for 16 hours. The product was extracted into diethyl ether (3 x 50 mL), the combined organic phases washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified using flash silica column chromatography (petrol/diethyl ether 95:5) to yield the title compound, a yellow oil (89 mg, 48%) (74% deuterium incorporation determined by ^{13}C NMR analysis).

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.82 (1H, broad s, H_{10}), 4.74 (1H, broad s, H_{10}), 3.34 (3H, s, H_1 or H_2), 3.33 (3H, s, H_1 or H_2), 3.27–3.17 (4H, m, H_3 and H_4), 2.53 (1H, m, H_8), 2.31–2.18 (2H, m, H_6), 1.88 (1H, dd, J = 12.9, 8.3 Hz, H_9), 1.08 (1H, dd, J = 12.9, 10.4 Hz, H_9), 1.07 (3H, d, J = 6.6 Hz, H_{11} minor - protonated), 1.07–1.04 (2H, m, H_{11} major - deuterated) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 156.68 (C, C_7), 104.53 (CH_2, C_{10}), 77.52 (CH_2, C_3 or C_4), 75.89 (CH_2, C_3 or C_4), 59.40 (CH_3, C_1 or C_2), 59.38 (CH_3, C_1 or C_2), 45.51 (C, C_5), 40.62 (CH_2, C_9 minor), 40.59 (CH_2, C_9 major), 39.74 (CH_2, C_6), 36.79 (CH, C_8 minor), 36.71 (CH, C_8 major), 18.72 (CH_3, C_{11} minor), 18.42 (CH_2D, t, J = 19.4 Hz, C_{11} major) ppm.

5.2.16 Preparation of (*Z*)-1-[4,4-di(methoxymethyl)-2-methylcyclopentyliden]-2-nonen-4-yne (major) 388 and (*Z*)-1-[4,4-di(methoxymethyl)-2-methylenecyclopentyl]-2-nonen-4-yne (minor) 389



Magnesium (39 mg, 1.50 eq, 1.50 mmol) was weighed into a 3 neck schlenk flask fitted with an in-line cinter and dry stirred whilst being put under argon. It was suspended in THF (3 mL) and 1,2-dibromoethane (13 μL, 0.15 eq, 0.15 mmol) was added neat. After stirring at room temperature for 1 hour. The solvent was removed by vacuum transfer. The 4,4-bis(methoxymethyl)hept-1-en-6-yne (0.182 g, 1.00 eq, 1.00 mmol) was added to the magnesium as a solution in THF (3 mL). After stirring for 30 minutes the reaction was cooled to 0 °C and Cp_2ZrCl_2 (0.322 g, 1.10 eq, 1.10 mmol) was added as a solution in THF (4 mL). The cold bath was removed and the reaction mixture was stirred at room temperature for 3 hours.

The reaction mixture was filtered to remove the magnesium and the filtrate cooled to –78 °C. (*E*)-1-chloromethyl-1-octene-3-yne (0.10 mL, 1.00 eq, 1.00 mmol) was added to the zirconacycle followed by the dropwise addition of LiTMP (1.4 mL, 1.00 eq. 1.00 mmol) over 20 minutes. The reaction mixture was kept at –78 °C for 1 hour, warmed to room temperature slowly over 16 hours and quenched with HCl (6 mL, 2M aqueous solution). After being stirred vigorously for 24 hours the product was extracted into diethyl ether (3 x 50 mL), the combined organic phases washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The products were purified using flash silica column chromatography ($AgNO_3$ doped silica, petrol/diethyl ether 95:5) to yield the title compounds: major **A** – clear oil (95 mg, 33%), minor **B** - a clear oil (27 mg, 9%). The ratio of isomers from crude NMR was 2.4:1 major:minor.

Major **A**

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.48 (1H, d, J = 11.6 Hz, H_{10}), 6.43 (1H, dd, J = 11.6, 10.0 Hz, H_{12}), 5.32 (1H, broad d, J = 10.0 Hz, H_{13}), 3.35 (3H, s, H_1 or H_2), 3.32–3.29 (2H, m, H_3 and/or H_4), 3.31 (3H, s, H_1 or H_2), 3.14–3.09 (2H, m, H_3 and/or H_4), 2.87 (1H, m, H_8), 2.42 (1H, d, J = 16.3 Hz, H_{16}), 2.39 (2H, td, J = 7.0, 2.2 Hz, H_{16}), 2.25 (1H, d, J = 16.3 Hz, H_6), 1.94 (1H, dd, J = 13.4, 8.6 Hz, H_9), 1.59–1.51 (2H, m, H_{17}), 1.49–1.41 (2H, m, H_{18}), 1.26 (1H, dd, J = 13.4, 6.6 Hz, H_9), 1.13 (3H, d, J = 7.0 Hz, H_{11}), 0.93 (3H, t, J = 7.3 Hz, H_{19}) ppm.

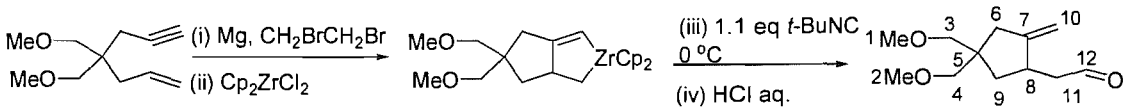
^{13}C NMR (100 MHz, $CDCl_3$): δ 154.44 (C, C_7), 135.51 (CH, C_{10} or C_{12}), 119.52 (CH, C_{10} or C_{12}), 106.81 (CH, C_{13}), 97.00 (C, C_{15}), 78.00 (C, C_{14}), 77.32 (CH_2, C_3 or C_4), 74.90 (CH_2, C_3 or C_4), 59.42 (CH_3, C_1 or C_2), 59.39 (CH_3, C_1 or C_2), 47.00 (C, C_5), 40.70 (CH_2, C_6), 40.22 (CH_2, C_9), 34.17 (CH, C_8), 31.11 (CH_2, C_{17}), 22.71 (CH_3, C_{11}), 22.14 (CH_2, C_{18}), 19.58 (CH_2, C_{16}), 13.74 (CH_3, C_{19}) ppm.

IR (film): 2957 (w), 2927 (w), 2872 (w), 2824 (w), 1643 (w), 1457 (w), 1430 (w), 1389 (w), 1197 (w), 1104 (s), 963 (w), 910 (w), 752 (w) cm^{-1}.

GCMS (EI) *m/z* (%): 290 ($(M)^+$, 30), 275 ($(M\text{-}CH_3)^+$, 6), 258 ($(M\text{-}CH_3O)^+$, 25), 213 (90), 143 (100).

HRMS (EI) for $C_{19}H_{30}O_2$ $(M+H)^+$ calculated 290.2246, found 290.2251.

5.2.17 Preparation of 2-[4,4-di(methoxymethyl)-2-methylenecyclopentyl]acetaldehyde 393



$C_{12}H_{20}O_3$

Magnesium (39 mg, 1.50 eq, 1.50 mmol) was weighed into a 3 neck schlenk flask fitted with an in-line cinter and dry stirred whilst being put under argon. It was suspended in THF (3 mL) and 1,2-dibromoethane (13 μL, 0.15 eq, 0.15 mmol) was added neat. After stirring at room temperature for 1 hour. The solvent was removed by vacuum transfer. The 4,4-bis(methoxymethyl)hept-1-en-6-yne (0.182 g, 1.00 eq,

1.00 mmol) was added to the magnesium as a solution in THF (3 mL). After stirring for 30 minutes the reaction was cooled to 0 °C and Cp_2ZrCl_2 (0.322 g, 1.10 eq, 1.10 mmol) was added as a solution in THF (4 mL). The cold bath was removed and the reaction mixture was stirred at room temperature for 3 hours.

The reaction mixture was filtered to remove the magnesium and the filtrate cooled to 0 °C. *tert*-Butyl isocyanide (100 μL, 1.00 eq, 1.00 mmol) was added to the zirconacycle, which changed colour from brown/black to dark brown. The reaction mixture was stirred at 0 °C for 30 minutes and at room temperature for 1 hour before being quenched with HCl (6 mL, 2M aqueous solution) and stirred vigorously for 16 hours. The product was extracted into diethyl ether (3 x 50 mL), the combined organic phases washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The products were purified using flash silica column chromatography (petrol/diethyl ether 9:1) to yield the title compound, a clear oil (52 mg, 25%), also recovered was protonated zirconacycle 5.2.14 (18 mg, 10%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.80 (1H, s, H_{12}), 4.89 (1H, d, J = 1.8 Hz, H_{10}), 4.73 (1H, d, J = 1.8 Hz, H_{10}), 3.34 (3H, s, H_1 or H_2), 3.33 (3H, s, H_1 or H_2), 3.24 (2H, s, H_3 and/or H_4), 3.23 (2H, s, H_3 and/or H_4), 2.99 (1H, m, H_8), 2.70 (1H, dd, J = 16.8, 5.2 Hz, H_{11}), 2.44 (1H, dd, J = 16.8, 8.0 Hz, H_{11}), 2.30 (1H, d, (AB quartet), J = 19.7 Hz, H_6), 2.26 (1H, d, (AB quartet), J = 19.7 Hz, H_6), 2.00 (1H, dd, J = 13.0, 8.4 Hz, H_9), 1.21 (1H, dd, J = 13.0, 10.3 Hz, H_9) ppm.

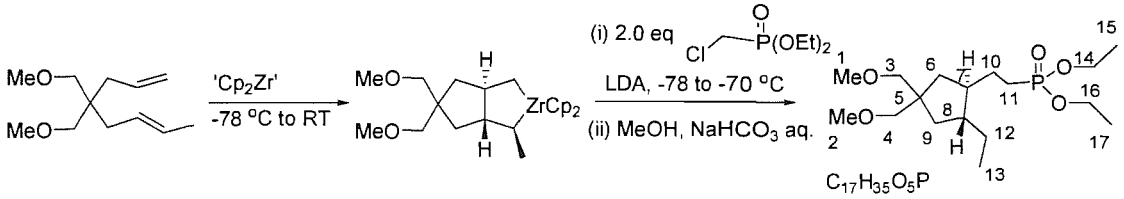
^{13}C NMR (100 MHz, $CDCl_3$): δ 202.14 (CH, C_{12}), 153.82 (C, C_7), 106.03 (CH_2, C_{10}), 77.16 (CH_2, C_3 or C_4), 75.79 (CH_2, C_3 or C_4), 59.43 (CH_3, C_1 or C_2), 59.38 (CH_3, C_1 or C_2), 48.63 (CH_2, C_{11}), 45.98 (C, C_5), 39.37 (CH_2, C_6), 38.29 (CH_2, C_9), 36.52 (CH, C_8) ppm.

IR (film): 2980 (w), 2877 (m), 2825 (m), 2722 (w), 1723 (s), 1656 (w), 1477 (w), 1451 (w), 1390 (w), 1198 (m), 1105 (s), 966 (m), 908 (w), 882 (m), 734 (m) cm^{-1}.

GCMS (CI) *m/z* (%): 213 ($(M+H)^+$, 75), 181 ($(M-CH_3O)^+$, 68), 163 (78), 149 (100), 105 (74).

HRMS (EI self CI) for $C_{12}H_{21}O_3$ $(M+H)^+$ calculated 213.1491, found 213.1487.

5.2.18 Preparation of (2-(2-ethyl-4,4-methoxymethyl-cyclopentyl)-ethyl)-phosphinic acid diethyl ester 394



A solution of *n*-BuLi (0.80 ml, 2.00 eq, 2.00 mmol) (2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) at –78 °C. After 10 minutes a solution of 4,4-bis-methoxymethyl-octa-1,6-diene (0.196 g, 1.00 eq, 1.00 mmol) in THF (1 mL) was added. The reaction mixture was allowed to warm to room temperature over 3 hours.

The reaction mixture was cooled to -78 °C before addition of diethylchloromethyl phosphonate (0.373 g, 2.00 eq, 2.00 mmol) in THF (1 mL). This was followed by the dropwise addition of LDA (1.8 mL, 2.00 eq, 2.00 mmol) over 10 minutes. The reaction was quenched after warming to -70 °C by addition of MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (5 mL) then stirred vigorously for 24 hours. The product was extracted into diethyl ether (3 x 30 mL), the combined organic phases were washed with sat. $NaHCO_3$ aqueous solution (30 mL), water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash silica column chromatography (ethyl acetate/DCM 7:3) to yield a clear colourless oil, the title product (0.257 g, 73%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.10–4.01 (4H, m, H_{14} and H_{16}), 3.311 (3H, s, H_1 or H_2), 3.309 (3H, s, H_1 or H_2), 3.19–3.13 (4H, m, H_3 and H_4), 1.85 (1H, m), 1.81–1.69 (3H, m), 1.66–1.58 (3H, m), 1.40 (1H, m), 1.30 (6H, t, J = 7.0 Hz, H_{15} and H_{17}), 0.99 (4H, m), 0.85 (3H, t, J = 7.3 Hz, H_{13}) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 77.84 (CH_2, C_3 or C_4), 77.70 (CH_2, C_3 or C_4), 61.52 (CH_2, d, J = 2.8 Hz, C_{14} or C_{16}), 61.42 (CH_2, d, J = 2.3 Hz, C_{14} or C_{16}), 59.31 ($2CH_3$, C_1 and C_2), 46.62 (CH, C_8), 45.45 (CH, d, J = 16.9 Hz, C_7), 45.10 (C, C_5), 38.86 (CH_2, C_6 or C_9), 38.81 (CH_2, C_6 or C_9), 26.56 (CH_2, C_{12}), 26.52 (CH_2, d, J = 5.7 Hz,

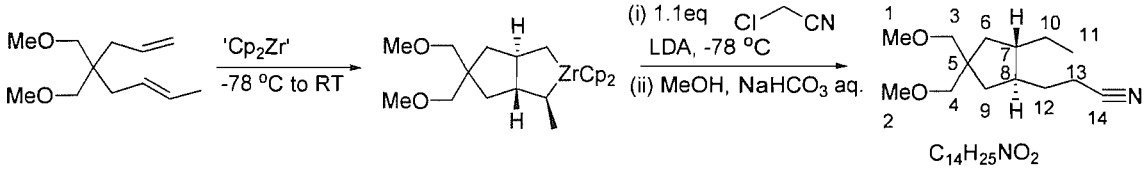
C_{10}), 24.47 (CH_2, d, J = 40.2 Hz, C_{11}), 16.61 (CH_3, C_{15} or C_{17}), 16.53 (CH_3, C_{15} or C_{17}), 12.58 (CH_3, C_{13}) ppm.

IR (film): 2977 (w), 2956 (w), 2927 (m), 2872 (m), 2825 (w), 1450 (m), 1390 (w), 1236 (m), 1199 (m), 1166 (s), 1055 (s), 1027 (s), 956 (s), 786 (m), 729 (s) cm^{-1}.

GCMS (EI) *m/z* (%): 351 (self CI, $(M+H)^+$, 76), 335 ($(M-CH_3)^+$, 20), 321 ($(M-C_2H_5)^+$, 10), 286 ($(M-C_9H_{10}O_2)^+$, 13), 152 ($(C_5H_{13}PO_3)^+$, 100).

HRMS (CI) for $C_{17}H_{36}O_5P$ $(M+H)^+$ calculated 351.2300, found 351.2310.

5.2.19 Preparation of 3-(2-ethyl-4,4-bis-methoxymethyl-cyclopentenyl)-proprionitrile 395



$C_{14}H_{25}NO_2$

A solution of *n*-BuLi (0.80 ml, 2.00 eq, 2.00 mmol) (2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) at –78 °C. After 10 minutes a solution of 4,4-bis-methoxymethyl-octa-1,6-diene (0.196 g, 1.00 eq, 1.00 mmol) in THF (1 mL) was added. The reaction mixture was allowed to warm to room temperature over 3 hours.

The reaction mixture was cooled to –78 °C before addition of chloroacetonitrile (0.083 g, 1.10 eq, 1.10 mmol) in THF (1 mL). This was followed by the dropwise addition of LDA (1.4 mL, 1.10 eq, 1.10 mmol) over 20 minutes. The reaction mixture changed from yellow to red. The reaction was quenched after a 10 minutes at –78 °C by addition of MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (5 mL) then stirred vigorously for 24 hours. The product was extracted into diethyl ether (3 x 30 mL), the combined organic phases were washed with sat. $NaHCO_3$ aqueous solution (30 mL), water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified twice by column chromatography (petrol/ethyl acetate 87.5:12.5) to yield a clear colourless oil, the title product (0.123 g, 51%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.33 (6H, s, H_1 and H_2), 3.23–3.15 (4H, m, H_3 and H_4), 2.39 (1H, ddd, J = 13.8, 8.3, 5.3 Hz, H_{13}), 2.28 (1H, m, H_{13}), 1.96 (1H, tdd, J = 11.6, 8.3, 3.1 Hz, H_{12}), 1.82 (1H, dd, J = 6.7, 2.6 Hz, H_9), 1.77 (1H, dd, J = 7.1, 2.2 Hz, H_6), 1.63–1.47 (2H, m, H_7 and H_{10}), 1.45–1.31 (2H, m, H_8 and H_{12}), 1.06 (1H, d, J = 10.9, 7.1 Hz, H_6), 1.05 (1H, m, H_{10}), 1.00 (1H, dd, J = 10.7, 6.7 Hz, H_9), 0.88 (3H, t, J = 7.3 Hz, H_{11}) ppm.

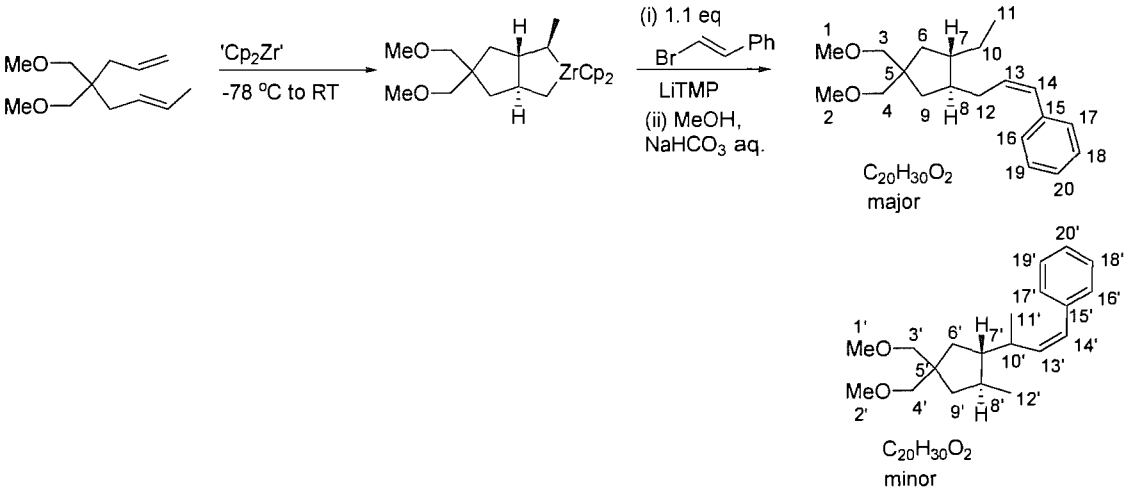
^{13}C NMR (100 MHz, $CDCl_3$): δ 120.07 (C, C_{14}), 77.86 (CH_2, C_3 or C_4), 77.81 (CH_2, C_3 or C_4), 59.41 ($2CH_3$, C_1 and C_2), 46.77 (CH, C_8), 45.37 (C, C_5), 43.99 (CH, C_7), 38.84 (CH_2, C_6), 38.62 (CH_2, C_9), 29.94 (CH_2, C_{12}), 26.57 (CH_2, C_{10}), 16.23 (CH_2, C_{13}), 12.61 (CH_3, C_{11}) ppm.

IR (film): 2956 (m), 2924 (m), 2873 (m), 2825 (m), 2244 (w), 1450 (m),1197 (s), 956 (m) cm^{-1}.

GCMS (CI) *m/z* (%): 257 ($(M+NH_4)^+$, 5), 240 ($(M+H)^+$, 100), 208 ($(M-CH_3O)^+$, 45), 192 ($(M-C_2H_6O)^+$, 15), 176 ($(M-C_2H_6O_2)^+$, 100).

HRMS (EI) for $C_{14}H_{25}NO_2$ $(M)^+$ calculated 239.1885, found 239.1891.

5.2.20 Preparation of an inseparable mixture of 1-{(Z)-3-[2-ethyl-4,4-di(methoxymethyl)cyclopentyl]-1-propenyl}benzene (major) 400 and 1-{(Z)-3-[4,4-di(methoxymethyl)-2-methylcyclopentyl]-1-butenyl}benzene (minor) 401



A solution of *n*-BuLi (0.80 ml, 2.00 eq, 2.00 mmol) (2.5 M in hexanes) was added to

a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) at –78 °C. After 10 minutes a solution of 4,4-bis-methoxymethyl-octa-1,6-diene (0.196 g, 1.00 eq, 1.00 mmol) in THF (1 mL) was added. The reaction mixture was allowed to warm to room temperature over 3 hours.

A solution of β-bromostyrene (0.14 mL, 1.10 eq, 1.10 mmol) in THF (1mL) was added to the reaction mixture at –78 °C before the dropwise addition of LiTMP (1.2 mL, 1.10 eq, 1.10 mmol) over 10 minutes. The reaction was quenched after 3 hours at –78 °C by addition of MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (5 mL) and stirred vigorously for 16 hours. The product was extracted into diethyl ether (3 x 30 mL), the combined organic phases were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash silica column chromatography (petrol/diethyl ether 95:5) to yield a clear colourless oil, an inseparable mixture of the title products (0.192 g, 64%, ratio major:minor 4:1).

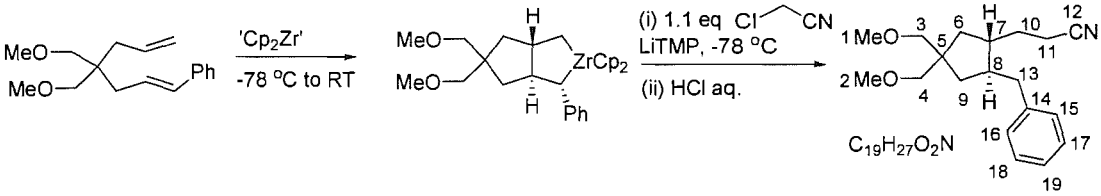
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.19 (10H, m, $H_{16\text{-}20}$, $H_{16'\text{-}20'}$), 6.39 (1H, d, J = 11.6 Hz, H_{14}), 6.31 (1H, d, J = 11.6 Hz, $H_{14'}$), 5.66 (1H, td, J = 11.6, 7.3 Hz, H_{13}), 5.54 (1H, dd, J = 11.6, 10.7 Hz, $H_{13'}$), 3.321 (3H, s, H_1 or H_2), 3.317 (3H, s, $H_{1'}$or $H_{2'}$), 3.30 (6H, s, H_1 or H_2 and $H_{1'}$ or $H_{2'}$), 3.21–3.13 (8H, m, H_3, H_4, $H_{3'}$ and $H_{4'}$), 2.80 (1H, m, $H_{10'}$), 2.59 (1H, m, H_{12}), 2.06 (1H, m, H_{12}), 1.79 (1H, t, J = 13.0 Hz, H_6 or H_9), 1.77 (1H, t, J = 13.0 Hz, H_6 or H_9), 1.71–1.49 (6H, m, H_6, H_7 or H_8, $H_{7'}$ or $H_{8'}$, $H_{9'}$ and H_{10}), 1.48–1.32 (2H, m, H_7 or H_8 and $H_{7'}$ or $H_{8'}$), 1.21 (1H, dd, J = 13.1, 11.1 Hz, $H_{6'}$ or $H_{9'}$), 1.09–0.92 (9H, m, H_6, H_9, $H_{11'}$, $H_{12'}$ and $H_{6'}$ or $H_{9'}$), 0.85 (3H, t, J = 7.4 Hz, H_{11}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.22 (CH, $C_{13'}$), 138.11 (C, $C_{15'}$), 137.97 (C, C_{15}), 132.00 (CH, C_{13}), 129.21 (CH, C_{14}), 128.94 (2CH, C_{Ar}), 128.74 (2CH, C_{Ar}), 128.26 (2CH, C_{Ar}), 128.20 (2CH, C_{Ar}), 126.85 (CH, $C_{14'}$), 126.52 (2CH, C_{20} and $C_{20'}$), 77.99 (CH_2, C_3 or C_4), 77.96 (CH_2, C_3 or C_4), 77.73 ($2CH_2$, $C_{3'}$ and $C_{4'}$), 59.37 ($2CH_3$, C_1 or C_2, and $C_{1'}$ or $C_{2'}$), 59.35 ($2CH_3$, C_1 or C_2, and $C_{1'}$ or $C_{2'}$), 51.57 (CH, $C_{7'}$ or $C_{8'}$), 46.74 (CH, C_7 or C_8), 45.42 (CH, C_7 or C_8), 45.30 (C, C_5), 44.96 (C, $C_{5'}$), 42.08 (CH_2, $C_{6'}$ or $C_{9'}$), 39.33 (CH_2, C_6 or C_9), 38.83 (CH_2, C_6 or C_9), 37.30 (CH, $C_{7'}$ or $C_{8'}$), 35.66 (CH_2, $C_{6'}$ or $C_{9'}$),

34.44 (CH, $C_{10'}$), 32.77 (CH_2, C_{12}), 26.71 (CH_2, C_{10}), 19.32 (CH_3, $C_{11'}$ or $C_{12'}$), 17.32 (CH_3, $C_{11'}$ or $C_{12'}$), 12.67 (CH_3, C_{11}) ppm.

GCMS (CI) *m/z* (%): minor - 303 $((M+H)^+$, 28), 271 $((M-CH_3O)^+$, 32), 239 (84), 131 (100), 107 (100); major – 303 $((M+H)^+$, 44), 271 $((M-CH_3O)^+$, 62), 239 (100), 117 (88).

5.2.21 Preparation of 3-[2-benzyl-4,4-di(methoxymethyl)cyclopentyl] propanenitrile 402



A solution of *n*-BuLi (0.80 mL, 2.00 eq, 2.00 mmol) (2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) in THF (5 mL) at –78 °C. This was stirred for 10 minutes before the addition of (4,4-bis-methoxymethyl-hepta-1,6-dienyl)-benzene (0.260 g, 1.00 eq, 1.00 mmol) as a solution in THF (1 mL). The cold bath was then removed and the reaction mixture was allowed to warm to room temperature over 4 hours.

A solution of chloroacetonitrile (70 μL, 1.10 eq, 1.10 mmol) in THF (1mL) was added to the reaction mixture at –78 °C before the dropwise addition of LiTMP (1.2 mL, 1.10 eq, 1.10 mmol) over 15 minutes, upon which the reaction mixture changed from red to very dark red in colour. The reaction was quenched after 15 minutes by addition of HCl (6 mL, 2M aqueous solution) and stirred vigorously for 16 hours. The product was extracted into diethyl ether (3 x 30 mL), the combined organic phases were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash silica column chromatography (petrol/diethyl ether 1:1) to yield a clear colourless oil, the title product (0.179 g, 59%). Quenched zirconacycle 5.2.25 (0.046 g, 18%) was also recovered.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (2H, t, J = 7.3 Hz, H_{17} and H_{18}), 7.16 (1H, t, J = 7.3 Hz, H_{19}), 7.12 (2H, d, J = 7.3 Hz, H_{15} and H_{16}), 3.31 (3H, s, H_1 or H_2), 3.26 (3H, s, H_1 or H_2), 3.18–3.10 (4H, m, H_3 and H_4), 2.83 (1H, dd, J = 13.3, 4.5 Hz, H_{13}), 2.38 (1H, dd, J = 13.3, 9.2 Hz, H_{13}), 2.33 (1H, dd, J = 8.1, 5.4 Hz, H_{11}), 2.24 (1H, m, H_{11}), 1.94 (1H, m, H_{10}), 1.83 (1H, dd, J = 12.9, 7.4 Hz, H_6), 1.77 (1H, m, H_8), 1.69 (1H, m, H_7), 1.72 (1H, dd, J = 13.3, 7.4, H_9), 1.38 (1H, m, H_{10}), 1.16 (1H, dd, J = 13.3, 10.6 Hz, H_9), 1.05 (1H, dd, J = 12.9, 10.3 Hz, H_6) ppm.

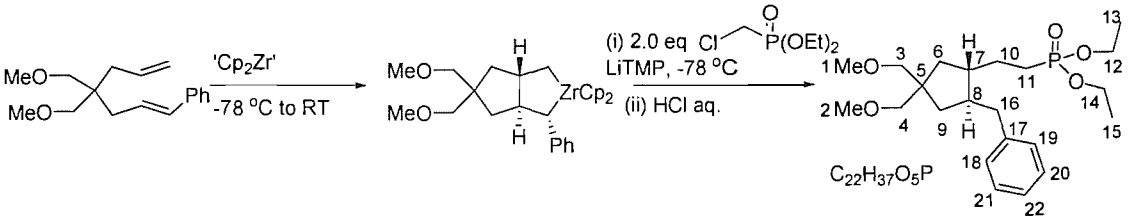
^{13}C NMR (100 MHz, $CDCl_3$): δ 144.05 (C, C_{14}), 128.95 (2CH, C_{15} and C_{16}), 128.43 (2CH, C_{17} and C_{18}), 126.03 (CH, C_{19}), 119.87 (C, C_{12}), 77.82 ($2CH_2$, C_3 and C_4), 59.36 (CH_3, C_1 or C_2), 59.31 (CH_3, C_1 or C_2), 46.77 (CH, C_8), 45.45 (C, C_5), 44.13 (CH, C_7), 40.41 (CH_2, C_{13}), 39.35 (CH_2, C_9), 38.05 (CH_2, C_6), 29.98 (CH_2, C_{10}), 16.13 (CH_2, C_{11}) ppm.

IR (film): 3027 (w), 2976 (w), 2922 (m), 2872 (m), 2826 (m), 1602 (w), 1495 (m), 1452 (m), 1198 (m), 1102 (s), 963 (m) cm^{-1}.

GCMS (EI) *m/z* (%): 301 ($(M)^+$, 20), 286 ($(M\text{-}CH_3)^+$, 6), 239 ($(M\text{-}C_2H_6O_2)^+$, 36), 224 ($(M\text{-}C_6H_5)^+$, 26), 91 ($(C_6H_5CH_2)^+$, 100).

HRMS (EI) for $C_{19}H_{27}NO_2$ $(M)^+$ calculated 301.2042, found 301.2043.

5.2.22 Preparation of diethyl{2-[2-benzyl-4,4-di(methoxymethyl) cyclopentyl]ethyl}phosphate 403



A solution of *n*-BuLi (0.80 mL, 2.00 eq, 2.00 mmol) (2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) in THF (5 mL) at –78 °C. This was stirred for 10 minutes before the addition of (4,4-bis-methoxymethyl-hepta-1,6-dienyl)-benzene (0.260 g, 1.00 eq, 1.00 mmol) as a solution in THF (1 mL).

The cold bath was then removed and the reaction mixture was allowed to warm to room temperature over 4 hours.

A solution of diethyl chloromethyl phosphonate (0.373 g, 2.00 eq, 2.00 mmol) in THF (1mL) was added to the reaction mixture at –78 °C before the dropwise addition of LiTMP (1.5 mL, 2.00 eq, 2.00 mmol) over 20 minutes. The reaction was quenched after slowly warming to room temperature over 16 hours by addition of HCl (6 mL, 2M aqueous solution) and stirred vigorously for 3 hours. The product was extracted into diethyl ether (3 x 30 mL), the combined organic phases were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash silica column chromatography (ethyl acetate) to yield a clear colourless oil, the title product (0.267 g, 65%). Quenched zirconacycle 5.2.25 (0.045 g, 17%) was also recovered.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (2H, t, J = 7.4 Hz, H_{20} and H_{21}), 7.14 (1H, t, J = 7.4 Hz, H_{22}), 7.13 (2H, d, J = 7.4 Hz, H_{18} and H_{19}), 4.24–4.04 (4H, m, H_{12} and H_{14}), 3.30 (3H, s, H_1 or H_2), 3.26 (3H, s, H_1 or H_2), 3.17–3.07 (4H, m, H_3 and H_4), 2.90 (1H, dd, J = 13.3, 4.9 Hz, H_{16}), 2.30 (1H, dd, J = 13.3, 9.8 Hz, H_{16}), 1.94 (1H, m, H_8), 1.84–1.63 (3H, m, H_7, H_{10} and H_{11}), 1.80 (1H, dd, J = 12.9, 7.5 Hz, H_6), 1.61–1.48 (2H, m, H_{10} and H_{11}), 1.57 (1H, dd, J = 13.4, 7.3 Hz, H_9), 1.31 (6H, t, J = 7.0 Hz, H_{13} and H_{15}), 1.12 (1H, dd, J = 13.4, 10.8 Hz, H_9), 1.03 (1H, dd, J = 12.9, 10.8 Hz, H_6) ppm.

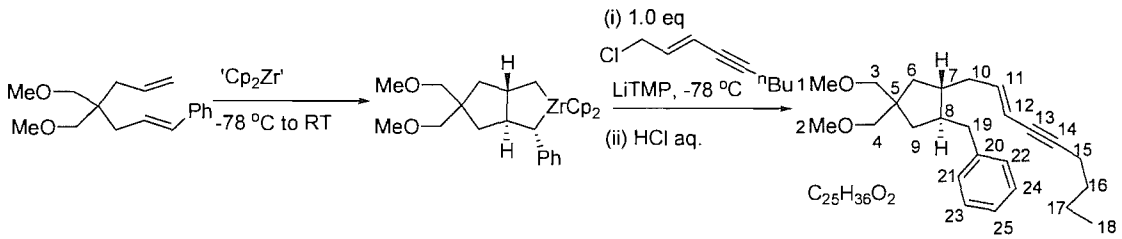
^{13}C NMR (100 MHz, $CDCl_3$): δ 141.44 (C, C_{17}), 128.98 (2CH, C_{18} and C_{19}), 128.32 (2CH, C_{20} and C_{21}), 125.83 (CH, C_{22}), 77.87 (2CH_2, C_3 and C_4), 61.65 (CH_2, d, J = 1.9 Hz, C_{12} or C_{14}), 61.53 (CH_2, d, J = 1.5 Hz, C_{12} or C_{14}), 59.34 (CH_3, C_1 or C_2), 59.29 (CH_3, C_1 or C_2), 46.78 (CH, C_8), 45.61 (CH, d, J = 17.0 Hz, C_7), 45.21 (C, C_5), 40.38 (CH_2, C_{16}), 39.31 (CH_2, C_9), 38.70 (CH_2, C_6), 26.64 (CH_2, d, J = 19.3 Hz, C_{10}), 24.53 (CH_2, d, J = 61.2 Hz, C_{11}), 16.65 (CH_3, C_{13} or C_{15}), 16.58 (CH_3, C_{13} or C_{15}) ppm.

IR (film): 2979 (w), 2922 (m), 2870 (m), 2852 (w), 1452 (m), 1390 (s), 1230 (s), 1200 (m), 1102 (s), 1055 (s), 1027 (s), 958 (s) cm^{-1}.

MS (ES)$^+$ *m/z* (%): 413 ($(M+H)^+$, 100), 435 ($(M+Na)^+$, 65)

HRMS (ES)$^+$ for $C_{22}H_{38}NaO_5P$ $(M+Na)^+$ calculated 435.2271, found 435.2264.

5.2.23 Preparation of (*E*)-1-[2-benzyl-4,4-di(methoxymethyl) cyclopentyl]-2-nonen-4-yne 404



A solution of *n*-BuLi (0.80 mL, 2.00 eq, 2.00 mmol) (2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) in THF (5 mL) at –78 °C. This was stirred for 10 minutes before the addition of (4,4-bis-methoxymethyl-hepta-1,6-dienyl)-benzene (0.260 g, 1.00 eq, 1.00 mmol) as a solution in THF (1 mL). The cold bath was then removed and the reaction mixture was allowed to warm to room temperature over 4 hours.

A solution of (*E*)-1-chloromethyl-1-octene-3-yne (0.1 mL, 1.00 eq, 1.00 mmol) in THF (1mL) was added to the reaction mixture at –78 °C before the dropwise addition of LiTMP (1.30 mL, 1.00 eq, 1.00 mmol) over 20 minutes. The reaction was quenched after 1.5 hours at –78 °C by addition of HCl (6 mL, 2M aqueous solution) and stirred vigorously for 16 hours. The products ware extracted into diethyl ether (3 x 30 mL), the combined organic phases were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash silica column chromatography (petrol/diethyl ether 92.5:7.5) to yield a clear colourless oil, the title product (0.185 g, 50%). Quenched zirconacycle 5.2.25 (0.081 g, 31%) was also recovered.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (2H, t, J = 7.4 Hz, H_{23} and H_{24}), 7.15–7.12 (3H, m, H_{21}, H_{22} and H_{25}), 5.83 (1H, dt, J = 10.5, 7.5 Hz, H_{11}), 5.47 (1H, d, J =10.5 Hz, H_{12}), 3.30 (3H, s, H_1 or H_2), 3.26 (3H, s, H_1 or H_2), 3.17–3.09 (4H, m, H_3 and H_4), 3.00 (1H, dd, J = 13.3, 3.6 Hz, H_{19}), 2.60 (1H, m, H_{10}), 2.33 (2H, m, H_{15}), 2.28 (1H, dd, J = 13.3, 9.8 Hz, H_{19}), 2.20 (1H, dt, J = 14.8, 7.5 Hz, H_{10}), 1.77 (1H, m, H_8), 1.74 (1H, dd, J = 13.3, 7.3 Hz, H_6 or H_9), 1.65 (1H, m, H_7), 1.57 (1H, dd, J = 13.3, 7.0 Hz,

H_6 or H_9), 1.55–1.48 (2H, m, H_{16}), 1.45–1.38 (2H, m, H_{17}), 1.14 (1H, dd, J = 13.3, 10.6 Hz, H_6 or H_9), 1.09 (1H, dd, J = 13.3, 10.8 Hz, H_6 or H_9), 0.90 (3H, t, J = 7.2 Hz, H_{18}) ppm.

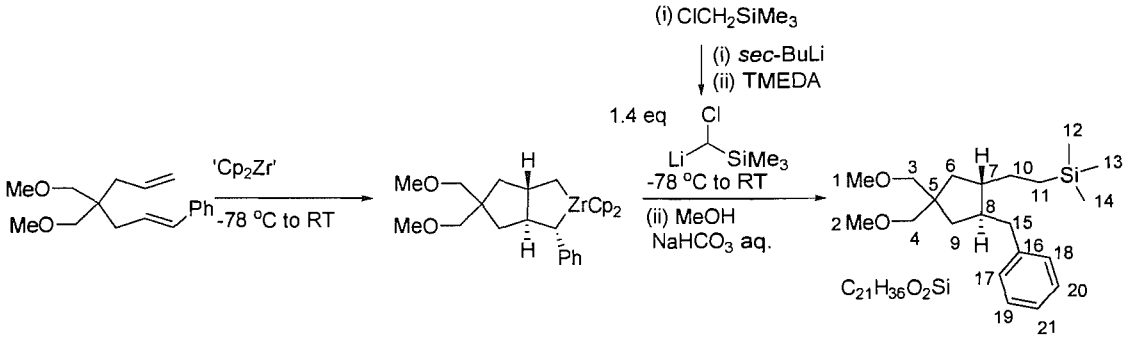
^{13}C NMR (100 MHz, $CDCl_3$): δ 141.76 (C, C_{20}), 140.71 (CH, C_{11}), 129.06 (2CH, C_{21} and C_{22}), 128.29 (2CH, C_{23} and C_{24}), 125.76 (CH, C_{25}), 110.36 (CH, C_{12}), 94.86 (C, C_{13} or C_{14}), 77.87 ($2CH_2$, C_3 and C_4), 77.69 (C, C_{13} or C_{14}), 59.37 (CH_3, C_1 or C_2), 59.31 (CH_3, C_1 or C_2), 46.58 (CH, C_7 or C_8), 45.27 (C, C_5), 44.69 (CH, C_7 or C_8), 40.43 (CH_2, C_{19}), 39.08 (CH_2, C_6 or C_9), 38.81 (CH_2, C_6 or C_9), 33.93 (CH_2, C_{10}), 31.12 (CH_2, C_{15}), 22.14 (CH_2, C_{16}), 19.39 (CH_2, C_{17}), 13.75 (CH_3, C_{18}) ppm.

IR (film): 3025 (w), 2955 (m), 2925 (m), 2872 (m), 2824 (m), 1603 (w), 1494 (w), 1453 (m), 1198 (m), 1104 (s), 963 (m), 750 (m) cm^{-1}.

GCMS (EI) *m/z* (%): 368 ($(M)^+$, 4), 304 ($(M-C_6H_5)^+$, 6), 291 ($(M-C_6H_5CH_2)^+$, 12), 91 ($(C_6H_5CH_2)^+$, 100), 77 ($(C_6H_5)^+$, 45).

HRMS (EI) for $C_{25}H_{36}O_2$ $(M)^+$ calculated 368.2715, found 368.2708.

5.2.24 Preparation of {2-[2-benzyl-4,4-di(methoxymethyl) cyclopentyl]ethyl}(trimethyl)silane 405



A solution of *n*-BuLi (0.80 mL, 2.00 eq, 2.00 mmol) (2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) in THF (5 mL) at –78 °C. This was stirred for 10 minutes before the addition of (4,4-bis-methoxymethyl-hepta-1,6-dienyl)-benzene (0.260 g, 1.00 eq, 1.00 mmol) as a solution in THF (1 mL). The cold bath was then removed and the reaction mixture was allowed to warm to room temperature over 4 hours.

A solution of chloromethyltrimethylsilane (0.19 mL, 1.39 eq, 1.39 mmol) in THF (10 mL) was cooled to –78 °C before the dropwise addition of *sec*-BuLi (0.99 mL, 1.39 eq, 1.39 mmol) (1.4 M solution in hexanes) followed by TMEDA (0.21 mL, 1.39 eq, 1.39 mmol). After stirring for 30 minutes at –78 °C, the zirconacycle (≈ 7.0 mL, 1.00 eq, 1.00 mmol) was added dropwise to the carbenoid over 30 minutes. The reaction was quenched after warming slowly to room temperature over 24 hours. The reaction was quenched by addition of MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (5 mL) and stirred vigorously for 16 hours. The product was extracted into diethyl ether (3 x 30 mL), the combined organic phases were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash silica column chromatography (petrol/diethyl ether 96:4) to yield a clear colourless oil, the title product (0.187 g, 54%). Quenched zirconacycle 5.2.25 was also recovered (0.041 g, 16%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (2H, t, J = 7.3 Hz, H_{19} and H_{20}), 7.14–7.11 (3H, m, H_{17}, H_{18} and H_{21}), 3.30 (3H, s, H_1 or H_2), 3.27 (3H, s, H_1 or H_2), 3.19–3.09 (4H, m, H_3 and H_4), 2.87 (1H, dd, J = 13.4, 4.1 Hz, H_{15}), 2.28 (1H, dd, J = 13.4, 9.7 Hz, H_{15}), 1.79 (1H, dd, J = 13.1, 7.5 Hz, H_6), 1.68 (1H, m, H_8), 1.64–1.53 (2H, m, H_9 and H_{10}), 1.48 (1H, m, H_7), 1.09 (1H, dd, J = 13.1, 10.8 Hz, H_9), 1.02 (1H, m, H_{10}), 0.99 (1H, dd, J = 13.1, 10.8 Hz, H_6), 0.54 (1H, ddd, J = 14.3, 12.5, 4.3 Hz, H_{11}), 0.38 (1H, ddd, J = 14.0, 12.5, 5.02 Hz, H_{11}), -0.05 (9H, s, $H_{12\text{-}14}$) ppm.

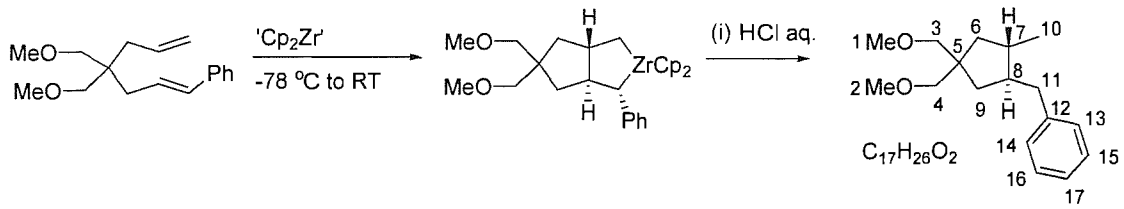
^{13}C NMR (100 MHz, $CDCl_3$): δ 141.95 (C, C_{16}), 129.02 (2CH, C_{17} and C_{18}), 128.28 (2CH, C_{19} and C_{20}), 125.72 (CH, C_{21}), 78.01 (CH_2, C_3 or C_4), 77.97 (CH_2, C_3 or C_4), 59.38 (CH_3, C_1 or C_2), 59.33 (CH_3, C_1 or C_2), 47.99 (CH, C_8), 46.50 (CH, C_7), 45.06 (C, C_5), 40.71 (CH_2, C_{15}), 39.58 (CH_2, C_9), 39.05 (CH_2, C_6), 27.98 (CH_2, C_{10}), 14.85 (CH_2, C_{11}), -1.56 ($3CH_3$, $C_{12\text{-}14}$) ppm.

IR (film): 2951 (m), 2913 (m), 2872 (m), 2823 (m), 1602 (w), 1452 (m), 1247 (m), 1106 (s), 963 (m), 861 (s), 831 (s) cm^{-1}.

GCMS (CI) *m/z* (%): 349 ($(M+H)^+$, 80), 271 ($(M-C_6H_5)^+$, 10), 257 ($(M-C_6H_5CH_2)^+$, 5), 91 ($(C_6H_5CH_2)^+$, 100), 73 ($(Si(CH_3)_3)^+$, 85).

HRMS (EI) for $C_{21}H_{36}SiO_2$ $(M)^+$ calculated 348.2485, found 348.2487.

5.2.25 Preparation of 1-{[4,4-di(methoxymethyl)-2-methylcyclopentyl]methyl}benzene 406



A solution of *n*-BuLi (0.80 mL, 2.00 eq, 2.00 mmol) (2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) in THF (5 mL) at –78 °C. This was stirred for 10 minutes before the addition of (4,4-bis-methoxymethyl-hepta-1,6-dienyl)-benzene (0.260 g, 1.00 eq, 1.00 mmol) as a solution in THF (1 mL). The cold bath was then removed and the reaction mixture was allowed to warm to room temperature over 16 hours.

The reaction was quenched by addition of HCl (6 mL, 2 M aqueous solution) and stirred vigorously for 3 hours. The product was extracted into diethyl ether (3 x 30 mL), the combined organic phases were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash silica column chromatography (petrol/diethyl ether 92:8) to yield a clear colourless oil, the title product (0.208 g, 83%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (2H, t, J = 7.5, H_{15} and H_{16}), 7.15–7.12 (3H, m, H_{13}, H_{14} and H_{17}), 3.30 (3H, s, H_1 or H_2), 3.26 (3H, s, H_1 or H_2), 3.18–3.07 (4H, m, H_3 or H_4), 2.89 (1H, dd, J = 13.3, 3.2 Hz, H_{11}), 2.28 (1H, dd, J = 13.3, 8.9 Hz, H_{11}), 1.74 (1H, dd, J = 13.3, 6.6 Hz, H_6), 1.61–1.54 (3H, m, H_7, H_8 and H_9), 1.11–0.96 (2H, m, H_6 and H_9), 0.96 (3H, d, J = 5.8 Hz, H_{10}) ppm.

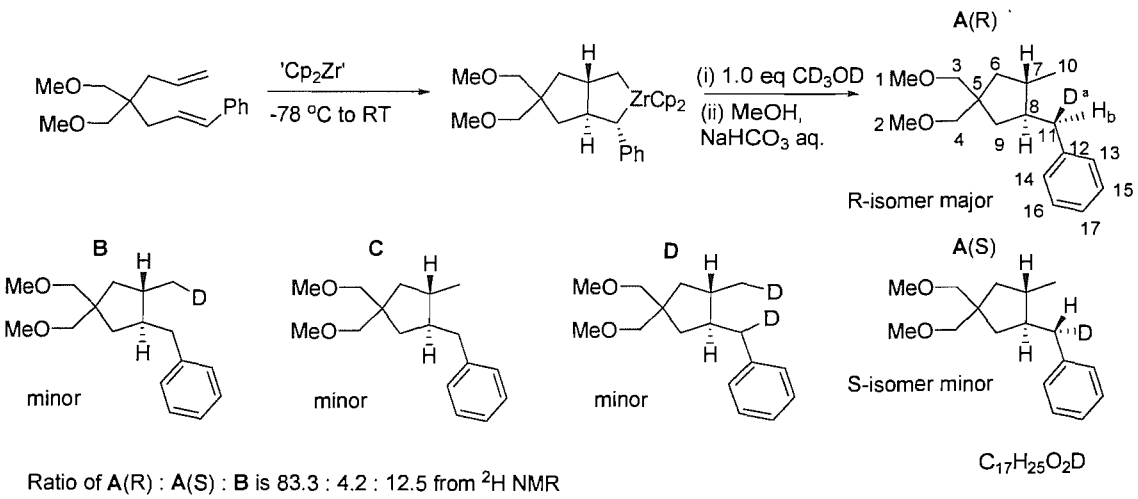
^{13}C NMR (100 MHz, $CDCl_3$): δ 141.90 (C, C_{12}), 129.02 (2CH, C_{15} and C_{16}), 128.27 (2CH, C_{13} and C_{14}), 125.71 (CH, C_{17}), 78.08 (CH_2, C_3 or C_4), 78.00 (CH_2, C_3 or C_4), 59.36 (CH_3, C_1 or C_2), 59.09 (CH_3, C_1 or C_2), 48.66 (CH, C_8), 45.20 (C, C_5), 41.92 (CH_2, C_6), 40.33 (CH_2, C_{11}), 39.81 (CH, C_7), 39.54 (CH_2, C_9), 18.33 (CH_3, C_{10}) ppm.

IR (film): 3026 (w), 2957 (w), 2949 (m), 2921 (m), 2870 (m), 2823 (m), 1453 (m), 1376 (w), 1198 (m), 1105 (s), 964 (m) cm^{-1}.

GCMS (CI) *m/z* (%): 262 ($(M)^+$, 45), 231 ($(M\text{-}CH_3O)^+$, 12), 185 ($(M\text{-}C_6H_5)^+$, 57), 138 (91), 91 ($(C_7H_7)^+$, 100).

HRMS (EI) for $C_{17}H_{26}O_2$ $(M)^+$ calculated 262.1933, found 262.1935.

5.2.26 Preparation of mono-deuterated 1-{[4,4-di(methoxymethyl)-2-methylcyclopentyl]methyl}benzene (*R*) 406b-d



Ratio of A(R) : A(S) : B is 83.3 : 4.2 : 12.5 from ^2H NMR
Ratio of protonated : deuterated : bis-deuterated 11 : 85 : 4 by MS

A solution of *n*-BuLi (0.80 mL, 2.00 eq, 2.00 mmol) (2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) in THF (5 mL) at –78 °C. This was stirred for 10 minutes before the addition of (4,4-bis-methoxymethyl-hepta-1,6-dienyl)-benzene (0.260 g, 1.00 eq, 1.00 mmol) as a solution in THF (1 mL). The cold bath was then removed and the reaction mixture was allowed to warm to room temperature over 4 hours.

A solution of CD_3OD (41 μL, 1.00 eq, 1.00 mmol) in THF (1mL) was added to the reaction mixture at room temperature and stirred for 1 hour. The reaction was quenched by addition of sat. $NaHCO_3$ solution (5 mL) and MeOH (5 mL) and stirred vigorously for 16 hours. The product was extracted into diethyl ether (3 x 30 mL), the combined organic phases were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by

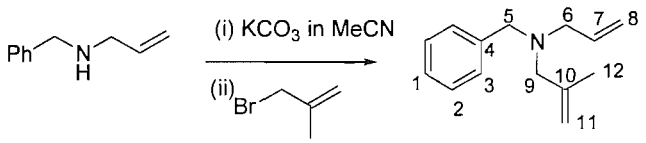
flash silica column chromatography (petrol/diethyl ether 92:8) to yield a clear colourless oil, the title product (0.202 g, 77%). A combination of ^{2}H NMR spectroscopy and mass spectrometry (EI and CI) were used to calculate the approximate composition of the mixture of isomers as **A**(R) - 71%, **A**(S) - 3%, **B** - 11%, **C** - 11% and **D** - 4%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (2H, t, J = 7.5, H_{15} and H_{16}), 7.16–7.12 (3H, m, H_{13}, H_{14} and H_{17}), 3.30 (3H, s, H_1 or H_2), 3.26 (3H, s, H_1 or H_2), 3.18–3.08 (4H, m, H_3 and H_4), 2.87 (<0.3H, dd, J = 13.3, 3.0 Hz, H_{11b}(**A**-*S*, **B**, **C**, **D**)), 2.28 (<0.2H, dd, J = 13.3, 8.5 Hz, H_{11a}(**B**, **C**, **D**)), 2.26 (<0.8H, d, J = 8.5 Hz, H_{11a}(**A**-*R*)) 1.74 (1H, dd, J = 13.2, 6.1 Hz, H_6), 1.60–1.53 (3H, m, H_7, H_8 and H_9), 1.15–0.97 (2H, m, H_6 and H_9), 0.96 (3H, d, J = 5.5 Hz, H_{10}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 141.87 (C, C_{12}), 129.02 (2CH, C_{15} and C_{16}), 128.27 (2CH, C_{13} and C_{14}), 125.72 (CH, C_{17}), 78.07 (CH_2, C_3 or C_4), 78.00 (CH_2, C_3 or C_4), 59.36 (CH_3, C_1 or C_2), 59.31 (CH_3, C_1 or C_2), 48.66 (CH, C_8 α carbon protonated), 48.60 (CH, C_8 α carbon deuterated), 45.21 (C, C_5), 41.92 (CH_2, C_6), 40.32 (CH_2, C_{11} protonated), 40.06 (CHD, t, J = 17.9 Hz, C_{11} deuterated), 39.78 (CH, C_7 α carbon protonated), 39.72 (CH, C_7 α carbon deuterated), 39.54 (CH_2, C_9 β carbon protonated), 39.52 (CH_2, C_9 β carbon deuterated), 18.33 (CH_3, C_{10} protonated), 18.03 (CH_2D, t, J = 19.2 Hz, C_{10} deuterated) ppm.

GCMS (EI) *m/z*: 263($(M)^+$, 30), 232 ($(M-CH_3O)^+$, 5), 186 ($(M-C_6H_5)^+$, 35), 92 ($(C_6H_5CHD)^+$, 100).

5.2.27 Preparation of *N*-benzyl-*N*-(2-methylallyl)prop-2-en-1-amine



$C_{14}H_{19}N$

This compound was previously made within the group and is found in the literature, however does not appear to have been fully characterised.

Potassium carbonate (11.92 g, 3.75 eq, 86.25 mmol) was suspended in acetonitrile (70 mL) before *N*-allyl-benzyl amine (3.38 g, 1.00 eq, 23.00 mmol) was added as a solution in acetonitrile (5 mL). This was followed by the addition of 3-bromo-2-methyl propene (3.02 mL, 1.30 eq, 30.00 mmol). The reaction was stirred at room temperature for 16 hours. The product was extracted into diethyl ether (3 x 50 mL), washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by Kugelrohr distillation (70-77 °C / 3 mm Hg) to yield a clear colourless oil (4.12 g, 88%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.22 (5H, m, H_1, H_2 and H_3), 5.89 (1H, ddt, J = 17.1, 10.3, 6.3 Hz, H_7), 5.21 (1H, dq, J = 17.1, 1.5 Hz, H_8), 5.15 (1H, d+fs, J =10.3 Hz, H_8), 4.96 (1H, d, J = 0.9 Hz, H_{11}), 4.87 (1H, d, J = 0.9 Hz, H_{11}), 3.54 (2H, s, H_5), 3.03 (2H, d+fs, J = 6.3 Hz, H_6), 2.95 (2H, s, H_9), 1.78 (3H, s, H_{12}) ppm.

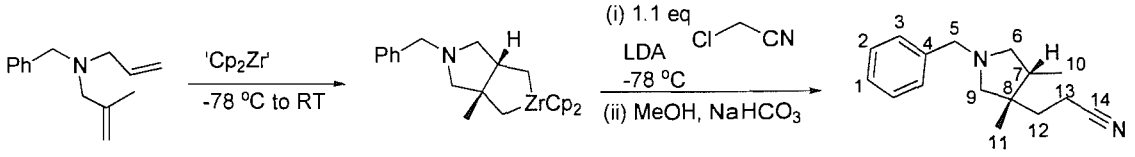
^{13}C NMR (75 MHz, $CDCl_3$): δ 144.15 (C, C_{10}), 140.05 (C, C_4), 136.26 (CH, C_7), 128.79 (CH, C_2 or C_3), 128.26 (CH, C_2 or C_3), 126.81 (CH, C_1), 117.17 (CH_2, C_8 or C_{11}), 112.67 (CH_2, C_8 or C_{11}), 60.62 (CH_2, C_5 or C_6 or C_9), 57.81 (CH_2, C_5 or C_6 or C_9), 56.42 (CH_2, C_5 or C_6 or C_9), 20.92 (CH_3, C_{12}) ppm.

IR (film): 3073 (w), 3028 (w), 2976 (w), 2917 (w), 2879 (w), 2791 (m), 1643 (w), 1444 (m), 1369 (m), 1123 (m), 1027 (m), 988 (m), 916 (s), 894 (s), 736 (s) cm^{-1}.

GCMS (CI) *m/z* (%): 203 ($(M+H)^+$, 10), 202 ($(M)^+$, 50), 160 ($(M-C_3H_6)^+$, 45), 91 ($(PhCH_2)^+$, 100).

HRMS (ES)$^+$ for $C_{14}H_{19}N$ $(M)^+$, calculated 202.1590, found 202.1592.

5.2.28 Preparation of 3-(1-benzyl-3,4-dimethylpyrrolidin-3-yl)propanenitrile 408



$C_{16}H_{22}N_2$

A solution of *n*-BuLi (0.80 ml, 2.00 eq, 2.00 mmol) (2.5 M solution in hexanes) was

added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) at -78 °C. After 10 minutes a solution of *N*-allyl-*N*-benzyl-*N*-(2-methylallyl)-amine (0.201 g, 1.00 eq, 1.00 mmol) in THF (1 mL) was added. The cool bath was removed and the reaction mixture was warmed to room temperature over 3 hours.

The reaction mixture was cooled to –78 °C before addition of chloroacetonitrile (0.083 g, 1.10 eq, 1.10 mmol) in THF (1 mL), followed by the dropwise addition of LDA (1.4 mL, 1.10 eq, 1.10 mmol) over 20 minutes. The reaction mixture changed from orange/yellow to dark red. The reaction was quenched after a further 10 minutes at –78 °C by addition of MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (5 mL) and stirred for 24 hours. The product was extracted into diethyl ether (3 x 30 mL), the combined organic phases were washed with sat. $NaHCO_3$ aqueous solution (30 mL), water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash silica column chromatography (petrol/diethyl ether/Et_3N 73:25:2 to 48:50:2) to yield a clear colourless oil, the title product (0.155 g, 64%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.19 (5H, m, H_1, H_2 and H_3), 3.61 (1H, d, J = 13.1 Hz, H_5), 3.54 (1H, d, J = 13.1 Hz, H_5), 2.84 (1H, dd, J = 9.5, 8.5 Hz, H_6), 2.36 (2H, s, H_9), 2.34–2.16 (3H, m, H_6 and H_{13}), 1.92 (1H, apparent sextet, J = 7.7 Hz, H_7), 1.78 (1H, ddd, J = 13.6, 10.8, 5.5 Hz, H_{12}), 1.58 (1H, ddd, J = 13.4, 10.8, 5.8 Hz, H_{12}), 0.99 (3H, s, H_{11}), 0.87 (3H, d, J = 7.3 Hz, H_{10}) ppm.

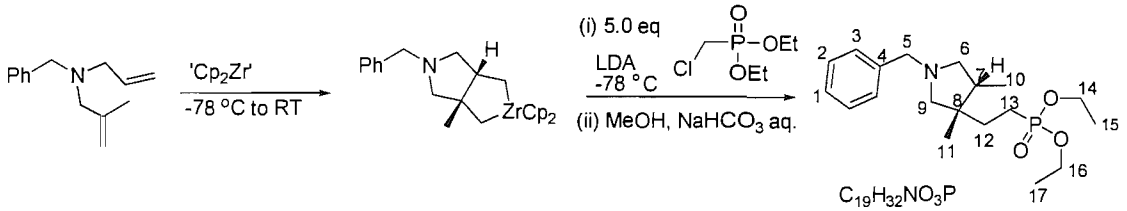
^{13}C NMR (100 MHz, $CDCl_3$): δ 139.63 (C, C_4), 128.56 (2CH, C_2 or C_3), 128.36 (2CH, C_2 or C_3), 126.90 (CH, C_1), 120.69 (C, C_{14}), 64.67 (CH_2, C_5), 60.94 (CH_2, C_6 or C_9), 60.57 (CH_2, C_6 or C_9), 43.18 (CH, C_7), 42.27 (C, C_8), 31.16 (CH_2, C_{12}), 24.19 (CH_3, C_{11}), 13.12 (CH_3, C_{10}), 13.07 (CH_2, C_{13}) ppm.

IR (film): 2957 (s), 2932 (m), 2905 (m), 2873 (m), 2786 (m), 2246 (w), 1494 (m), 1453 (s), 1375 (m), 1127 (m), 737 (s) cm^{-1}.

GCMS (EI) *m/z* (%): 242 ($(M)^+$, 6), 202 ($(M-C_2H_2N)^+$, 5), 151 ($(M-PhCH_2)^+$, 8), 91 ($(PhCH_2)^+$, 100).

HRMS (ES)$^+$ for $C_{16}H_{23}N_2$ $(M+H)^+$ calculated 243.1856, found 243.1857.

5.2.29 Preparation of (2-(1-benzyl-3,4-dimethyl-pyrrolidin-3-yl)ethyl)-phosphonic acid diethylester 409



A solution of *n*-BuLi (0.80 ml, 2.00 eq, 2.00 mmol) (2.5 M solution in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) at -78 °C. After 10 minutes a solution of *N*-allyl-*N*-benzyl-*N*-(2-methylallyl)-amine (0.201 g, 1.00 eq, 1.00 mmol) in THF (1 mL) was added. The cool bath was removed and the reaction mixture was warmed to room temperature over 3 hours.

The reaction mixture was cooled to –78 °C before addition of diethylchloromethyl phosphonate (0.373 g, 2.00 eq, 2.00 mmol) in THF (1 mL). This was followed by the dropwise addition of LDA (1.8 mL, 2.00 eq, 2.00 mmol) over 10 minutes. A further 3 equivalents of phosphonate and LDA were added over 2 hours. The reaction was quenched after a further 30 minutes at –78 °C by addition of MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (5 mL) and stirred for 24 hours. The product was extracted into diethyl ether (3 x 30 mL), the combined organic phases were washed with sat. $NaHCO_3$ aqueous solution (30 mL), water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by flash silica column chromatography (petrol/ethyl acetate/Et_3N 48:50:2) followed by radial chromatography (petrol/ethyl acetate/Et_3N 83:15:2) to yield a clear colourless oil, the title product (0.199 g, 56%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26–7.17 (5H, m, $H_{1\text{-}3}$), 4.11–4.01 (4H, m, H_{14} and H_{16}), 3.59 (1H, d, J = 13.0 Hz, H_5), 3.51 (1H, d, J = 13.0 Hz, H_5), 2.87 (1H, dd, J = 9.0, 7.9 Hz, H_6), 2.38 (1H, d, J = 9.3 Hz, H_9), 2.28 (1H, d, J = 9.3 Hz, H_9), 2.18 (1H, t, J = 9.0 Hz, H_6), 1.91 (1H, sextet, J = 7.3 Hz, H_7), 1.73–1.50 (3H, m, H_{12} and H_{13}), 1.47–1.42 (1H, m, H_{12} or H_{13}), 1.29 (3H, t, J = 7.0 Hz, H_{15} or H_{17}), 1.28 (3H, t, J = 7.0 Hz, H_{15} or H_{17}), 0.96 (3H, s, H_{11}), 0.86 (3H, d, J = 7.0 Hz, H_{10}) ppm.

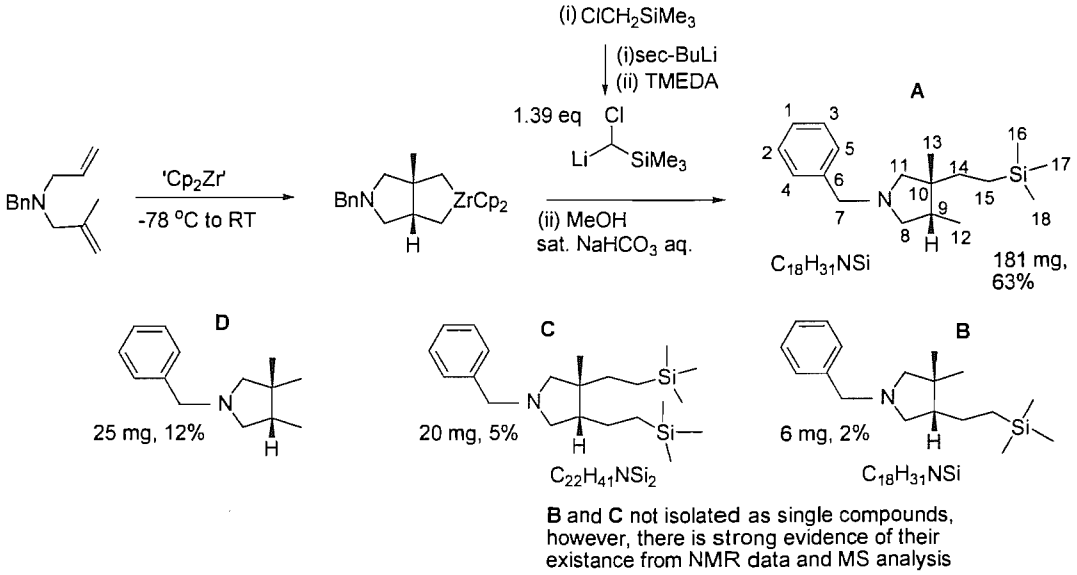
^{13}C NMR (100 MHz, $CDCl_3$): δ 139.79 (C, C_4), 128.56 (2CH, C_2 or C_3), 128.25 (2CH, C_2 or C_3), 126.83 (CH, C_1), 65.12 (CH_2, C_9), 61.62 (CH_2, broad s, C_{14} or C_{16}), 61.55 (CH_2, broad s, C_{14} or C_{16}), 61.43 (CH_2, C_6), 60.76 (CH_2, C_5), 43.40 (CH, C_7), 42.41 (C, d, J = 16.4 Hz, C_8), 27.62 (CH_2, d, J = 4.5 Hz, C_{12}), 24.86 (CH_3, C_{11}), 21.46 (CH_2, d, J = 140.7 Hz, C_{13}), 16.65 (CH_3, C_{16} or C_{17}), 16.58 (CH_3, C_{16} or C_{17}), 13.32 (CH_3, C_{10}) ppm.

IR (film): 2957 (w), 2928 (w), 2906 (w), 2872 (w), 2783 (w), 1453 (w), 1374 (w), 1250 (m), 1230 (m), 1162 (w), 1055 (s), 1026 (s), 956 (s), 787 (m), 734 (m) cm^{-1}.

MS (ES)$^+$ *m/z* (%): 354 ($(M+H)^+$, 30%).

HRMS (ES)$^+$ for $C_{19}H_{33}NO_3P$ $(M+H)^+$ calculated 354.2193, found 354.2186.

5.2.30 Preparation of 1-benyl-3,4-dimethyl-3[(1,1,1-trimethyl silyl)methyl]tetrahydro-1*H*-pyrrole 410



A solution of *n*-BuLi (0.80 ml, 2.00 eq, 2.00 mmol) (2.5 M solution in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) at -78 °C. After 10 minutes a solution of *N*-allyl-*N*-benzyl-*N*-(2-methylallyl)-amine (0.201 g, 1.00 eq, 1.00 mmol) in THF (1 mL) was added. The cool bath was removed and the reaction mixture was warmed to room temperature over 3 hours.

A solution of chloromethyltrimethylsilane (0.19 mL, 1.39 eq, 1.39 mmol) in THF (10 mL) was cooled to –78 °C before the dropwise addition of *sec*-BuLi (0.99 mL, 1.39 eq, 1.39 mmol) followed by TMEDA (0.21 mL, 1.39 eq, 1.39 mmol). After stirring for 30 minutes at –78 °C, the zirconacycle (≈7.0 mL, 1.0 eq, 1.0 mmol) was added dropwise to the carbenoid over 30 minutes. The reaction was quenched after 30 minutes at –78 °C by addition of MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (5 mL) and stirred vigorously for 16 hours. The products were extracted into diethyl ether (3 x 30 mL), the combined organic phases were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash silica column chromatography (petrol/diethyl ether/Et_3N 93:5:2) to yield a mixture of products as clear colourless oils. The major product **A** was isolated in part as a single compound and the spectral data recorded for it is related below (0.181 g, 63%). Quenched zirconacycle **D** was also recovered (0.025 g, 12%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33–7.25 (4H, m, $H_{2\text{-}5}$), 7.23 (1H, t, J = 6.9 Hz, H_1), 3.66 (1H, d, J = 13.3 Hz, H_7), 3.60 (1H, d, J = 13.3 Hz, H_7), 2.96 (1H, dd, J = 9.0, 7.5 Hz, H_8), 2.47 (1H, d, J = 9.3 Hz, H_{11}), 2.37 (1H, d, J = 9.3 Hz, H_{11}), 2.21 (1H, t, J = 9.0 Hz, H_8), 1.95 (1H, apparent sextet, J = 7.4 Hz, H_9), 1.31 (1H, apparent td, J = 13.4, 4.5 Hz, H_{14}), 1.17 (1H, apparent td, J = 13.4, 4.5 Hz, H_{14}), 1.00 (3H, s, H_{13}), 0.88 (3H, d, J = 7.0 Hz, H_{12}), 0.42 (1H, apparent td, J = 13.4, 4.5 Hz, H_{15}), 0.32 (1H, apparent td, J = 13.4, 4.5 Hz, H_{15}), 0.00 (9H, s, $H_{16\text{-}18}$) ppm.

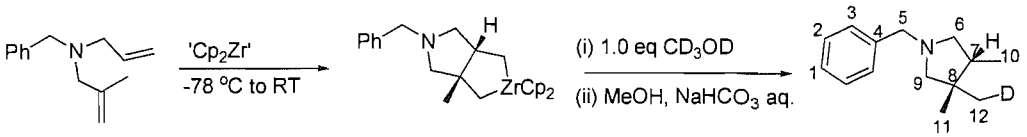
^{13}C NMR (100 MHz, $CDCl_3$): δ 139.73 (C, C_6), 128.73 (2CH, C_2 and C_3, or, C_4 and C_5), 128.29 (2CH, C_2 and C_3, or, C_4 and C_5), 126.88 (CH, C_1), 65.36 (CH_2, C_{11}), 61.79 (CH_2, C_8), 61.03 (CH_2, C_7), 43.43 (C, C_{10}), 43.38 (CH, C_9), 28.94 (CH_2, C_{14}), 25.16 (CH_3, C_{13}), 13.31 (CH_3, C_{12}), 10.91 (CH_2, C_{15}), -1.67 ($3CH_3$, $C_{16\text{-}18}$) ppm.

IR (film): 2953 (m), 2909 (m), 2781 (m), 1495 (w), 1454 (m), 1372 (m), 1247 (s), 1139 (m), 860 (s), 830 (s), 737 (m) cm^{-1}.

GCMS (EI) *m/z*: 289 ($(M)^+$, 100), 274 ($(M\text{-}CH_3)^+$, 15), 212 ($(M\text{-}C_6H_5)^+$, 18), 91 ($(C_6H_5)^+$, 90), 73 ($(Si(CH_3)_3)^+$, 83).

HRMS (EI) for $C_{18}H_{31}NSi$ $(M)^+$ calculated 289.2226, found 289.2224.

5.2.31 Deuterated 1-benzyl-3,3,4-trimethyl-pyrrolidine 412b



$C_{14}H_{20}DN$

A solution of *n*-BuLi (0.80 ml, 2.00 eq, 2.00 mmol) (2.5 M solution in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) at -78 °C. After 10 minutes a solution of *N*-allyl-*N*-benzyl-*N*-(2-methylallyl)-amine (0.201 g, 1.00 eq, 1.00 mmol) in THF (1 mL) was added. The cool bath was removed and the reaction mixture was warmed to room temperature over 3 hours.

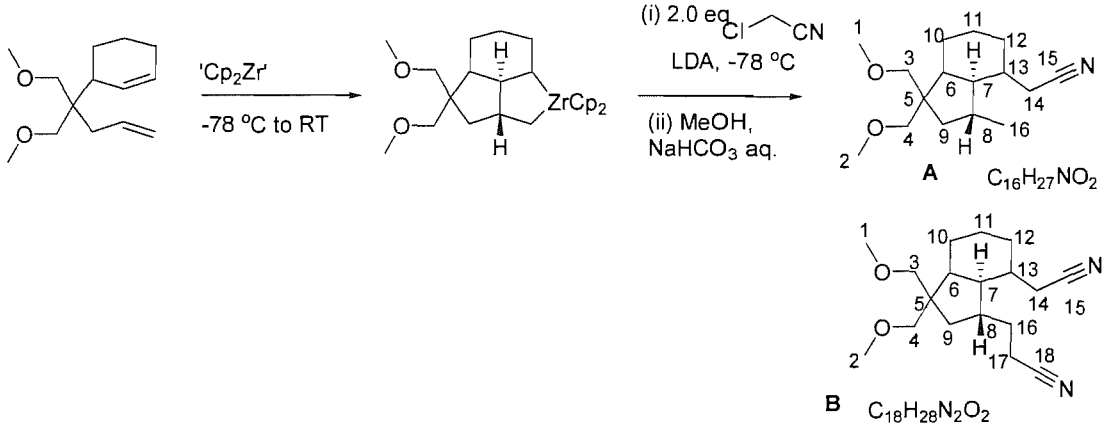
A solution of CD_3OD (0.036 g, 1.00 eq, 1.00 mmol) in THF (1 mL) was added to the reaction mixture, which changed from an orange to a yellow colour. After stirring for 1 hour, the reaction mixture was quenched with sat. $NaHCO_3$ aqueous solution (5 mL) and stirred for 16 hours. The product was extracted into diethyl ether (3 x 30 mL), the combined organic phases were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. This yielded a clear colourless oil, the title product (0.124 g, 61%) with 86% deuterium incorporation – determined by ^{13}C NMR integrals of C_8.

The non-deuterated compound is known.[172]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33–7.24 (5H, m, $H_{1\text{-}3}$), 3.67 (1H, d, J = 13.1 Hz, H_5), 3.57 (1H, d, J = 13.1 Hz, H_5), 2.89 (1H, dd, J = 9.0, 7.7 Hz, H_6), 2.58 (1H, d, J = 9.0 Hz, H_9), 2.30 (1H, d, J = 9.0 Hz, H_9), 2.24 (1H, t, J = 9.0 Hz, H_6), 1.90 (1H, m, H_7), 1.03 (3H, s, H_{11}), 0.90 (2H, m, H_{12}), 0.87 (3H, d, J = 7.0 Hz, H_{10}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.02 (C, C_4), 128.70 (2CH, C_2 or C_3), 128.24 (2CH, C_2 or C_3), 126.77 (CH, C_1), 68.92 (CH_2, C_5), 61.77 (CH_2, C_6 or C_9), 61.11 (CH_2, C_6 or C_9), 42.56 (CH, C_7), 39.55 (C, C_8), 28.48 (CH_3, C_{11}), 22.82 (CH_2, t, J = 19.2 Hz, C_{12}), 13.26 (CH_3, C_{10}) ppm.

5.2.32 Preparation of (1,1-bis-methoxymethyl-3-methyl-octahydro-inden-4-yl)-acetonitrile 413 and 3-(7-cyanomethyl-3,3-bis-methoxymethyl-octahydro-inden-1-yl)-propionitrile 414



A solution of *n*-BuLi (0.80 mL, 2.00 eq, 2.00 mmol) (2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) in THF (5 mL) at –78 °C. This was stirred for 10 minutes before the addition of 3-(1,1-bis-methoxymethyl-but-3-enyl)-cyclohexene (0.224 g, 1.00 eq, 1.00 mmol) as a solution in THF (1 mL). The cool bath was removed and the reaction mixture was allowed to warm to room temperature over 2 hours.

The reaction mixture was cooled to –78 °C before the addition of chloroacetonitrile (0.075 g, 1.00 eq, 1.00 mmol) as a solution in THF (1 mL) followed by the dropwise addition of LDA (1.40 mL, 1.00 eq, 1.00 mmol) over 20 minutes. The reaction mixture was stirred at –78 °C for 30 minutes. A mixture of 2 products emerged. In order to try and drive the reaction to 1 product further chloroacetonitrile (0.075 g, 1.00 eq, 1.00 mmol) was added as a solution in THF (1 mL) followed by LDA (1.00 mL, 1.00 eq, 1.00 mmol). The reaction mixture was stirred for 30 minutes before quenching by addition of MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (5 mL), and stirring for 16 hours. The products were extracted into diethyl ether (3 x 30 mL), the combined organic phases were washed with sat. $NaHCO_3$ aqueous solution (30 mL), water (30 mL) and brine (30 mL) dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by flash silica column chromatography (petrol/ethyl acetate 85:15 to 65:35). The mono-inserted product was purified further by Kugelrohr distillation (140-150 °C / 0.8 mm Hg) to yield a clear colourless oil (0.020 g, 9%). The bis-inserted product was a yellow oil (0.106 g, 39%).

Mono-inserted product: **A**

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.38–3.22 (4H, m, H_3 and H_4), 3.35 (3H, s, H_1 or H_2), 3.30 (3H, s, H_1 or H_2), 2.37 (1H, dd, J = 16.6, 7.3 Hz, H_{14}), 2.27 (1H, dd, J = 16.6, 7.5 Hz, H_{14}), 2.15–2.01 (3H, m), 1.84 – 1.75 (3H, m), 1.65 (1H, broad d, J = 10.3 Hz), 1.56 (1H, m), 1.30–1.15 (3H, m), 1.07 (3H, d, J = 10.8 Hz, H_{16}), 1.07 (1H, dq, J = 13.0, 3.8 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 119.52 (C, C_{15}), 75.74 (CH_2, C_3 or C_4), 74.05 (CH_2, C_3 or C_4), 59.41 (CH_3, C_1 or C_2), 59.25 (CH_3, C_1 or C_2), 48.86 (C, C_5), 48.44 (CH, C_6 or C_7), 45.83 (CH, C_6 or C_7), 40.02 (CH_2, C_9), 36.79 (CH, C_8 or C_{13}), 29.67 (CH, C_8 or C_{13}), 27.67 (CH_2, C_{10} or C_{12}), 25.66 (CH_2, C_{10} or C_{12}), 23.83 (CH_3, C_{16}), 23.80 (CH_2, C_{11} or C_{14}), 23.73 (CH_2, C_{11} or C_{14}) ppm.

IR (film): 2970 (m), 2926 (m), 2888 (m), 2870 (m), 2808 (m), 2245 (w), 1449 (m), 1197 (m), 1099 (s), 958 (m), 732 (m) cm^{-1}.

GCMS (CI) *m/z* (%): 266 ($(M+H)^+$, 100), 250 ($(M-CH_3)^+$, 5), 234 (38), 218 (10), 202 (70).

HRMS (EI) for $C_{16}H_{27}NO_2$ $(M)^+$, calculated 265.2042, found 265.2036.

Bis-inserted product: **B**

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.36–3.20 (4H, m, H_4 and H_3), 3.33 (3H, s, H_1 or H_2), 3.29 (3H, s, H_1 or H_2), 2.45 (1H, ddd, J = 17.1, 7.0, 5.0 Hz, H_{17}), 2.35 – 2.21 (4H, m, H_{14}, H_{17} and other), 2.17–2.02 (2H, m, H_{13} and other), 1.92–1.79 (3H, m), 1.74 (1H, dd, J = 14.1, 10.5 Hz, H_9), 1.65–1.49 (3H, m), 1.27 (1H, dd, J = 14.3, 5.0 Hz), 1.28–1.21 (2H, m), 1.04 (1H, dq, J = 12.8, 3.5 Hz) ppm.

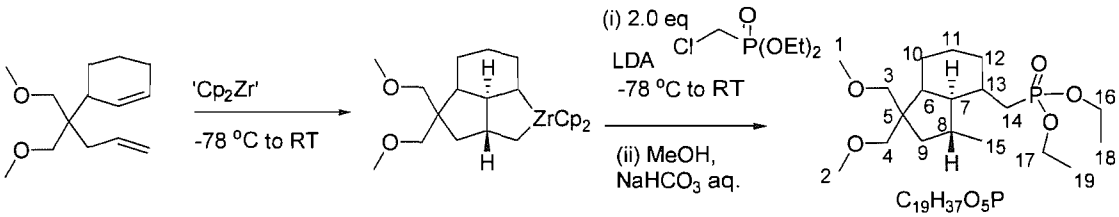
^{13}C NMR (100 MHz, $CDCl_3$): δ 119.64 (C, C_{15}), 119.06 (C, C_{18}), 75.33 (CH_2, C_3 or C_4), 73.74 (CH_2, C_3 or C_4), 59.53 (CH_3, C_1 or C_2), 59.22 (CH_3, C_1 or C_2), 49.21 (C, C_5), 46.18 (CH, C_6 or C_7), 45.26 (CH, C_6 or C_7), 36.57 (CH, C_{13}), 35.91 (CH_2, C_9), 34.19 (CH, C_8), 33.71 (CH_2, C_{10} or C_{12} or C_{16}), 27.64 (CH_2, C_{10} or C_{12} or C_{16}), 25.42 (CH_2, C_{10} or C_{12} or C_{16}), 23.79 (CH_2, C_{11} or C_{14}), 23.67 (CH_2, C_{11} or C_{14}), 16.65 (CH_2, C_{17}) ppm.

IR (film): 2926 (m), 2890 (m), 2871 (m), 2809 (w), 2245 (w), 1449 (m), 1197 (m), 1099 (s), 961 (m), 913 (m), 729 (s) cm^{-1}.

GCMS (CI) *m/z* (%): 322 $((M+NH_4)^+$, 25), 305 $((M+H)^+$, 100), 289 (5), 273 (25), 257 (10), 241 (65).

HRMS (EI) for $C_{18}H_{28}N_2O_2$ $(M)^+$, calculated 304.2151, found 304.2159.

5.2.33 Preparation of (1,1-bis-methoxmethyl-3-methyl-octahydro-inden-4-ylmethyl)-phosphonic acid diethyl ester 415



A solution of *n*-BuLi (0.80 mL, 2.00 eq, 2.00 mmol) (2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) in THF (5 mL) at –78 °C. This was stirred for 10 minutes before the addition of 3-(1,1-bis-methoxymethyl-but-3-enyl)-cyclohexene (0.224 g, 1.00 eq, 1.00 mmol) as a solution in THF (1 mL). The cool bath was removed and the reaction mixture was allowed to warm to room temperature over 2 hours.

The reaction mixture was cooled to –78 °C before addition of diethylchloromethyl phosphonate (0.373 g, 2.00 eq, 2.00 mmol) in THF (1 mL), followed by the dropwise addition of LDA (1.80 mL, 2.00 eq, 2.00 mmol) over 15 minutes. The reaction was quenched, after warming to room temperature over 16 hours, by addition of MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (5 mL) and stirred vigorously for 24 hours. The product was extracted into diethyl ether (3 x 30 mL), the combined organic phases were washed with sat. $NaHCO_3$ aqueous solution (30 mL), water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by flash silica column chromatography (ethyl acetate/petrol 1:1 to 3:1) to yield a clear colourless oil, the title product (0.212 g, 56%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.11–4.01 (4H, m, H_{16} and H_{17}), 3.32 (3H, s, H_1 or H_2), 3.27 (3H, s, H_1 or H_2), 3.34–3.17 (4H, m, H_3 and H_4), 2.09 (2H, m, H_{14}), 1.90–1.60 (8H, m), 1.47 (1H, broad dd, J = 6.3, 3.0 Hz, H_9), 1.30 (6H, t, J = 7.1 Hz, H_{18} and H_{19}), 1.22–1.06 (3H, m), 1.03 (3H, d, J = 6.5 Hz, H_{15}) ppm.

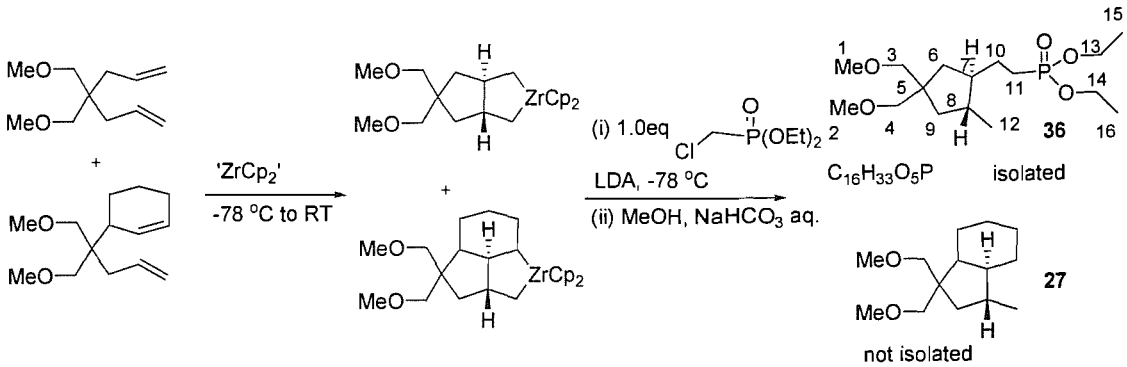
^{13}C NMR (100 MHz, $CDCl_3$): δ 75.85 (CH_2, C_3 or C_4), 74.06 (CH_2, C_3 or C_4), 61.50 (CH_2, d, J = 6.8 Hz, C_{16} or C_{17}), 61.33 (CH_2, d, J = 6.8 Hz, C_{16} or C_{17}), 59.33 (CH_3, C_1 or C_2), 59.14 (CH_3, C_1 or C_2), 50.57 (CH, d, J = 15.0 Hz, C_{13}), 48.46 (C, C_5), 45.96 (CH, d, J = 1.9 Hz, C_7 or C_8), 40.23 (CH_2, C_9), 33.96 (CH, d, J = 4.4 Hz, C_7 or C_8), 32.09 (CH_2, d, J = 182.7 Hz, C_{14}), 29.92 (CH, C_6), 27.99 (CH_2, d, J = 3.9 Hz, C_{12}), 25.96 (CH_2, C_{10} or C_{11}), 23.89 (CH_3, C_{15}), 23.65 (CH_2, C_{10} or C_{11}), 16.61 (CH_3, d, J = 1.9 Hz, C_{18} or C_{19}), 16.54 (CH_3, d, J = 1.9 Hz, C_{18} or C_{19}) ppm.

IR (film): 2977 (w), 2926 (m), 2890 (m), 2871 (m), 2808 (w), 1449 (w), 1246 (m), 1197 (m), 1161 (w), 1101 (s), 1052 (s), 1025 (s), 955 (s), 819 (m), 729 (s) cm^{-1}.

GCMS (CI) *m/z* (%): 377 ($(M+H)^+$, 35), 361 ($(M-CH_3)^+$, 6), 345 ($(M-CH_3O)^+$, 5), 286 ($(M-C_4H_{10}O_2)^+$, 20), 152 ($(C_5H_{13}O_3P)^+$, 100)

HRMS (EI) for $C_{19}H_{37}O_5P$ $(M)^+$ calculated 376.2379, found 376.2377.

5.2.34 Preparation of (2-(2-methyl-4,4-methoxymethyl-cyclopentyl)-ethyl)-phosphinic acid diethyl ester 417



A solution of *n*-BuLi (1.60 mL, 4.00 eq, 4.00 mmol) (2.5 M solution in hexanes) was added to a solution of zirconocene dichloride (0.584 g, 2.00 eq, 2.00 mmol) at –78 °C. After 10 minutes a solution of 4,4-bis-methoxymethyl-hepta-1,6-diene (0.196 g, 1.00 eq, 1.00 mmol) and 3-(1,1-bis-methoxymethyl-but-3-enyl)-cyclohexene (0.224 g, 1.00

eq, 1.00 mmol) in THF (1 mL) were added. The reaction mixture was allowed to warm to room temperature over 3 hours. Cyclisation was monitored by GC.

The reaction mixture was cooled to –78 °C before addition of diethylchloromethyl phosphonate (0.187 g, 1.00 eq, 1.00 mmol) in THF (1 mL). This was followed by the dropwise addition of LDA (1.0 mL, 1.00 eq, 1.00 mmol) over 15 minutes. It was allowed to warm to room temperature slowly over 16 hours. The reaction was quenched by addition of MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (5 mL) and stirred vigorously for 24 hours. The products ware extracted into diethyl ether (3 x 30 mL), the combined organic phases were washed with sat. $NaHCO_3$ aqueous solution (30 mL), water (30 mL) and brine (30 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash silica column chromatography (ethyl acetate/petrol 4:1) to yield a clear colourless oil, the title product (202 mg, 60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.12–4.00 (4H, m, H_{13} and H_{14}), 3.32 (6H, s, H_1 and H_2), 3.20–3.14 (4H, m, H_3 and H_4), 1.89–1.84 (2H, m), 1.77–1.72 (3H, m, H_6, H_9 and other), 1.64 (1H, m), 1.48 (1H, m, H_8), 1.35 (1H, m, H_7), 1.30 (6H, t, J = 7.0 Hz, H_{15} and H_{16}), 1.04–0.96 (2H, m, H_6 and H_9), 0.94 (3H, d, J = 6.5 Hz, H_{12}) ppm.

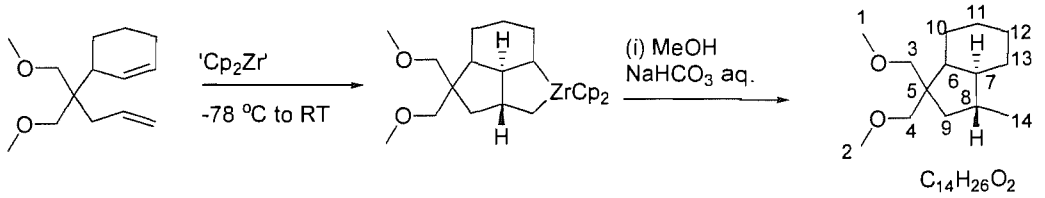
^{13}C NMR (100 MHz, $CDCl_3$): δ 78.04 (CH_2, C_3 or C_4), 77.95 (CH_2, C_3 or C_4), 61.53 (CH_2, d, J = 2.9 Hz, C_{13} or C_{14}), 61.47 (CH_2, d, J = 3.9 Hz, C_{13} or C_{14}), 59.34 ($2CH_3$, C_1 and C_2), 47.35 (CH, d, J = 16.5 Hz, C_7), 45.26 (C, C_5), 41.93 (CH_2, C_6), 39.70 (CH, C_8), 38.97 (CH_2, C_9), 26.33 (CH_2, d, J = 4.9 Hz, C_{10}), 24.60 (CH_2, d, J = 140.9 Hz, C_{11}), 18.14 (CH_3, H_{12}) 16.63 (CH_3, C_{15} or C_{16}), 16.56 (CH_3, C_{15} or C_{16}) ppm.

IR (film): 2978 (w), 2949 (m), 2932 (m), 2869 (m), 2824 (w), 1449 (m), 1389 (w), 1246 (s), 1199 (s), 1163 (m), 1104 (s), 1055 (s), 1025 (s), 956 (s), 834 (m), 787 (m) cm^{-1}.

GCMS (EI) *m/z* (%): 337 ($(M+H)^+$, 100), 321 ($(M-CH_3)^+$, 2).

HRMS (ES)$^+$ for $C_{16}H_{33}O_5P$ $(M+Na)^+$ calculated 359.1958, found 359.1960.

5.2.35 Preparation of 3-methyl-1,1-bis(methoxymethyl)-octahydro-indene 418a



$C_{14}H_{26}O_2$

A solution of *n*-BuLi (0.80 mL, 2.00 eq, 2.00 mmol) (2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) in THF (5 mL) at –78 °C. This was stirred for 10 minutes before the addition of 3-(1,1-bis-methoxymethyl-but-3-enyl)-cyclohexene (0.224 g, 1.00 eq, 1.00 mmol) as a solution in THF (1 mL). The cool bath was removed and the reaction mixture was allowed to warm to room temperature over 2 hours. The reaction was quenched by addition of MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (5 mL) and stirred vigorously for 16 hours. The product was extracted into diethyl ether (3 x 30 mL), the combined organic phases were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by flash silica column chromatography (petrol/diethyl ether 95:5) to yield a clear colourless oil, the title product (0.181 g, 80%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.34 (3H, s, H_1 or H_2), 3.33–3.14 (4H, m, H_3 and H_4), 3.31 (3H, s, H_1 or H_2), 2.02 (1H, m, H_8), 1.75–1.63 (5H, m, H_6, H_7, H_9, H_{11}, H_{13}), 1.52–1.42 (3H, m, H_{10}, H_{12}, H_{13}), 1.26 (1H, m, H_{12}), 1.18–1.09 (2H, m, H_{10}, H_{11}), 1.07 (1H, dd, J = 14.0, 8.1 Hz. H_9), 0.92 (3H, d, J = 6.4 Hz, H_{14}) ppm.

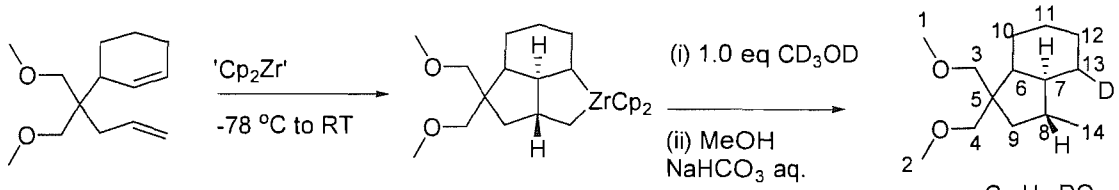
^{13}C NMR (75 MHz, $CDCl_3$): δ 76.98 (CH_2, C_3 or C_4), 74.34 (CH_2, C_3 or C_4), 59.35 (CH_3, C_1 or C_2), 59.15 (CH_3, C_1 or C_2), 48.82 (C, C_5), 45.32 (CH, C_7), 44.28 (CH, C_6), 39.48 (CH_2, C_9), 31.17 (CH, C_8), 26.11 (CH_2, C_{11}), 25.16 (CH_2, C_{13}), 24.08 (CH_2, C_{10}), 21.43 (CH_2, C_{12}), 19.90 (CH_3, C_{14}) ppm.

IR (film): 2974 (w), 2921 (m), 2888 (m), 2865 (m), 2806 (w), 1451 (m), 1389 (w), 1373 (w), 1196 (m), 1156 (w), 1102 (s), 960 (m) cm^{-1}.

GCMS (CI) *m/z* (%): 227 ($(M+H)^+$, 90), 195 ($(M-CH_3O)^+$, 10), 180 ($(M-C_2H_5O)^+$, 3), 164 ($(M-C_2H_6O_2)^+$, 8), 150 ($(M-C_3H_8O_2)^+$, 6).

HRMS (EI) for $C_{14}H_{26}O_2$ $(M)^+$ calculated 226.1933, found 226.1936.

5.2.36 Mono deuterated 3-methyl-1,1-bis(methoxymethyl)-octahydro-indene 418b



$C_{14}H_{25}DO_2$

A solution of *n*-BuLi (0.80 mL, 2.00 eq, 2.00 mmol) (2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) in THF (5 mL) at – 78 °C. This was stirred for 10 minutes before the addition of 3-(1,1-bis-methoxymethyl-but-3-enyl)-cyclohexene (0.224 g, 1.00 eq, 1.00 mmol) as a solution in THF (1 mL). The cool bath was removed and the reaction mixture was allowed to warm to room temperature over 2 hours.

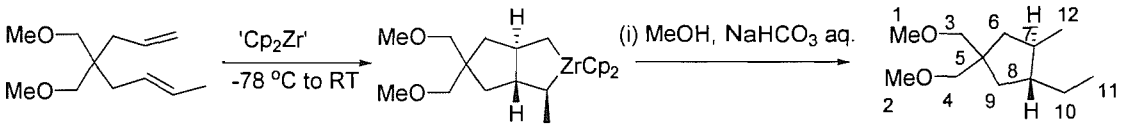
A solution of CD_3OD (41μL, 1.00 eq, 1.00 mmol) in THF (1mL) was added to the reaction mixture and stirred for 1 hour. The reaction was quenched by addition of MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (5 mL) and stirred vigorously for 16 hours. The product was extracted into diethyl ether (3 x 30 mL), the combined organic phases were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by flash silica column chromatography (petrol/diethyl ether 95:5) to yield a clear colourless oil, the title product (162 mg, 71% yield, 60% deuterium incorporation). Deuterium incorporation was determined from ^{13}C NMR, comparing the ratios of the area under the signals which correspond to the deuterated and non-deuterated C_{12} and C_7 signals.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.33 (3H, s, H_1 or H_2), 3.32–3.16 (4H, m, H_3 and H_4), 3.29 (3H, s, H_1 or H_2), 2.01 (1H, m, H_8), 1.72–1.61 (4H, m, H_6, H_7, H_9 and H_{11}), 1.52–1.40 (3H, m, H_{10}, H_{12} and H_{13}), 1.23 (1H, m, H_{12}), 1.16–1.05 (2H, m, H_{10} and H_{11}), 1.08 (1H, dd, J = 13.9, 8.1 Hz, H_9), 0.91 (3H, d, J = 6.4 Hz, H_{14}) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 76.98 (CH_2, C_3 or C_4), 74.32 (CH_2, C_3 or C_4), 59.31 (CH_3, C_1 or C_2), 59.12 (CH_3, C_1 or C_2), 48.81 (C, C_5), 45.31 (CH, C_7 non-deuterated), 45.23 (CH, C_7 deuterated), 44.28 (CH, C_6 non-deuterated), 44.25 (CH, C_6 deuterated), 39.47 (CH_2, C_9), 32.14 (CH, C_8), 26.10 (CH_2, C_{11} non-deuterated), 26.06 (CH_2, C_{11} deuterated), 25.14 (CH_2, C_{13} non-deuterated), 24.76 (CH, t, J = 19.3 Hz, C_{13} deuterated), 24.06 (CH_2, C_{10}), 21.42 (CH_2, C_{12} non-deuterated), 21.30 (CH_2, C_{12} deuterated), 19.87 (CH_3, C_{14}) ppm.

GCMS (CI) *m/z* (%): 228 ($(M+H)^+$, 100 - deuterated), 227 ($(M+H)^+$, 68 non-deuterated).

5.2.37 Preparation of 3-ethyl-1,1-bis-methoxymethyl-4-methyl-cyclopentane 419a



$C_{12}H_{24}O_2$

A solution of *n*-BuLi (0.80 ml, 2.00 eq, 2.00 mmol) (2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) at –78 °C. After 10 minutes a solution of 4,4-bis-methoxymethyl-octa-1,6-diene (0.196 g, 1.00 eq, 1.00 mmol) in THF (1 mL) was added. The reaction mixture was allowed to warm to room temperature over 3 hours.

The reaction was quenched by addition of MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (5 mL), then stirred for 16 hours. The product was extracted into diethyl ether (3 x 30 mL), the combined organic phases were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash silica column chromatography (petrol/diethyl ether 92:8) to yield a colourless clear oil, the title product (0.119 g, 60%). This is not a novel compound.[79]

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.35 (3H, s, H_1 or H_2), 3.34 (3H, s, H_1 or H_2), 3.25–3.16 (4H, m, H_3 and H_4), 1.77 (1H, dd, J = 12.9, 7.1 Hz, H_6), 1.72 (1H, dd, J = 12.9, 7.1 Hz, H_9), 1.60 (1H, m, H_{10}), 1.46 (1H, m, H_8), 1.23 (1H, m, H_7), 1.05–0.93 (3H, m, H_6, H_9 and H_{10}), 0.93 (3H, d, J = 6.5 Hz, H_{12}), 0.88 (3H, t, J = 7.3 Hz, H_{11}) ppm.

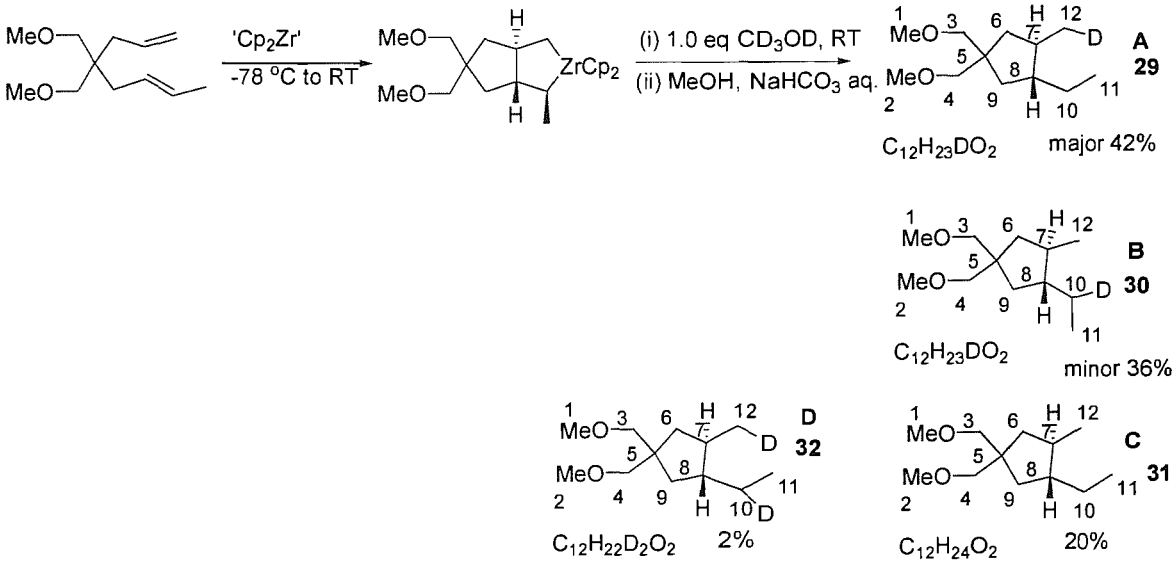
^{13}C NMR (100 MHz, $CDCl_3$): δ 78.19 (CH_2, C_3 or C_4), 78.04 (CH_2, C_3 or C_4), 59.39 ($2CH_3$, C_1 and C_2), 48.56 (CH, C_7), 45.24 (C, C_5), 42.12 (CH_2, C_6), 39.67 (CH, C_8), 39.21 (CH_2, C_9), 26.55 (CH_2, C_{10}), 18.31 (CH_3, C_{12}), 12.76 (CH_3, C_{11}) ppm.

IR (film): 2953 (m), 2921 (m), 2870 (m), 2822 (w), 1457(m), 1377 (w), 1168 (m), 1106 (s), 956 (m) cm^{-1}.

GCMS (CI) *m/z* (%): 201($(M+H)^+$, 100), 185 ($(M-CH_3)^+$, 5), 169 ($(M-C_2H_5)^+$, 12), 137 (50), 123 (25).

HRMS (EI) for $C_{12}H_{24}O_2$ $(M)^+$ calculated 200.1776, found 200.1772.

5.2.38 Preparation of mono deuterated 3-ethyl-1,1-bis-methoxymethyl-4-methyl-cyclopentane 419b-d



A solution of *n*-BuLi (0.80 ml, 2.00 eq, 2.00 mmol) (2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) at –78 °C. After 10 minutes a solution of 4,4-bis-methoxymethyl-octa-1,6-diene (0.196 g, 1.00 eq, 1.00 mmol) in THF (1 mL) was added. The reaction mixture was allowed to warm to room temperature over 3 hours.

A solution of CD_3OD (41 μL, 1.00 eq, 1.00 mmol) in THF (1 mL) was slowly added to the reaction mixture that changed colour from orange to yellow. After stirring for an hour at room temperature the reaction was quenched by addition of MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution and stirred vigorously for 16 hours. The product was extracted into diethyl ether (3 x 30 mL), the combined organic phases were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash silica column chromatography (petrol/diethyl ether 95:5) to yield an inseparable mixture of the title products as a colourless oil (0.105g, 53%). The ratio of **A** to **B** was determined by ^{13}C NMR. Mass spectrometry (CI) was used to determine the ratio of **A**+**B** to **C** to **D**.

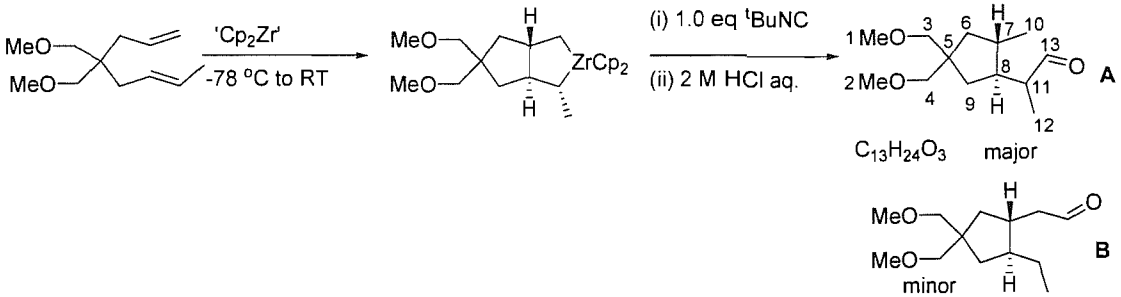
Mixture of isomers **A-D**

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.41–3.32 (6H, m, H_1 and H_2), 3.25–3.15 (4H, m, H_3 and H_4), 1.76 (1H, dd, J = 13.0, 7.3 Hz, H_6), 1.71 (1H, dd, J = 13.0, 7.3 Hz, H_9), 1.59 (1H, m, H_{10}), 1.44 (1H, m, H_8), 1.22 (1H, m, H_7), 1.02–0.96 (3H, m, H_6, H_9 and H_{10}), 0.92 (3H, d+fs, J = 6.5 Hz, H_{12}), 0.87 (3H, t+fs, J = 7.3 Hz, H_{11}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 78.01 (CH_2, C_3 or C_4), 77.48 (CH_2, C_3 or C_4), 59.37 ($2CH_3$, C_1 and C_2), 48.54 (CH, C_7-**C**), 48.52 (CH, C_7-**A**), 48.46 (CH, C_7-**B**), 45.21 (C, C_5), 42.11 and 42.08 (CH_2, C_6), 39.65 (CH, C_8-**B**+**C**), 39.58 (CH, C_8-**A**), 39.19 (CH_2, C_9), 39.15 (CH_2, C_9), 26.54 (CH_2, C_{10}-**A**+**C**), 26.16 (CHD, t, J = 19.2 Hz, C_{10}-**B**), 18.29 (CH_3, C_{12}-**B**+**C**), 17.99 (CH_2D, t, J = 19.2 Hz, C_{12}-**A**), 12.75 (CH_3, C_{11}-**A**+**C**), 12.65 (CH_3, C_{11}-**B**) ppm.

GCMS (CI) *m/z* (%): 202 ($(M+H)^+$, 100), 170 ($(M-C_2H_5)^+$, 12), 138 (40), 124 (18), 108 (10).

5.2.39 Preparation of 2-[4,4-di(methoxymethyl)-2-methyl cyclopentyl]propanal - A 421



A solution of *n*-BuLi (0.80 ml, 2.00 eq, 2.00 mmol) (2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) at –78 °C. After 10 minutes a solution of 4,4-bis-methoxymethyl-octa-1,6-diene (0.196 g, 1.00 eq, 1.00 mmol) in THF (1 mL) was added. The reaction mixture was allowed to warm to room temperature over 3 hours.

The reaction mixture was cooled to 0 °C and *tert*-butyl isocyanide (0.10 mL, 1.00 eq, 1.00 mmol) was added. It was quenched after 30 minutes by addition of HCl (5 mL, 2.0 M aqueous solution) and stirred for 24 hours. The products were extracted into diethyl ether (3 x 30 mL) before the combined organic phases were washed with water (30 mL), brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash silica column chromatography (petrol/diethyl ether 8:2) yielded aldehydes **A** and **B** (0.108 g, 48%) in a ratio of 74:26 (**A**:**B**). The two diastereoisomers of **A** were in a 1:2 ratio, determined by ^{1}H NMR. A portion of compound **A** was isolated pure and characterized.

Data for compound **A**, as a 1:2 mixture of diastereoisomers.

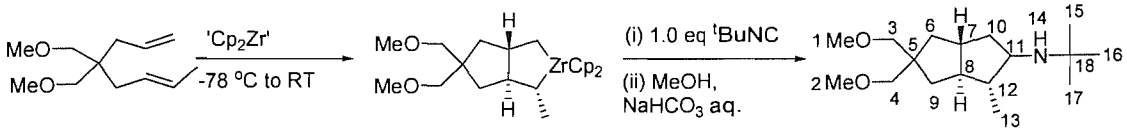
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.72 (1H, d, J = 1.8 Hz, H_{13} minor), 9.63 (1H, d, J = 1.8 Hz, H_{13} major), 3.32 (6H, s+fs, H_1 and H_2), 3.21–3.16 (4H, m, H_3 and H_4), 2.44 (1H, t+fs, J = 6.2 Hz, H_{11}), 1.84 (1H, m, H_8), 1.79–1.59 (4H, m, H_7, H_6 or H_9 major, H_6 minor, H_9 minor), 1.53 (1H, dd, J = 13.0, 7.5 Hz, H_6 or H_9 major), 1.27 (1H, m, H_6 or H_9 minor), 1.17 (1H, t, J = 12.3 Hz, H_6 or H_9 major), 1.09 (3H, d, J = 7.0 Hz, H_{12} minor), 1.05 (2H, m, H_6 or H_9 major, H_6 or H_9 minor), 1.00 (3H, d, J = 7.0 Hz, H_{13} major), 0.94 (3H, d, J = 5.0 Hz, H_{10}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 205.7 (CH, C_{13} minor), 205.4 (CH, C_{13} major), 78.01 (CH_2, C_3 or C_4), 77.76 (CH_2, C_3 or C_4), 60.94 ($2CH_3$, C_1 and C_2), 47.81 (CH, C_{11} minor), 47.79 (CH, C_{11} major), 47.63 (CH, C_8 minor), 46.04 (CH, C_8 major), 45.16 (C, C_5), 41.76 (CH_2, C_6 or C_9 minor), 41.37 (CH_2, C_6 or C_9 major), 36.83 (CH, C_7 major), 36.56 (CH_2, C_6 or C_9 minor), 36.13 (CH, C_7 minor), 34.22 (CH_2, C_6 or C_9 major), 18.73 (CH_3, C_{12} minor), 18.09 (CH_3, C_{12} major), 11.35 (CH_3, C_{10} minor), 8.85 (CH_3, C_{10} major) ppm.

IR (film): 2950 (w), 2924 (w), 2872 (m), 2824 (w), 1724 (s), 1451 (m), 1378 (w), 1198 (m), 1104 (s), 964 (m) cm^{-1}.

GCMS (CI) *m/z* (%): 229 ($(M+H)^+$, 100), 213 ($(M-CH_3)^+$, 2), 166 ($(M-C_2H_6O_2)^+$, 10), 138 ($(M-C_4H_{10}O_2)^+$, 40), 137(85).

5.2.40 Preparation of *N*-(*tert*-butyl)-*N*-[5,5-di(methoxymethyl) -1-methylperhydro-2-pentalenyl]amine 424



A solution of *n*-BuLi (0.80 ml, 2.00 eq, 2.00 mmol) (2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) at –78 °C. After 10 minutes a solution of 4,4-bis-methoxymethyl-octa-1,6-diene (0.196 g, 1.00 eq, 1.00 mmol) in THF (1 mL) was added. The reaction mixture was allowed to warm to room temperature over 3 hours.

The reaction mixture was cooled to 0 °C before the addition of *tert*-butyl isocyanide (0.10 mL, 1.00 eq, 1.00 mmol). The reaction was quenched after 1 hour by addition of sat. $NaHCO_3$ aqueous solution (5 mL) and MeOH (5 mL) and stirred vigorously for 16 hours. The product was extracted into diethyl ether (3 x 30 mL), the combined organic phases were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by an acid base extraction, to yield a clear colourless oil, the title product (0.206 g, 73%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.33 (3H, s, H_1 or H_2), 3.31 (3H, s, H_1 or H_2), 3.23–3.19 (4H, m, H_3 and H_4), 2.98 (1H, ddd, J = 9.2, 7.2, 2.3 Hz, H_{11}), 1.91 (1H, m, H_7 or H_8), 1.57–1.49 (3H, m, H_6, H_9 and H_{10}), 1.40 (1H, m, H_{10}), 1.23 (1H, m, H_7 or H_8), 1.14–1.01 (2H, m, H_{12} and H_{14}), 1.05 (9H, s, $H_{15\text{-}17}$), 1.00 (3H, d, J = 6.3 Hz, H_{13}), 0.90 (1H, t, J = 12.0 Hz, H_6 or H_9), 0.89 (1H, t, J = 12.0 Hz, H_6 or H_9) ppm.

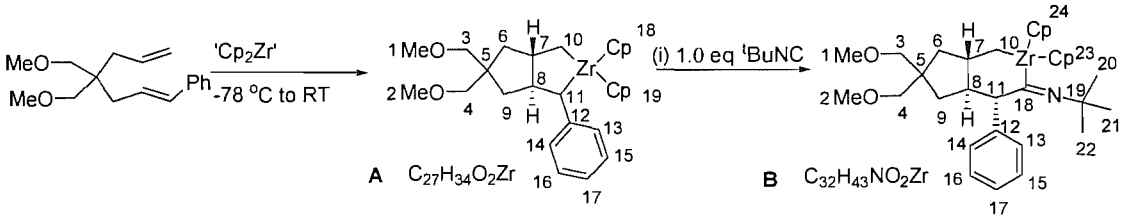
^{13}C NMR (100 MHz, $CDCl_3$): δ 78.18 (CH_2, C_3 or C_4), 78.01 (CH_2, C_3 or C_4), 66.65 (CH, C_{11}), 59.33 ($2CH_3$, C_1 and C_2), 56.40 (CH, C_7 or C_8), 53.68 (C, C_5 or C_{18}), 50.83 (C, C_5 or C_{18}), 49.44 (CH, C_7 or C_8), 45.84 (CH, C_{12}), 39.16 (CH_2, C_{10}), 35.15 (CH_2, C_6 or C_9), 33.58 (CH_2, C_6 or C_9), 30.09 ($3CH_3$, $C_{15\text{-}17}$), 17.26 (CH_3, C_{13}) ppm.

IR (film): 2951 (m), 2922 (m), 2867(m), 2824 (w), 1475 (w), 1450 (m), 1386 (w), 1361 (w), 1230 (w), 1198 (m), 1163 (w), 1106 (s), 962 (m) cm^{-1}.

GCMS (ES)$^+$ *m/z*: 284 ($(M+H)^+$, 100).

HRMS (ES)$^+$ for $C_{17}H_{34}NO_2$ $(M+H)^+$ calculated 284.2584, found 284.2580.

5.2.41 Preparation of 2,2-di(cyclopentadienyl)-5,5-di(methoxymethyl)-1-phenylperhydro-2-zirconapentalene 320 and *N*-(tert-butyl)-*N*-[5,5-di(cyclopentadienyl)-2,2-di(methoxymethyl)-7-phenylperhydro-5-zirconainden-6-yliden]amine 425



A solution of *n*-BuLi (0.80 mL, 2.00 eq, 2.00 mmol) (2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) in THF (5 mL) at –78 °C. This was stirred for 10 minutes before the addition of (4,4-bis-methoxymethyl-hepta-1,6-dienyl)-benzene (0.260 g, 1.00 eq, 1.00 mmol) as a solution in THF (1 mL). The cold bath was then removed and the reaction mixture was allowed to warm to room temperature over 4 hours. Cyclisation was monitored by GC. THF was removed

by vacuum transfer and the remaining solid was dissolved in benzene (5 mL). An aliquot of the zirconacycle (2 mL) was transferred to a second schlenk flask, the solvent removed using vacuum transfer and dissolved in C_6D_6 (1 mL). Half the sample was transferred to a NMR tube, under an argon atmosphere, for spectroscopy – confirming the structure of zirconacycle **A** (quantitative reaction by ^{1}H NMR).

Zirconacyclopentane **A**

^{1}H NMR (300 MHz, C_6D_6): δ 7.24 (2H, t, J = 7.4 Hz, H_{15} and H_{16}), 6.86 (1H, t, J = 7.4 Hz, H_{17}), 6.81 (2H, d, J = 7.4 Hz, H_{13} and H_{14}), 5.75 (5H, s, H_{18} or H_{19}), 5.45 (5H, s, H_{18} or H_{19}), 3.36–3.19 (4H, m, H_3 and H_4), 3.25 (1H, m, H_{11}), 3.23 (3H, s, H_1 or H_2), 3.19 (3H, s, H_1 or H_2), 2.24 (1H, dd, J = 13.2, 6.6 Hz, H_9), 2.17 (1H, m, H_{10}), 1.64 (1H, m, H_8), 1.51 – 1.22 (4H, m, H_6, H_7 and H_{10}), 1.00 (1H, dd, J = 13.2, 10.6 Hz, H_9) ppm.

^{13}C NMR (75 MHz, C_6D_6): δ 154.30 (C, C_{12}), 128.55 (2CH, C_{13} and C_{14} or C_{15} and C_{16}), 123.79 (2CH, C_{13} and, C_{14} or C_{15}, and C_{16}), 120.25 (CH, C_{17}), 112.04 (5CH, C_{18} or C_{19}), 110.59 (5CH, C_{18} or C_{19}), 78.96 (CH_2, C_3 or C_4), 78.77 (CH_2, C_3 or C_4), 64.20 (CH, C_{11}), 59.11 (CH_3, C_1 or C_2), 58.98 (CH_3, C_1 or C_2), 49.40 (CH_2, C_{10}), 45.48 (CH_2, C_9), 45.29 (CH_2, C_6), 40.95 (C, C_5), 38.40 (CH, C_8), 34.71 (CH, C_7) ppm.

The zirconacycle sample in the NMR tube was treated with *tert*-butyl isocyanide (0.20 mL, 1.00 eq, 0.20 mmol), the addition resulted in a colour change from dark red to light yellow, resulting in complex *N*-(tert-butyl)-*N*-[5,5-di(cyclopentadienyl)-2,2-di(methoxymethyl)-7-phenylperhydro-5-zirconainden-6-yliden]amine (quantitative reaction by ^{1}H NMR).

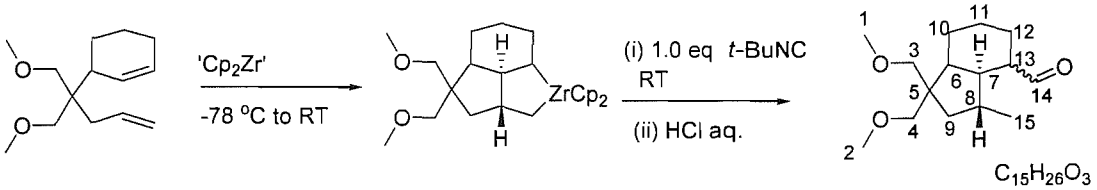
Zirconacyclohexene **B**

^{1}H NMR (300 MHz, C_6D_6): δ 7.38–7.28 (2H, m, H_{13} and H_{14}, or, H_{15} and H_{16}), 7.24–7.18 (2H, m, H_{13} and H_{14}, or, H_{15} or H_{16}), 6.86 (1H, t, J = 7.0 Hz, H_{17}), 5.56 (5H, s, H_{23} or H_{24}), 5.09 (5H, s, H_{23} or H_{24}), 3.43–3.25 (4H, m, H_3 and H_4), 3.24 (3H, s, H_1 or H_2), 3.16 (3H, s, H_1 or H_2), 3.11 (1H, d, J = 10.7 Hz, H_{11}), 2.96 (1H, dd, J = 17.1, 4.6 Hz, H_{10}), 2.67 (1H, dd, J = 13.8, 7.2 Hz, H_9), 2.48 (1H, m, H_8), 2.21 (1H, dd, J = 12.7, 7.8 Hz, H_6), 1.92 (1H, m, H_7), 1.72 (1H, dd, J = 17.1, 12.4 Hz, H_{10}), 1.52 (1H, dd, J =

12.7, 11.5 Hz, H_6), 1.28 (1H, dd, J = 13.8, 10.0 Hz, H_9), 0.93 (^{t}BuNC), 0.91 (3H, s, H_{20}, H_{21} or H_{22}), 0.90 (3H, s, H_{20}, H_{21} or H_{22}), 0.89 (3H, s, H_{20}, H_{21} or H_{22}) ppm.

^{13}C NMR (75 MHz, C_6D_6): δ 230.59 (C, C_{18}), 159.97 (C, C_{12}), 128.23 (CH, C-Ar), 127.40 (2CH, C-Ar), 124.57 (CH, C-Ar), 118.80 (CH, C-Ar), 108.02 (5CH, C_{23} or C_{24}), 107.10 (5CH, C_{23} or C_{24}), 79.23 (CH_2, C_3 or C_4), 78.81 (CH_2, C_3 or C_4), 59.45 (C, C_{19}), 59.10 (CH_3, C_1 or C_2), 58.94 (CH_3, C_1 or C_2), 51.94 (CH, C_8), 50.76 (CH, C_{11}), 48.56 (CH, C_7), 44.50 (C, C_5), 44.09 (CH_2, C_9), 41.15 (CH_2, C_6), 38.46 (CH_2, C_{10}), 30.39 ($3CH_3$, $C_{20\text{-}22}$), 29.08 (CH_3, ^{t}BuNC – excess starting material) ppm.

5.2.42 Preparation of 1,1-bis(methoxymethyl)-3-methyloctahydro-1H-indene-4-carbaldehyde 426



$C_{15}H_{26}O_3$

A solution of *n*-BuLi (0.80 mL, 2.00 eq, 2.00 mmol) (2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) in THF (5 mL) at –78 °C. This was stirred for 10 minutes before the addition of 3-(1,1-bis-methoxymethyl-but-3-enyl)-cyclohexene (0.224 g, 1.00 eq, 1.00 mmol) as a solution in THF (1 mL). The cool bath was removed and the reaction mixture was allowed to warm to room temperature over 2 hours.

The reaction mixture was cooled to 0 °C and *tert*-butyl isocyanide (0.10 mL, 1.00 eq, 1.00 mmol) was added. This made the soluition change colour from orange to pale yellow. The reaction was quenched after 30 minutes by addition of HCl (5 mL, 2.00 M aqueous solution) and stirred for 24 hours. The products ware extracted into diethyl ether (3 x 30 mL), the combined organic phases were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product were purified by flash silica column chromatography (petrol/diethyl ether 3:1) resulting in the title product, a clear colourless oil (0.143 g, 56%) as 2.7:1 mixture of isomers. With further purification by column chromatography (petrol/diethyl ether 3:1) a small portion of the major isomer was isolated pure.

Major isomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.69 (1H, s, H_{14}), 3.32 (3H, s, H_1 or H_2), 3.31–3.16 (4H, m, H_3 and H_4), 3.26 (3H, s, H_1 or H_2), 3.25 (1H, d, J = 5.5 Hz), 2.11–2.03 (2H, m), 1.97 (1H, d+fs, J = 13.8 Hz), 1.69–1.63 (2H, m), 1.58–1.46 (3H, m), 1.17–1.06 (3H, m), 0.95 (3H, d, J = 6.3 Hz, H_{15}) ppm.

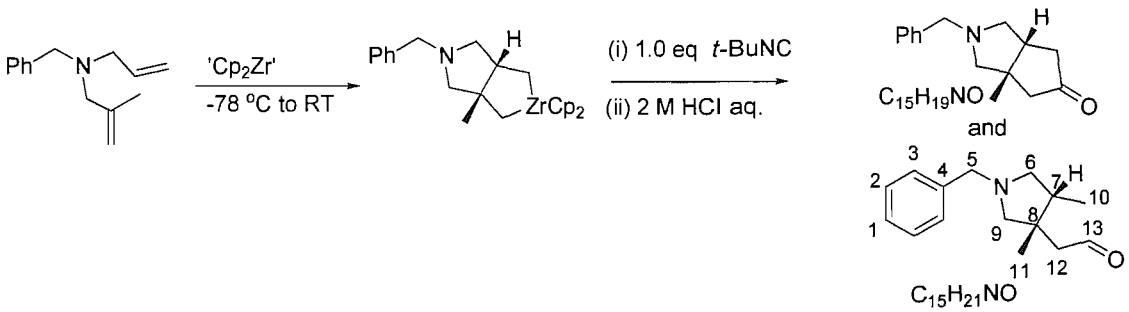
^{13}C NMR (100 MHz, $CDCl_3$): δ 205.03 (CH, C_{14}), 76.84 (CH_2, C_3 or C_4), 73.93 (CH_2, C_3 or C_4), 59.30 (CH_3, C_1 or C_2), 59.04 (CH_3, C_1 or C_2), 49.01 (C, C_5), 47.51 (CH, C_6), 44.13 (CH, C_7), 41.92 (CH, C_8), 38.54 (CH_2, C_9), 33.12 (CH, C_{13}), 23.28 (CH_2), 22.33 (CH_2), 21.21 (CH_2), 19.59 (CH_3, C_{15}) ppm.

IR (film): 2926 (m), 2887 (m), 2867 (m), 2807 (m), 2728 (w), 2696 (w), 1724(s), 1451 (m), 1389 (w), 1376 (w), 1197 (m), 1100 (s), 961 (m) cm^{-1}.

GCMS (CI) *m/z* (%): 255($(M+H)^+$, 100), 240 ($(M+H-CH_3)^+$, 5), 233 ($(M-CH_3O)^+$, 50), 164 ($(C_{11}H_{16}O)^+$, 30), 149 ($(C_{10}H_{13}O)^+$, 28)

HRMS (EI) for $C_{15}H_{26}O_3$ $(M)^+$ calculated 254.1882, found 254.1882.

5.2.43 Preparation of 2-benzyl-3a-methyl-hexahydro-cyclopenta[c]pyr-5-one 428 and (1-benzyl-3,4-dimethyl-pyrrolidin-3-yl)-acetaldehyde 427



A solution of *n*-BuLi (0.80 ml, 2.00 eq, 2.00 mmol) (2.5 M solution in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) at -78 °C. After 10 minutes a solution of *N*-allyl-*N*-benzyl-*N*-(2-methylallyl)-amine (0.201 g, 1.00 eq, 1.00 mmol) in THF (1 mL) was added. The cool bath was removed and the reaction mixture was warmed to room temperature over 3 hours.

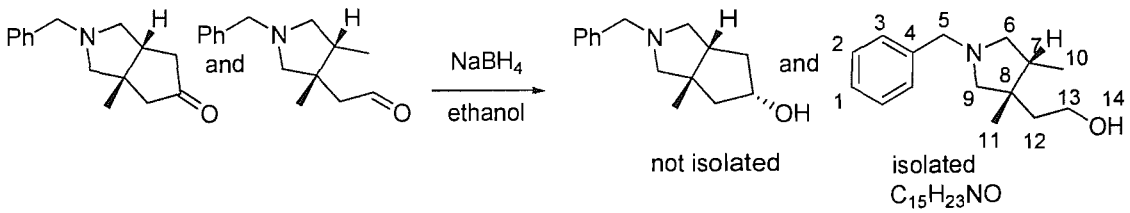
The reaction mixture was cooled to 0 °C and *tert*-butyl isocyanide (0.10 mL, 1.00 eq, 1.00 mmol) was added. The reaction mixture changed from orange to red to brown to green and was quenched after 30 minutes by addition of HCl (5 mL, 2 M aqueous solution) and stirred for 24 hours. The product was extracted into diethyl ether (3 x 30 mL) after the solution had been basifed by addition of NaOH (10 mL, 2 M aqueous solution). The combined organic phases were subjected to an acid base extraction before the combined organics were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo.* Attempts were made to separate the two products using column chromatography (petrol/diethyl ether/ Et_3N 88:10:2) proved to be unsuccessful. The yields were estimated using ^1H NMR at 31% for aldehyde and 30% for the ketone. The ketone is a known compound and the values for the ^{13}C NMR matched those in the literature.[93]

Ketone - literature **^{13}C NMR** (100 MHz, $CDCl_3$): δ 219.1, 139.2, 128.4, 128.2, 126.9, 68.2, 61.9, 59.4, 52.2, 45.4, 45.3, 45.2, 26.8 ppm.

Ketone - observed **^{13}C NMR** (100 MHz, $CDCl_3$): δ 219.0, 139.2, 128.5, 128.3, 127.0, 68.3, 61.9, 59.5, 52.2, 45.5, 45.4, 45.3, 26.9 ppm.

In order to obtain separable products a portion of the products recovered from the experiment above reduced to the alcohols.

5.2.44 Preparation of 2-(1-benzyl-3,4-dimethylpyrrolidin-3-yl)-ethanol 429



A solution of the aldehyde and ketone (0.080 g, 1.00 eq, 0.35 mmol) in ethanol (2 mL), was added slowly to a suspension of sodium borahydride (0.026 g, 2.00 eq, 0.70 mmol) in ethanol (2 mL). The reaction mixture was quenched after 2 hours by addition of HCl (3 mL, 2 M aqueous solution) to the reaction mixture at 0 °C. The reaction mixture was basified by addition of NaOH (10 mL, 2 M aqueous solution)

and the products were extracted into diethyl ether (3 x 30 mL) and the combined organic phases were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by flash silica column chromatography (petrol/diethyl ether/Et_3N 48:50:2) to yield the title product (20 mg, 24%) as a clear colourless oil.

Data for novel primary alcohol

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.21 (5H, m, $H_{1\text{-}3}$), 3.73 (1H, d, J = 12.8 Hz, H_5), 3.71 (1H, m, H_{13}), 3.58 (1H, m, H_{13}), 3.57 (1H, d, J = 12.8 Hz, H_5), 2.85 (1H, d, J = 9.0 Hz, H_9), 2.74 (1H, t, J = 10.3 Hz, H_6), 2.70 (1H, t, J = 10.3 Hz, H_6), 2.30 (1H, d, J = 9.0 Hz, H_9), 1.98 (1H, m, H_7), 1.64–1.51 (2H, m, H_{12}), 0.97 (3H, s, H_{11}), 0.90 (3H, d, J = 7.0 Hz, H_{10}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.52 (C, C_4), 128.89 (2CH, C_2 or C_3), 128.60 (2CH, C_2 or C_3), 127.34 (CH, C_1), 66.48 (CH_2, C_{13}), 61.08 (CH_2, C_5 or C_6 or C_9), 60.84 (CH_2, C_5 or C_6 or C_9), 60.72 (CH_2, C_5 or C_6 or C_9), 43.02 (C, C_8), 42.59 (CH, C_7), 39.62 (CH_2, C_{12}), 26.74 (CH_3, C_{11}), 12.18 (CH_3, C_{10}) ppm.

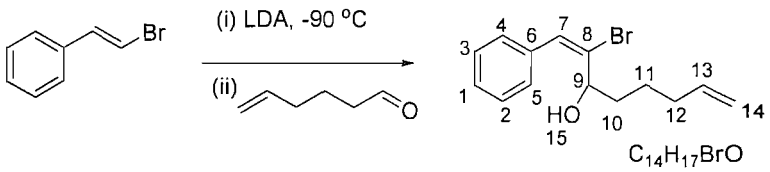
IR (film): 3500 – 3200 broad (m), 2954 (s), 2906 (s), 2872 (s), 2785 (m), 1453 (s), 1373 (s), 1263 (m), 1119 (m), 1073 (m), 1047 (s), 976 (m), 737 (s) cm^{-1}.

GCMS (CI) *m/z* (%): 234 ($(M+H)^+$, 5%).

HRMS (EI) for $C_{15}H_{23}NO$ $(M)^+$ calculated 233.17796, found 233.177779.

5.2.45 Preparation of 1-(octa-1,2,7-trienyl)benzene 439 in 3 steps

Step1



A solution of β-bromostyrene (1.54 mL, 1.00 eq, 12.04 mmol) in THF (10 mL) was cooled to –90 °C before the addition of LDA (10 mL, 1.00 eq, 12.04 mmol) over 30

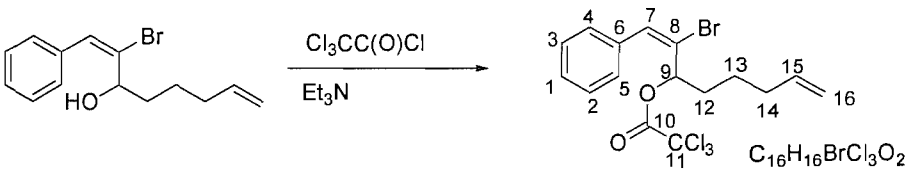
minutes. After stirring at –90 °C for 30 minutes a solution of hex-5-enal[95] (1.18 g, 1.00 eq, 12.04 mmol) in THF (4 mL) was added to the reaction mixture over 30 minutes. The solution was allowed to warm –30 °C over 3.5 hours. It was quenched with sat. $NaHCO_3$ aqueous solution (30 mL). The products were extracted into diethyl ether (3 x 50 mL), the combined organic phases washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified using flash silica column chromatography (hexane/diethyl ether 4:1) to yield (*E*)-2-bromo-1-phenyl-octa-1,7-dien-3-ol, a clear oil (1.445 g, 43%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.50–7.30 (6H, m, $H_{1\text{-}5}$ and H_7), 5.89 (1H, ddt, J = 17.0, 10.3, 6.7 Hz, H_{13}), 5.09 (1H, d+fs, J = 17.0 Hz, H_{14} *trans*), 5.07 (1H, d+fs, J = 10.3 Hz, H_{14} *cis*), 4.66 (1H, t, J = 6.9 Hz, H_9), 2.16 (2H, apparent q, J = 6.9 Hz, H_{10}), 1.92–1.77 (3H, m, H_{12} and H_{15}), 1.56 (2H, apparent pentet, J = 7.6 Hz, H_{11}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.39 (CH, C_7 or C_{13}), 135.82 (C, C_6 or C_8), 134.19 (CH, C_7 or C_{13}), 134.03 (C, C_6 or C_8), 128.75 (2CH, C_2 and C_3, or, C_4 and C_5), 128.41 (2CH, C_2 and C_3, or, C_4 and C_5), 128.00 (CH, C_1), 115.03 (CH_2, C_{14}), 69.95 (CH, C_9), 36.09 (CH_2, C_{10} or C_{12}), 33.46 (CH_2, C_{10} or C_{12}), 24.56 (CH_2, C_{11}) ppm.

IR (film): 3571- 3250 broad (m), 3075 (m), 2960 (s), 2921 (s), 2864 (m), 1639 (m), 1491 (m), 1443 (s), 1261 (m), 1069 (s), 1029 (s), 998 (s), 912 (s), 805 (m), 783 (w) 756 (s) cm^{-1}.

Step 2



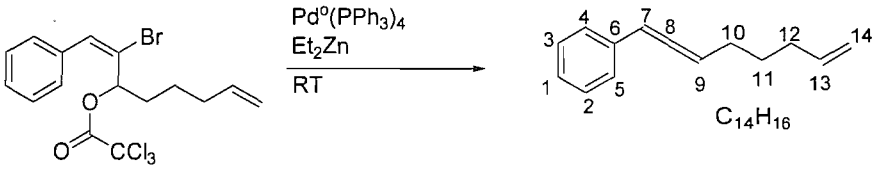
A solution of 2-bromo-1-phenyl-octa-1,7-dien-3-ol (0.70 g, 1.00 eq, 2.50 mmol) and triethylamine (3.48 mL, 10.00 eq, 25.00 mmol) in THF (20 mL) was cooled to 0 °C before the dropwise addition of trichloroacetylchloride (1.40 mL, 5.00 eq, 15.00 mmol). After stirring for 30 minutes the reaction was quenched with sat. $NaHCO_3$ aqueous solution (30 mL). The products were extracted into diethyl ether (3 x 50 mL), the combined organic phases washed with water (50 mL) and brine (50 mL), dried

over $MgSO_4$ and concentrated *in vacuo*. The product was purified using flash silica column chromatography (hexane/diethyl ether 9:1) to yield (*E*)-2-bromo-1-phenylocta-1,7-dien-3-yl 2,2,2-trichloroacetate, a clear oil (0.847 g, 79%).[97]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42–7.22 (6H, m, $H_{1\text{-}5}$ and H_7), 5.74 (1H, m, H_{15}), 5.67 (1H, dd, J = 8.4, 6.0 Hz, H_9), 4.97 (1H, s+fs, H_{16}), 4.92 (1H, s+fs, H_{16}), 2.07–1.96 (3H, m, H_{12} and H_{14}), 1.85 (1H, m, H_{12} or H_{14}), 1.43 (2H, apparent pentet, J = 7.5 Hz, H_{13}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.92 (C, C_{10}), 137.73 (CH, C_7 or C_{15}), 137.59 (CH, C_7 or C_{15}), 135.30 (C, C_6), 128.92 (2CH, C_2 and C_3, or, C_4 and C_5), 128.43 (CH, C_1), 128.21 (2CH, C_2 and C_3, or, C_4 and C_5), 124.95 (C, C_8), 115.52 (CH_2, C_{16}), 77.10 (CH, C_9), 33.05 (CH_2, C_{12} or C_{14}), 32.58 (CH_2, C_{12} or C_{14}), 23.98 (CH_2, C_{13}) ppm. (C_{11} was not observed).

Step3



To a stirred solution of (*E*)-2-bromo-1-phenylocta-1,7-dien-3-yl 2,2,2-trichloroacetate (0.840 g, 1.00 eq, 1.98 mmol) and tetrakis palladium triphenyl phosphine (0.229 g, 10 mol %, 0.20 mmol) in THF (10 mL), under argon, was added diethyl zinc (3.96 mL, 2.00 eq, 3.96 mmol) (2 M solution in benzene). The solution went from cloudy to clear yellow. After stirring for 2 hours at room temperature the reaction had not gone to completion but was worked up anyway due to worries regarding the stability of the allene formed. The reaction was quenched by addition of sat. NH_4Cl aqueous solution (30 mL). The products were extracted into diethyl ether (3 x 100 mL), the combined organic phases washed with water (100 mL) and brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified using flash silica column chromatography (hexane) to yield the title compound, a clear oil (175 mg, 48%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.30 (4H, m, $H_{2\text{-}5}$), 7.21 (1H, m, H_1), 6.17 (1H, dt, J = 6.4, 3.1 Hz, H_7), 5.84 (1H, ddt, J = 17.1, 10.3, 6.8 Hz, H_{13}), 5.60 (1H, apparent

q, J = 6.4 Hz, H_9), 5.03 (1H, d+fs, J = 17.1 Hz, H_{14} *trans*), 4.98 (1H, d+fs, J = 10.3 Hz, H_{14} *cis*), 2.22–2.12 (4H, m, H_{10} and H_{12}), 1.62 (2H, apparent pentet, J = 7.3 Hz, H_{11}) ppm.

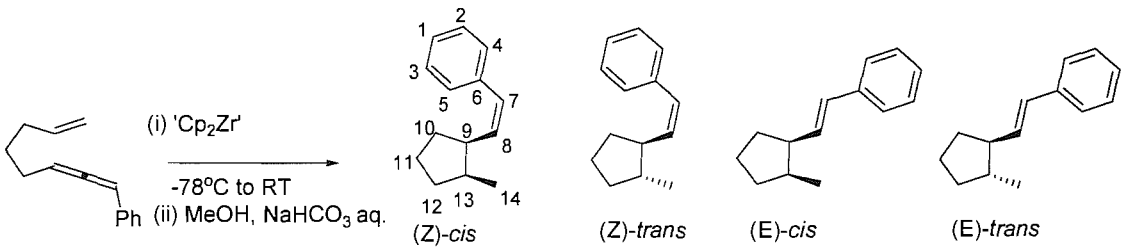
^{13}C NMR (100 MHz, $CDCl_3$): δ 205.40 (C, C_8), 138.62 (CH, C_{13}), 135.19 (C, C_6), 128.69 (2CH, C_2 and C_3, or, C_4 and C_5), 126.80 (CH, C_1), 126.73 (2CH, C_2 and C_3, or, C_4 and C_5), 114.89 (CH_2, C_{14}), 94.90 (2CH, C_7 and C_9), 33.40 (CH_2, C_{10} or C_{11} or C_{12}), 28.54 (CH_2, C_{10} or C_{11} or C_{12}), 28.28 (CH_2, C_{10} or C_{11} or C_{12}) ppm.

IR (film): 3076 (m), 3061 (m), 2974 (m), 2922 (s), 2852 (m), 1947 (m), 1638 (m), 1596 (m), 1494 (s), 1457 (s), 1437 (s), 991 (s), 908 (s), 875 (s) cm^{-1}.

GCMS (EI)$^+$ *m/z* (%): 184 ($(M)^+$, 74), 169 ($(M-CH_3)^+$, 58), 155 ($(M-C_2H_5)^+$, 64), 141 (100), 115 (100).

HRMS (EI) for $C_{14}H_{16}$ $(M)^+$ calculated 184.1252, found 184.1257.

5.2.46 Preparation of (*E*)- and (*Z*)- [2-(2-methyl-cyclopentyl)-vinyl]-benzene 445



$C_{14}H_{18}$

A solution of *n*-BuLi (0.40 mL, 2.00 eq, 1.00 mmol) (2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.146 g, 1.00 eq, 0.50 mmol) in THF (5 mL) at –78°C. After 5 minutes a solution of octa-1,2,7-trienyl benzene (0.092 mg, 1.00 eq, 0.50 mmol) in THF (1 mL). On removal of the cool bath and warming to room temperature the solution changed from yellow to dark brown. The solution was stirred for 6.5 hours, quenched with sat. $NaHCO_3$ aqueous solution (5 mL) and MeOH (5 mL) and stirred for a 16 hours. The products were extracted into diethyl ether (3 x 50 mL), the combined organic phases washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified using flash

silica column chromatography (hexane) to yield the title compound, a clear colourless oil (49 mg, 53%)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.22 (3H, m, H_{Ar}), 7.21–7.11 (2H, m, H_{Ar}), 6.42 (1H, d, J =11.5 Hz, H_7 (*Z*)-*cis* and (*Z*)-*trans*), 6.34 (1H, d, J = 15.8 Hz, H_7 (*E*)-*cis* and (*E*)-*trans*), 6.18 (1H, dd, J = 15.8, 8.5 Hz, H_8 (*E*)-*cis*), 6.08 (1H, dd, J = 15.8, 8.4 Hz, H_8 (*E*)-*trans*), 5.60 (1H, apparent t, J = 11.2 Hz, H_8 (*Z*)-*cis*), 5.47 (1H, apparent t, J = 10.9 Hz, H_8 (*Z*)-*trans*), 3.01 (1H, dq, J = 10.7, 7.3 Hz, H_9 (*Z*)-*cis*), 2.62 (1H, apparent pentet, J = 7.5 Hz, H_9 (*E*)-*cis*), 2.48 (1H, m, H_9 (*Z*)-*trans*), 2.11 (1H, m), 2.01 (1H, apparent pentet, J = 8.4 Hz, H_9 (*E*)-*trans*), 1.94–1.70 (2H, m), 1.69–1.44 (2H, m), 1.35 (1H, m), 1.17 (1H, m), 0.97 (3H, d, J = 6.8 Hz, H_{14} (*E*)-*trans*), 0.91 (3H, d, J = 7.0 Hz, H_{14} (*Z*)-*cis*), 0.87 (3H, d, J = 7.0 Hz, H_{14} (*E*)-*cis*).

^{13}C NMR (100 MHz, $CDCl_3$):

(*Z*)-*cis* δ: 138.16 (C, C_6), 135.28 (CH, C_7), 128.55 (CH, C_8), *128.83 (CH, C_{Ar}), 128.60 (CH, C_{Ar}), 128.23 (CH, C_{Ar}), 126.85 (CH, C_{Ar}), 126.51 (CH, C_{Ar}), 126.12 (CH, C_{Ar}), 126.10 (CH, C_{Ar}),* 41.82 (CH, C_9), 38.48 (CH, C_{13}), 34.03 (CH_2, C_{10} or C_{12}), 32.77 (CH_2, C_{10} or C_{12}), 23.76 (CH_2, C_{11}), 16.28 (CH_3, C_{14}) ppm.

(*Z*)-*trans*: very minor isomer, not able to identify ^{13}C NMR signals.

(*E*)-*trans* δ: 138.13 (C, C_6), 135.05 (CH, C_7), 129.17 (CH, C_8), *128.83 (CH, C_{Ar}), 128.60 (CH, C_{Ar}), 128.23 (CH, C_{Ar}), 126.85 (CH, C_{Ar}), 126.51 (CH, C_{Ar}), 126.12 (CH, C_{Ar}), 126.10 (CH, C_{Ar}),* 52.39 (CH, C_9), 41.44 (CH, C_{13}), 34.68 (CH_2, C_{10} or C_{12}), 33.37 (CH_2, C_{10} or C_{12}), 23.75 (CH_2, C_{11}), 18.59 (CH_3, C_{14}) ppm.

(*E*)- *cis* δ: 138.25 (C, C_6), 133.04 (CH, C_7), 129.42 (CH, C_8), *128.83 (CH, C_{Ar}), 128.60 (CH, C_{Ar}), 128.23 (CH, C_{Ar}), 126.85 (CH, C_{Ar}), 126.51 (CH, C_{Ar}), 126.12 (CH, C_{Ar}), 126.10 (CH, C_{Ar}),* 47.49 (CH, C_9), 38.66 (CH, C_{13}), 33.59 (CH_2, C_{10} or C_{12}), 30.98 (CH_2, C_{10} or C_{12}), 23.45 (CH_2, C_{11}), 16.35 (CH_3, C_{14}) ppm.

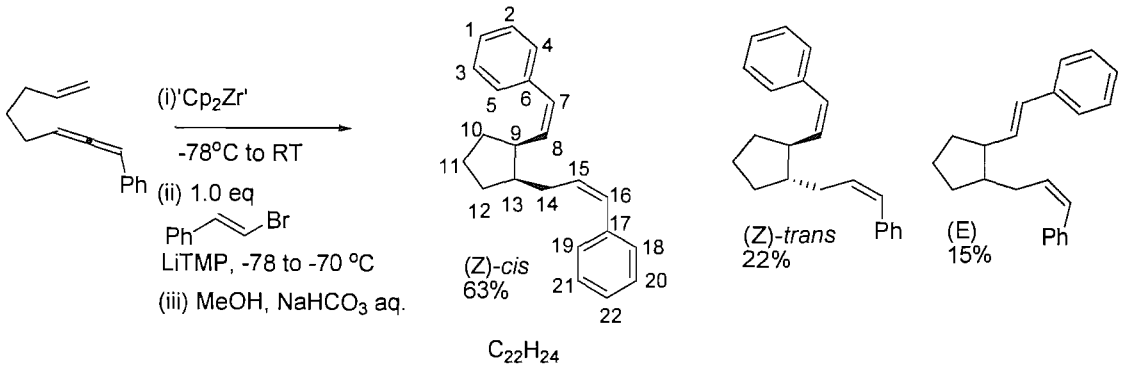
Generic Ar peaks: *128.83 (CH, C_{Ar}), 128.60 (CH, C_{Ar}), 128.23 (CH, C_{Ar}), 126.85 (CH, C_{Ar}), 126.51 (CH, C_{Ar}), 126.12 (CH, C_{Ar}), 126.10 (CH, C_{Ar})* could not be assigned to a particular isomer.

IR (film): 3023 (w), 2949 (s), 2866 (m), 1599 (w), 1492 (m), 1461 (m), 1446 (m), 962 (s), 743 (s) cm^{-1}.

GCMS (EI) *m/z*: 186 ($(M+H)^+$, 54), 157 ($(M-C_2H_5)^+$, 6), 143 ($(M-C_3H_7)^+$, 30), 129 ($(M-C_4H_9)^+$, 100), 104 (90).

HRMS (ES)$^+$ for $C_{14}H_{18}$ $(M)^+$ calculated 186.1409, found 186.1401.

5.2.47 Preparation of (*E*)- and (*Z*)- (2-{2-[(2*Z*)-3-phenylprop-2-enyl]cyclopentyl}vinyl)benzene 448



$C_{22}H_{24}$

A solution of *n*-BuLi (0.45 mL, 2.00 eq, 1.12 mmol) (2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.178 g, 1.00 eq, 0.58 mmol) in THF (5 mL) at –78°C. After 5 minutes a solution of octa-1,2,7-trienyl benzene (0.103 g, 1.00 eq, 0.58 mmol) in THF (1 mL). On removal of the cool bath and warming to room temperature the solution changed from yellow to dark brown.

The solution was stirred for 2 hours before being cooled to –78 °C. (*E*)-β-Bromostyrene (72 μL, 1.00 eq, 58 mmol) was added to the reaction mixture followed by the dropwise addition of LiTMP (0.90 mL, 1.00 eq, 0.58 mmol) over 15 minutes. The solution was allowed to was allowed to warm slowly to –70 °C over 2 hours before being quenched with sat. $NaHCO_3$ aqueous (5 mL) and MeOH (5 mL) and stirred for 16 hours. The products were extracted into diethyl ether (3 x 50 mL), the combined organic phases washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified using flash silica column chromatography (hexane) to yield the title compound as a mixture of three isomers, determined using NMR and GC data, a clear oil (61 mg, 38%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33–7.17 (10H, m, H_{Ar}), 6.44–6.32 (2H, m, H_7 or H_8, and, H_{15} or H_{16}), 6.11 (1H, dd, J = 15.8, 8.8 Hz, H_8 (*E*)-*cis* or (*E*)-*trans*) 5.64–5.49 (2H, m, H_7 or H_8, and, H_{15} or H_{16}), 3.14 (1H, dq, J = 10.8, 6.8 Hz, H_9 (*Z*)-*cis*), 2.76 (1H, apparent pentet, J = 6.8 Hz, H_9 (*E*)-*cis* or (*E*)-*trans*), 2.61 (1H, apparent pentet, J = 9.1 Hz, H_9 (*Z*)-*trans*), 2.45 (1H, m, H_{14}), 2.27 (1H, m, H_{14}), 2.09 (1H, m, H_{13}), 1.94–1.80 (2H, m, H_{10} and H_{12}), 1.74–1.38 (5H, m, H_{10}, H_{11}, H_{12} and H aliphatic-minor), 1.21 (1H, m, H aliphatic-minor) ppm.

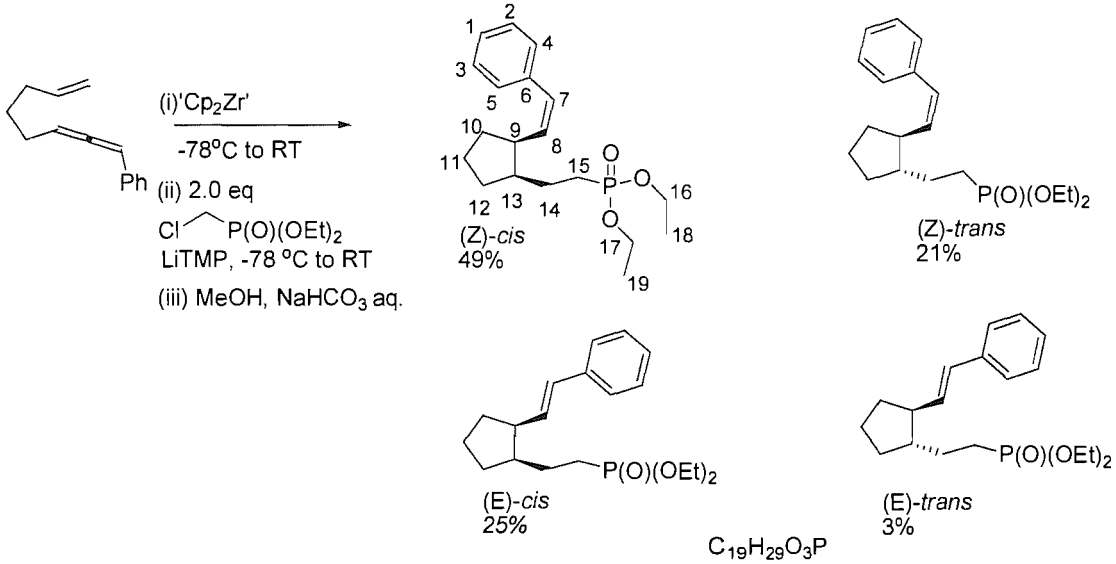
^{13}C NMR (100 MHz, $CDCl_3$) – some of CH signals in the aromatic region for the two minor compounds have not been clearly identified due to overlap with other signals.
(*Z*) *cis* δ: 138.00 (C), 134.49 (CH), 132.69 (CH), 129.22 (CH), 128.90 (CH), 128.86 (4CH), 128.25 (4CH), 126.58 (CH), 126.54 (CH), 44.97 (CH, C_{13}), 41.07 (CH, C_9), 33.29 (CH_2, C_{10} or C_{12}), 31.13 (CH_2, C_{10} or C_{12}), 30.16 (CH_2, C_{14}), 23.70 (CH_2, C_{11}) ppm.
(*Z*) *trans* δ: 138.10 (C), 132.12 (CH), 129.18 (CH), 129.05 (CH), 128.95 (CH), 128.77 (CH), 128.17 (CH), 126.50 (CH), 48.43 (CH, C_{13}), 45.01 (CH, C_9), 33.70 (CH_2, C_{10}, C_{12} or C_{14}), 33.21 (CH_2, C_{10}, C_{12} or C_{14}), 32.06 (CH_2, C_{10}, C_{12} or C_{14}), 23.94 (CH_2, C_{11}) ppm.
(*E*) δ: 137.90 (C), 137.49 (CH), 132.62 (CH), 132.21 (CH), 129.80 (CH), 129.15 (CH), 128.54 (CH), 126.88 (CH), 126.17 (CH), 46.43 (CH, C_9 or C_{13}), 45.42 (CH, C_9 or C_{13}), 31.45 (CH_2, C_{10}, C_{12} or C_{14}), 30.75 (CH_2, C_{10}, C_{12} or C_{14}), 30.30 (CH_2, C_{10}, C_{12} or C_{14}), 23.19 (CH_2, C_{11}) ppm.

IR (film): 3077 (w), 3053 (w), 3006 (m), 2946 (m), 2865 (m), 1598 (w), 1491 (m), 1445 (m), 1073 (w), 913 (w), 794 (m), 767 (s) cm^{-1}.

GCMS (CI) *m/z* (%): 306 ($(M+NH_4)^+$, 64), 289 ($(M+H)^+$, 10), 211 ($(M-C_6H_5)^+$, 30), 197 ($(M-C_7H_7)^+$, 86), 184 (100).

HRMS (ES)$^+$ for $C_{22}H_{24}$ $(M+H)^+$ calculated 288.1878, found 288.1877.

5.2.48 Preparation of {2-[2-((*E*)- or (*Z*)- styryl)-cyclopentyl]-ethyl}-phosphinic acid diethyl ester 449



$C_{19}H_{29}O_3P$

A solution of *n*-BuLi (0.45 mL, 2.00 eq, 1.12 mmol) (2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.178 g, 1.00 eq, 0.58 mmol) in THF (5 mL) at –78°C. After 5 minutes a solution of octa-1,2,7-trienyl benzene (0.103 g, 1.00 eq, 0.58 mmol) in THF (1 mL). On removal of the cool bath and warming to room temperature the solution changed from yellow to dark brown.

The solution was stirred for 2 hours before being cooled to –78 °C. A solution of diethyl chloromethyl phosphonate (0.208 g, 2.00 eq, 1.12 mmol) was added as a solution in THF (1 mL). This was followed by the dropwise addition of LiTMP (1.5 mL, 2.00 eq, 1.12 mmol) over 30 minutes. The solution was warmed slowly to room temperature over 16 hours, quenched with sat. $NaHCO_3$ aqueous solution (5 mL) and MeOH (5 mL), and then stirred for a further 5 hours. The products were extracted into diethyl ether (3 x 50 mL), the combined organic phases washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified using flash silica column chromatography (hexane/ethyl acetate 1:1) followed by Kugleror distillation (190 °C/ 10 mm Hg) to yield the title compound as a mixture of four isomers, a clear colourless oil (136 mg, 72%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.16 (5H, m, $H_{1\text{-}5}$), 6.44 (1H, d, J = 11.3 Hz, H_7 (*Z*)-*cis*), 6.42 (1H, d, J = 11.4 Hz, H_7 (*Z*)-*trans*), 6.36 (1H, d, J = 15.8 Hz, H_7 (*E*)-*cis* and (*E*)-*trans*), 6.13 (1H, dd, J = 15.8, 9.3 Hz, H_8 (*E*)-*cis*), 6.07 (1H, dd, J = 15.8, 8.5 Hz, H_8 (*E*)-*trans*), 5.60 (1H, t, J = 11.3 Hz, H_8 (*Z*)-*cis*), 5.50 (1H, dd, J = 11.4, 10.3

Hz, H_8 (*Z*)-*trans*), 4.12–3.92 (4H, m, H_{16} and H_{17}), 3.11 (1H, dtd, J = 11.3, 6.9, 5.2 Hz, H_9 (*Z*)-*cis*), 2.74 (1H, dtd, J = 9.3, 6.8, 4.6 Hz, H_9 (*E*)-*cis*), 2.57 (1H, apparent pentet, J = 9.0 Hz, H_9 (*Z*)-*trans*), 2.15 (1H, apparent pentet, J = 8.8 Hz, H_9 (*E*)-*trans*), 1.98–1.71 (4H, m), 1.70–1.47 (6H, m), 1.42–1.16 (7H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 137.90 (C, C_6), 137.85 (C, C_6), 137.78 (C, C_6 (Z)-*cis*), 137.34 (CH), 134.61 (CH), 133.82 (CH), 131.53 (CH), 130.04 (CH), 129.05 (CH), 128.98 (2CH), 128.80 (2CH), 128.67 (2CH), 128.56 (2CH), 128.23 (2CH), 127.01 (CH), 126.63 (CH), 126.14 (2CH), 126.10 (CH), 63.51 ($2CH_2$, d, J = 6.8 Hz, C_{16} and H_{17}), 61.47 ($2CH_2$, d, J = 5.8 Hz, C_{16} and C_{17}), 61.45 ($2CH_2$, d, J = 5.8 Hz, C_{16} and C_{17}), 48.45 (CH, d, J = 16.5 Hz, C_{13}), 46.15 (CH, C_9), 45.28 (CH, d, J = 16.5 Hz, C_{13}), 45.03 (CH, C_9), 45.00 (CH, d, J = 16.5 Hz, C_{13} (*Z*)-*cis*), 40.48 (CH, C_9 (*Z*)-*cis*), 33.90 (CH_2, C_{10} and C_{12}), 33.37 (CH_2, C_{10} and C_{12} (*Z*)-*cis*), 32.03 (CH_2, C_{10} and C_{12}), 31.90 (CH_2, C_{10} or C_{12}), 30.86 (CH_2, C_{10} or C_{12} (*Z*)-*cis*), 30.62 (CH_2, C_{10} or C_{12}), 27.05 (CH_2), 26.99 (CH_2), 25.63 (CH_2), 25.53 (CH_2), 25.36 (CH_2), 24.24 (CH_2), 24.18 (CH_2), 24.13 (CH_2), 24.06 (CH_2), 24.01 (CH_2), 23.97 (CH_2), 23.85 (CH_2), 23.65 (CH_2, C_{11} (*Z*)-*cis*), 23.21 (CH_2, C_{11}), 16.60 (CH_3, C_{18} and C_{19}), 16.54 (CH_3, C_{18} and C_{19}), 16.46 (CH_3, C_{18} and C_{19}) ppm.
The 5 extra CH_2 signals between 27.05 and 23.65 ppm can be accounted for as part of doublets – splitting created by adjacent phosphorous.

IR (film): 2978 (w), 2948 (m), 2907 (w), 2866 (m), 1493 (w), 1446 (w), 1390 (w), 1239 (s), 1054 (s), 1024 (s), 953 (s), 789 (s), 731 (s) cm^{-1}.

MS (ES)$^+$ ***m/z*** **(%)**: 337 ($(M+H)^+$, 100), 359 ($(M+Na)^+$, 43), 673 ($(2M+H)^+$, 30), 695 ($(2M+Na)^+$, 45).

HRMS (ES)$^+$ for $C_{19}H_{30}O_3P$ $(M+H)^+$ calculated 337.1927, found 337.1924.

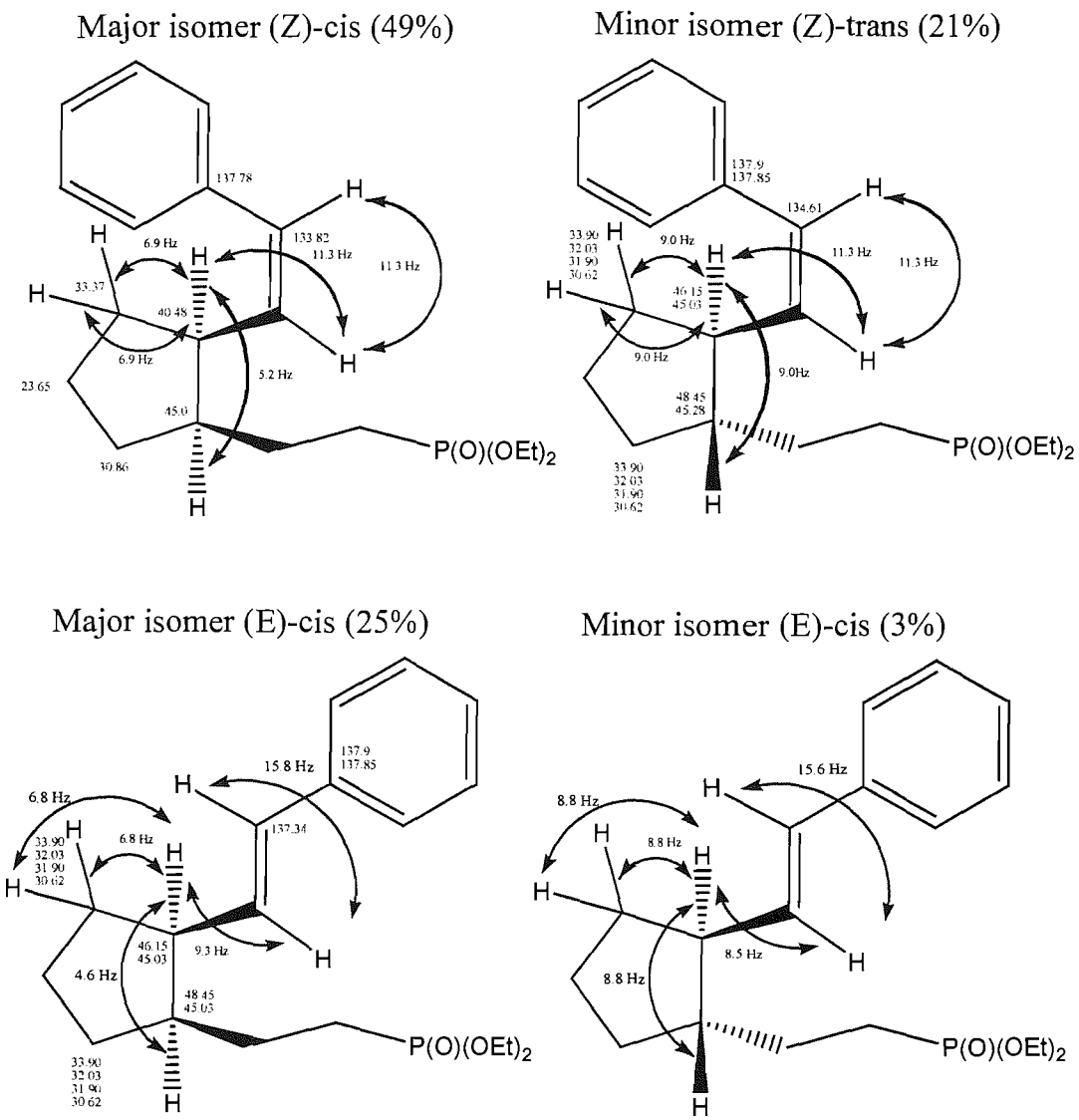
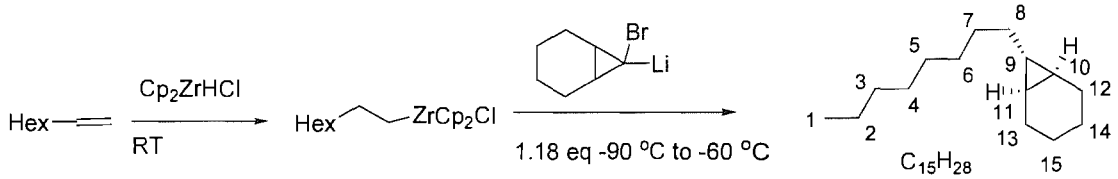


Figure 5-1 Coupling constants used to assign relative stereochemistry of products

5.3 Experimental from Chapter 3

5.3.1 Preparation of (1*S*,6*R*,7*R*)-7-octylbicyclo[4.1.0]heptane 565



A solution of 1-octene (0.112 g, 1.05 eq, 1.0 mmol) in THF (1 mL) was added to a suspension of zirconocene hydrogen chloride (0.244 g, 1.00 eq, 0.95 mmol) in THF (4 mL) at room temperature. This was stirred for 1 hour before use.

A solution of 7,7-dibromobicyclo[4.1.0]heptane (0.314 g, 1.30 eq, 1.24 mmol) in THF (4 mL) and diethyl ether (1 mL) was cooled to –108 °C before the dropwise addition of *n*-BuLi (0.45 mL, 1.18 eq, 1.121 mmol) (2.5 M in hexanes) over 10 minutes. This was stirred for 20 minutes and warmed to –95 °C before the dropwise addition of the organochlorozirconocene complex (≈5 mL, 1.00 eq, 0.95 mmol) over 30 minutes. The reaction was warmed to –60 °C over one hour, quenched with MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (5 mL) then stirred at room temperature for 16 hours. The products were extracted into diethyl ether (3 x 30 mL), the combined organic phases washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified using flash silica column chromatography (hexane), to yield the title compound (0.117 g, 59%)

^{1}H NMR (400 MHz, $CDCl_3$): 1.84 (2H, m), 1.61 (2H, m), 1.38–1.21 (12H, m), 1.20–1.07 (6H, m), 0.90 (3H, t, J = 5.2 Hz, H_1), 0.54 (2H, m, H_{10} and H_{11}), 0.32 (1H, tt, J = 6.8, 4.7 Hz, H_9) ppm.

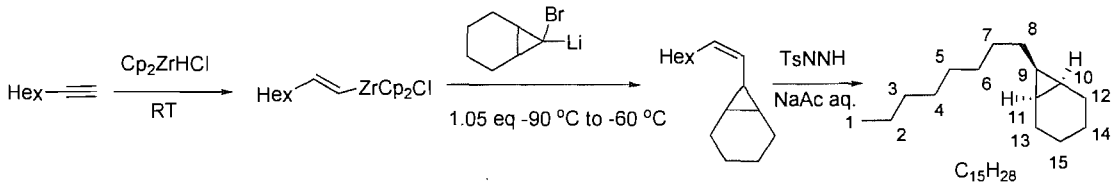
^{13}C NMR (100 MHz, $CDCl_3$): δ 34.70 (CH_2), 32.10 (CH_2), 29.88 (CH_2), 29.71 (CH_2), 29.69 (CH_2), 29.53 (CH_2), 24.18 (CH_2), 24.09 ($2CH_2$, C_{12} and C_{13}, or, C_{14} and C_{15}), 22.86 (CH, C_9), 21.92 ($2CH_2$, C_{12} and C_{13}, or, C_{14} and C_{15}), 17.14 (2CH, C_{10} and C_{11}), 14.27 (CH_3, C_1) ppm.

IR (film): 2920 (s), 2851 (s), 1449 (m), 1377 (w), 1071 (w), 767 (w), 721 (w) cm^{-1}.

GCMS (EI) *m/z* (%): 208 $((M)^+$, 94), 193 $((M\text{-}CH_3)^+$, 2), 180 $((M\text{-}C_2H_4)^+$, 14), 166 $((M\text{-}C_3H_6)^+$, 12), 81 (100).

HRMS (EI) for $C_{15}H_{28}$ $(M)^+$ calculated 208.2191, found 208.2192.

5.3.2 Preparation of (1S,6*R*,7*S*)-7-octylbicyclo[4.1.0]heptane 566



A solution of 1-octyne (0.118 g, 1.05 eq, 1.07 mmol) in THF (1 mL) was added to a suspension of zirconocene hydrogen chloride (0.264 g, 1.00 eq, 1.02 mmol) in THF (4 mL) at room temperature. This was stirred for 1 hour before use.

A solution of 7,7-dibromobicyclo[4.1.0]heptane (0.298 g, 1.15 eq, 1.17 mmol) in THF (4 mL) and diethyl ether (2 mL) was cooled to –108 °C before the dropwise addition of *n*-BuLi (0.43 mL, 1.05 eq, 1.07 mmol) (2.5 M in hexanes) over 10 minutes. This was stirred for 10 minutes and warmed to –90 °C before the dropwise addition of the organochlorozirconocene complex (≈5 mL, 1.00 eq, 1.02 mmol) over 30 minutes. The reaction was warmed to –60 °C over one hour, quenched with HCl (5 mL, 2 M aqueous solution) then stirred at room temperature for 30 minutes. The product was extracted into diethyl ether (3 x 30 mL), the combined organic phases washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield crude alkene (0.147 g, 0.71 mmol, 70%)

A solution of alkene (0.147 g, 1.00eq, 0.71 mmol) and *p*-toluene sulfonyl hydrazide (1.32 g, 10.0 eq, 7.1 mmol) in 1,2-dimethoxyethane was heated to reflux before the dropwise addition of a solution of sodium acetate (1.16 g, 20.0 eq, 14.2 mmol) in water (20 mL) over 3.5 hours. The solution was allowed to cool to room temperature, poured onto water (50 mL) and extracted with dichloromethane (3 x 40 mL). The combined organic phases were washed with water (100 mL) before being dried with $MgSO_4$ and were concentrated *in vacuo*. The crude product was purified by flash silica column chromatography (hexane) to yield the title compound (49 mg, 23%).[173]

^{1}H NMR (300 MHz, $CDCl_3$): 1.83 (2H, m), 1.42–1.20 (18H, m), 1.19–1.11 (2H, m), 0.90 (3H, t, J = 6.8 Hz, H_1), 0.84–0.79 (2H, m, H_{10} and H_{11}), 0.55 (1H, tt, J = 8.6, 7.0 Hz, H_9) ppm.

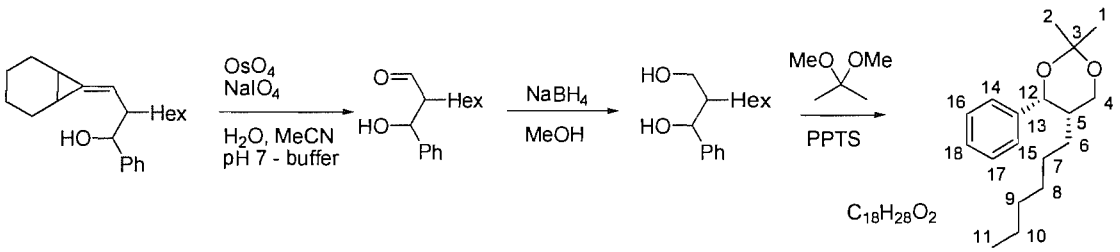
^{13}C NMR (75 MHz, $CDCl_3$): δ 32.11 (CH_2), 30.24 (CH_2), 29.98 (CH_2), 29.91 (CH_2), 29.54 (CH_2), 24.44 (CH_2), 22.86 (CH_2), 22.82 ($2CH_2$, C_{12} and C_{13}, or, C_{14} and C_{15}), 19.17 ($2CH_2$, C_{12} and C_{13}, or, C_{14} and C_{15}), 18.89 (CH, C_9), 14.27 (CH_3, C_1), 10.33 (2CH, C_{10} and C_{11}) ppm.

IR (film): 3006 (w), 2921 (s), 2852 (s), 1466 (m), 1377 (w), 1260 (w), 1019 (w), 807 (w), 769 (w), 713 (w) cm^{-1}.

GCMS (EI) *m/z* (%): 208 ($(M)^+$, 61), 180 ($(M-C_2H_4)^+$, 12), 166 ($(M-C_3H_6)^+$, 4), 152 ($(M-C_4H_8)^+$, 12), 81 (100).

HRMS (EI) for $C_{15}H_{28}$ $(M)^+$ calculated 208.2191, found 208.2195.

5.3.3 Preparation of (4S,5S)-4-hexyl-2,2-dimethyl-5-phenyl-[1,3]dioxane[143,174,146] 577



A solution of osmium tetroxide (1.69 mL, 0.50 eq, 0.14 mmol)(2.5 wt% in 2-methyl-2-propanol) was added to a suspension of 2-((bicyclo[4.1.0]heptan-7-ylidene)methyl)-1-phenyloctan-1-ol (82 mg, 1.00 eq, 0.27 mmol) and sodium periodate (2.843 g, 50.0 eq, 13.50 mmol) in acetonitrile (20 mL), water (10 mL) and phosphate buffer (10 mL) at room temperature. After stirring for 3 hours the reaction mixture was poured onto water (30 mL) and extracted with diethyl ether (4 x 30 mL). The combined organics were washed water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resuling black oil was dissolved in methanol (3 mL) and cooled to 0 °C before the portionwise addition of sodium borohydride (41

mg, 4.00 eq, 1.10 mmol). The reaction mixture was stirred at room temperature overnight and was quenched with sat. NH_4Cl aqueous solution (20 mL). After 5 minutes the products were extracted into diethyl ether (4x30 mL), washed with water (50 mL) and brine (50 mL) before being dried over $MgSO_4$ and concentrated *in vacuo*. The diol was purified using flash silica column chromatography (hexane/ethyl acetate 3:1) to yield the product as a clear colourless oil 6 mg, 11%).
A solution of the diol (6 mg, 1.00 eq, 0.03 mmol) and pyridinium toluene-4-sulfonate (2 mg) in benzene (1 mL) and 2,2-dimethoxypropane (1 mL) were stirred at room temperature for 16 hours. The reaction was quenched with triethylamine (0.10 mL) and stirred for 20 minutes before the solvent was removed *in vacuo*. The product was purified by flash silica column chromatography (hexane/diethyl ether 96.5:3.5), to yield the title product as a clear colourless oil (5 mg, 68%, overall 6% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.20 (5H, m, $H_{14\text{-}18}$), 5.16 (1H, d, J = 2.5 Hz, H_{12}), 4.17 (1H, dd, J = 11.8, 1.8 Hz, H_4), 3.87 (1H, dd, J = 11.8, 1.5 Hz, H_4), 1.68–1.48 (3H, m, H_5 and others), 1.52 (3H, s, H_1 or H_2), 1.50 (3H, s, H_1 or H_2), 1.26 (1H, m), 1.20–1.13 (2H, m), 1.12–1.05 (3H, m), 0.97–0.86 (2H, m), 0.80 (3H, t, J = 7.0 Hz, H_{11}) ppm.

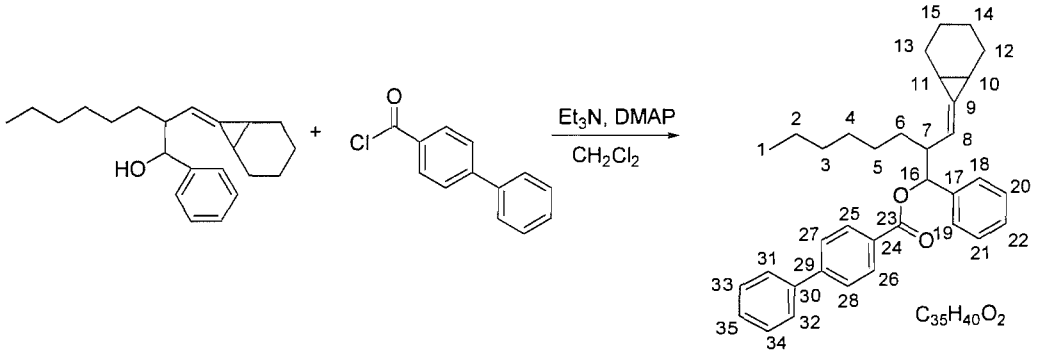
^{13}C NMR (100 MHz, $CDCl_3$): δ 141.17 (C, C_{13}), 128.18 (2CH, C_{16} and C_{17}), 126.88 (CH, C_{18}), 125.59 (2CH, C_{14} and C_{15}), 99.11 (C, C_3), 73.70 (CH, C_{12}), 63.30 (CH_2, C_4), 39.43 (CH, C_5), 31.91 (CH_2, C_6), 29.92 (CH_3, C_1 or C_2), 29.41 (CH_2), 27.62 (CH_2), 23.49 (CH_2), 22.71 (CH_2), 19.23 (CH_3, C_1 or C_2), 14.19 (CH_3, C_{11}) ppm.

IR (film): 2911 (w), 2930 (s), 2857 (m), 1450 (w), 1379 (s), 1260 (w), 1238 (m), 1196 (s), 1169 (m), 1138 (w), 1118 (s), 1051 (m), 954 (w), 818 (w), 760 (w), 718 (w), 699 (s) cm^{-1}.

GCMS (EI) *m/z* (%): 277 ($(M+H)^+$, 1), 261 ($(M\text{-}CH_3)^+$, 4), 107 (100), 91 ($(C_7H_7)^+$, 24), 77 ($(C_6H_5)^+$, 8).

HRMS (EI) for $C_{17}H_{25}O_2$ $(M\text{-}CH_3)^+$ calculated 261.1855, found 261.1855.

5.3.4 Preparation of biphenyl-4-carboxylic acid 2-bicyclo[4.1.0]hept-7-ylidenemethyl-1-phenyl-octyl ester 580



4-Biphenyl carbonylchloride (131 mg, 2.00 eq, 0.60 mmol), DMAP (11 mg, 0.30 eq, 0.09 mmol) and triethylamine (0.83 mL, 2.00 eq, 0.60 mmol) were added to a solution of 2-((bicyclo[4.1.0]heptan-7-ylidene)methyl)-1-phenyloctan-1-ol (94 mg, 1.00 eq, 0.30 mmol) in dichloromethane (4 mL) and stirred at room temperature for 72 hours. The reaction mixture was poured onto water (10 mL), the products were extracted into dicloromethane (3 x 10 mL). The combined organics were washed with water (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified using flash silica column chromatography (hexane/diethyl ether 95:5) to yield the title product as a clear colourless oil (90 mg, 61%).

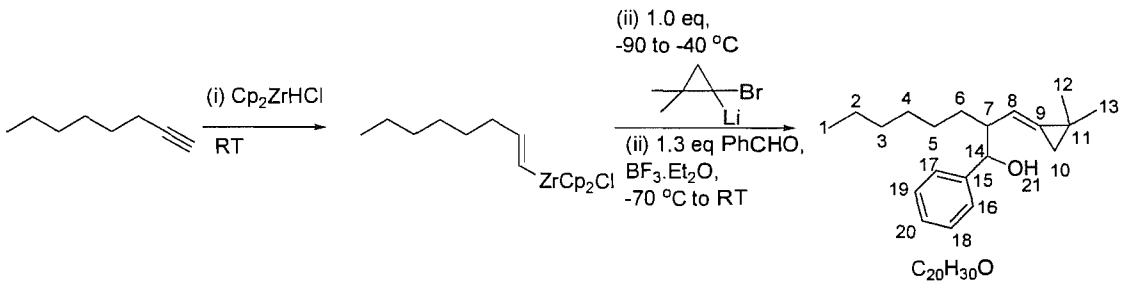
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (2H, d, J = 8.5 Hz, H_{25} and H_{26}), 7.64 (2H, d, J = 8.5 Hz, H_{27} and H_{28}), 7.60 (2H, d, J = 7.0 Hz), 7.45 (2H, t, J = 7.4 Hz), 7.39–7.35 (3H, m), 7.28 (2H, t, J = 7.7 Hz), 7.20 (1H, t, J = 7.3 Hz), 5.95 (1H, d, J = 7.5 Hz, H_{16}), 5.45 (1H, dt, J = 9.5, 1.9 Hz, H_8), 2.88 (1H, m, H_7), 1.75–1.59 (3H, m), 1.52–1.12 (15H, m), 0.98 (1H, m, H_{10} or H_{11}), 0.83 (3H, t, J = 6.9 Hz, H_1), 0.77 (1H, m, H_{10} or H_{11}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.84 (C), 145.79 (C), 140.26 (C), 140.08 (C), 135.38 (C), 130.34 (2CH, C_{25} and C_{26}), 129.53 (C), 129.07 (2CH), 128.27 (3CH), 127.74 (CH), 127.43 (2CH), 127.28 (2CH), 127.19 (2CH), 116.83 (CH, C_8), 79.91 (CH, C_{16}), 47.97 (CH, C_7), 32.00 (CH_2), 31.44 (CH_2), 29.42 (CH_2), 27.10 (CH_2), 23.19 (CH_2), 22.78 (CH_2), 22.39 (CH_2), 21.46 (CH_2), 20.85 (CH_2), 14.23 (CH_3, C_1), 13.08 (CH, C_{10} or C_{11}), 12.39 (CH, C_{10} or C_{11}) ppm.

IR (film): 2928 (s), 2855 (m), 1716 (s), 1609 (w), 1449 (w), 1310 (w), 1267 (s), 1177 (w), 1100 (s), 1008 (w), 857 (w), 747 (m), 698 (m) cm^{-1}.

It was not possible to obtain mass spectrometry data on this compound.

5.3.5 Preparation of 2-(2,2-dimethyl-cyclopropylidenemethyl)-1-phenyl-octan-1-ol 588



A solution of 1-octyne (0.114g, 1.0 eq, 1.04 mmol) in THF (1 mL) was added to a suspension of zirconocene hydrogen chloride (0.267 g, 1.0 eq, 1.04 mmol) in THF (5 mL) at room temperature and stirred for 1 hour. The zirconocene gradually dissolved resulting in a light yellow solution.

The carbenoid was prepared by cooling a solution of 1,1-dibromo-2,2-dimethylcyclopropane (0.237 g, 1.00 eq, 1.04 mmol) in THF (2 mL) to –90 °C before the dropwise addition of *n*-BuLi (0.42 ml, 1.00 eq, 1.04 mmol) (2.5 M in hexanes) over 10 minutes. After 30 minutes the zirconocene solution was added to the carbenoid over 30 minutes. The reaction mixture was allowed to warm to –40 °C over 4 hours. It was cooled to –70 °C before the dropwise addition of benzaldehyde (0.13 mL, 1.30 eq, 1.35 mmol) and boron trifluoride-diethyl-etherate (0.16 mL, 1.30 eq, 1.35 mmol). The solution was allowed to warm slowly to room temperature over 16 hours before being quenched with sat. $NaHCO_3$ aqueous solution (5 mL) and MeOH (5 mL) then stirred for a further 24 hours. The products were extracted into ether (3 x 50 mL), the combined organic phases washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified using flash silica column chromatography (hexane/diethyl ether 9:1 - co-eluting benzaldehyde removed under reduced pressure) to yield the title compound as a mixture of two isomers (d.r. ratio 85:15), a clear oil (136 mg, 72 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.28 (3H, m, H_{Ar}), 7.25–7.22 (2H, m, H_{Ar}), 5.58 (1H, dt, J = 9.2, 2.2 Hz, H_8 major), 5.45 (1H, d, J = 9.5 Hz, H_8 minor), 4.47 (1H, d, J = 7.3 Hz, H_{14} major), 4.38 (1H, d, J = 7.8 Hz, H_{14} minor), 2.42 (1H, m, H_7), 2.15 (1H, d, J = 2.0 Hz, H_{21}), 1.32 – 1.07 (16H, m, $H_{2\text{-}6}$, H_{12} and H_{13}), 0.80 (3H, t, J = 7.0 Hz, H_1), 0.77 (1H, d, J = 2.1 Hz, H_{10}), 0.75 (1H, d, J = 2.1 Hz, H_{10}) ppm.

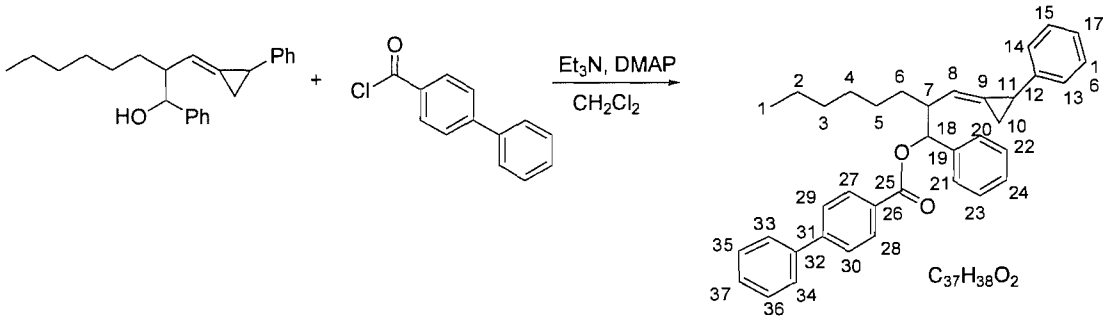
^{13}C NMR (100 MHz, $CDCl_3$):
Major δ: 143.20 (C, C_9), 139.86 (C, C_{15}), 128.17 (2CH, C_{Ar}), 127.44 (CH, C_{Ar}), 127.10 (2CH, C_{Ar}), 116.22 (CH, C_8), 77.55 (CH, C_{14}), 50.65 (CH, C_7), 31.94 (CH_2, C_3 or C_4), 31.25 (CH_2, C_3 or C_4), 29.23 (CH_2, C_5 or C_6), 27.40 (CH_2, C_6 or C_5), 24.64 (CH_3, C_{12} or C_{13}), 24.57 (CH_3, C_{12} or C_{13}), 22.72 (CH_2, C_2), 17.25 (CH_2, C_{10}), 16.55 (C, C_{11}), 14.18 (CH_3, C_1) ppm.
Minor δ: 143.14 (C, C_9), 139.32 (C, C_{15}), 128.24 (2CH, C_{Ar}), 127.94 (CH, C_{Ar}), 127.55 (CH, C_{Ar}), 127.14 (CH, C_{Ar}), 118.04 (CH, C_8), 77.36 (CH, C_{14}), 52.24 (CH, C_7), 31.94 (CH_2, C_3 or C_4), 31.25 (CH_2, C_3 or C_4), 29.39 (CH_2, C_5 or C_6), 27.77 (CH_2, C_5 or C_6), 24.47 (CH_3, C_{12} or C_{13}), 24.36 (CH_3, C_{12} or C_{13}), 22.72 (CH_2, C_2), 17.75 (CH_2, C_{10}), 16.24 (C, C_{11}), 14.18 (CH_3, C_1) ppm.

IR (film): 3550 – 3200 broad (m), 3028 (w), 2956 (s), 2922 (s), 2855 (s), 1451 (m), 1368 (m), 1192 (w), 1027 (m), 852 (w) cm^{-1}.

GCMS (CI) *m/z*: 287 ($(M+H)^+$, 14), 269 ($(M-H_2O+H)^+$, 100), 213 (10), 181 (30), 105 (28).

HRMS (ES)$^+$ for $C_{20}H_{30}O$ $(M+H)^+$ calculated 286.2297, found 286.2286.

5.3.6 Preparation of biphenyl-4-carboxylic acid 1-phenyl-2-[2-phenyl-cycloprop-(*E*)-ylidenemethyl]-octyl ester 595



4-Biphenyl carbonylchloride (34 mg, 2.00 eq, 0.16 mmol), DMAP (3 mg, 0.30 eq, 0.02 mmol) and triethylamine (0.02 mL, 2.00 eq, 0.16 mmol) were added to a solution of 1-phenyl-2-((*E*)-(2-phenylcyclopropylidene)methyl)octan-1-ol (26 mg, 1.00 eq, 0.08 mmol) in dichloromethane (1 mL) and stirred at room temperature for 72 hours. The reaction mixture was poured onto water (5 mL) the products were extracted into dicloromethane (3 x 5 mL). The combined organics were washed with water (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified using flash silica column chromatography (hexane/ethyl acetate 9:1eluent) to yield the title product as a clear colourless oil (26 mg, 63%). The starting alcohol was also recovered (8 mg, 30%).

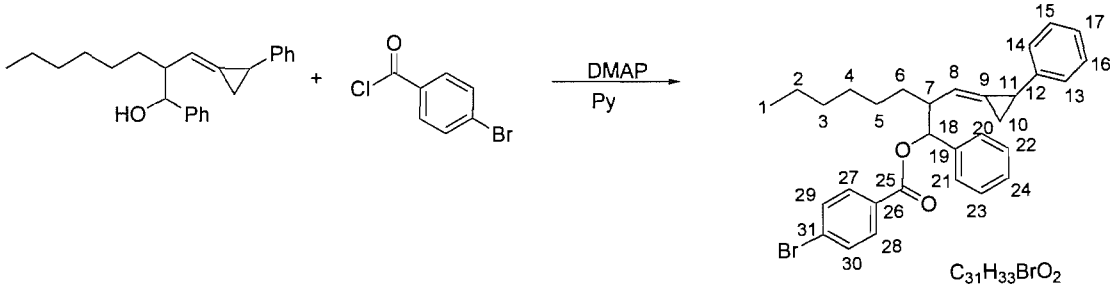
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (2H, d, J = 8.3 Hz, H_{27} and H_{28}), 7.65 (2H, d, J= 8.3 Hz, H_{29} and H_{30}), 7.62 (2H, d, J = 7.5 Hz), 7.49–7.25 (8H, m), 7.14–7.08 (3H, m), 6.63 (2H, dd, J = 7.5, 2.0 Hz), 6.00 (1H, d, J = 8.5 Hz, H_{18}), 5.64 (1H, d+fs, J = 9.4 Hz, H_8), 3.13 (1H, apparent qd, J = 9.3, 3.0 Hz, H_7), 2.52 (1H, ddd, J = 9.0, 4.8, 1.7 Hz, H_{11}), 1.82 (1H, m), 1.59 (1H, apparent td, J = 8.9, 2.3 Hz, H_{10}), 1.52 –1.17 (9H, m), 0.89 (3H, t, J = 6.3 Hz, H_1), 0.82 (1H, ddd, J = 8.3, 4.8, 2.5 Hz, H_{10}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.83 (C, C_{25}), 145.86 (C), 142.42 (C), 140.24 (C), 139.81 (C), 130.32 (2CH, C_{27} and C_{28}), 129.86 (C), 129.43 (C), 129.08 (2CH), 128.43 (2CH), 128.29 (3CH), 127.96 (CH), 127.89 (2CH), 127.44 (2CH), 127.23 (2CH), 126.27 (2CH), 125.67 (CH), 119.10 (CH, C_8), 79.74 (CH, C_{18}), 47.95 (CH, C_7), 31.99 (CH_2), 31.55 (CH_2), 29.42 (CH_2), 27.27 (CH_2), 22.79 (CH_2), 20.42 (CH, C_{11}), 14.61 (CH_2, C_{10}), 14.24 (CH_3, C_1) ppm.

IR (film): 3013 (w), 2927 (m), 2855 (m), 1713 (s), 1606 (m), 1495 (w), 1453 (w), 1404 (w), 1310 (w), 1264 (s), 1177 (m), 1098 (s), 1020 (w), 1008 (w), 962 (m), 857 (m), 840 (w), 746 (s), 695 (s), 585 (w), 542 (w) cm^{-1}.

It was not possible to obtain mass spectrometry data on this compound.

5.3.7 Preparation of 4-bromo-benzoic acid 1-phenyl-2-[2-phenyl-cycloprop-(*E*)-ylidenemethyl]-octyl ester[175] 597



p-Bromobenzoyl chloride (38 mg, 2.00 eq, 0.18 mmol) and DMAP (3 mg, 0.30 eq, 0.03 mmol) were added to a solution of 1-phenyl-2-((*E*)-(2-phenylcyclopropylidene)methyl)octan-1-ol (29 mg, 1.00 eq, 0.09 mmol) in pyridine (1 mL) and stirred at room temperature for 96 hours. The reaction mixture was quenched with sat. NH_4Cl aqueous solution (5 mL) and stirred for 30 minutes. The product was extracted into diethyl ether (3 x 5 mL). The combined organics were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified using flash silica column chromatography (hexane/ethyl acetate 9:1) to yield the title product as a clear colourless oil (7 mg, 18%). Some of the starting alcohol was also recovered (12 mg, 40%).

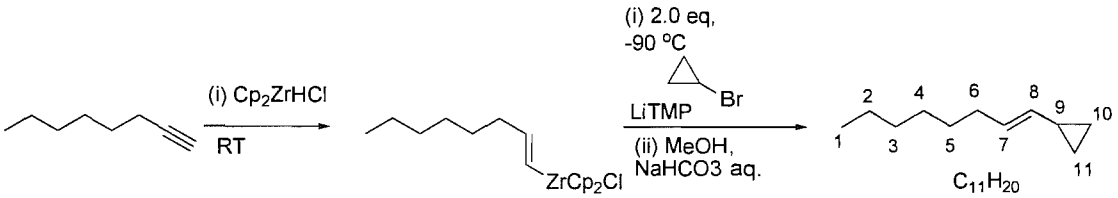
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (2H, d, J = 8.5 Hz, H_{27} and H_{28}), 7.57 (2H, d, J = 8.5 Hz, H_{29} and H_{30}), 7.45–7.42 (2H, m), 7.37–7.30 (3H, m), 7.14–7.09 (3H, m), 6.63–6.59 (2H, m), 5.96 (1H, d, J = 8.5 Hz, H_{18}), 5.62 (1H, d+fs, J = 9.5 Hz, H_8), 3.10 (1H, apparent qd, J = 9.5, 3.3 Hz, H_7), 2.52 (1H, ddd, J = 9.0, 4.9, 1.7 Hz, H_{11}), 1.77 (1H, m), 1.58 (1H, td, J = 9.0, 2.3 Hz, H_{10}), 1.51–1.18 (9H, m), 0.88 (3H, t, J = 6.9 Hz, H_1), 0.79 (1H, ddd, J = 8.5, 4.9, 2.5 Hz, H_{10}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.22 (C, C_{25}), 142.33 (C), 139.52 (C), 131.88 (2CH, C_{29} and C_{30}), 131.30 (2CH, C_{27} and C_{28}), 129.99 (C), 129.58 (C), 128.47 (2CH), 128.29 (2CH), 128.18 (C), 128.07 (CH), 127.85 (2CH), 126.25 (2CH), 125.71 (CH), 118.91 (CH, C_8), 80.04 (CH, C_{18}), 47.86 (CH, C_7), 31.97 (CH_2), 31.53 (CH_2), 29.53 (CH_2), 27.21 (CH_2), 22.77 (CH_2), 20.39 (CH, C_{11}), 14.54 (CH_2, C_{10}), 14.21 (CH_3, C_1) ppm.

IR (film): 2927 (m), 2855 (w), 1719 (s), 1590 (m), 1495 (w), 1484 (w), 1454 (w), 1397 (w), 1265 (s), 1172 (w), 1111 (m), 1099 (m), 1069 (w), 1012 (m), 959 (w), 845 (w), 754 (s), 697 (m) cm^{-1}.

It was not possible to obtain mass spectroscopy data on this compound.

5.3.8 Preparation of ((*E*)-oct-1-enyl)-cyclopropane 599



A solution of 1-octyne (0.110 g, 1.05 eq, 0.99 mmol) in THF (1 mL) was added to a suspension of zirconocene hydrogen chloride (0.246 g, 1.00 eq, 0.95 mmol) in THF (5 mL) at room temperature and stirred for 45 minutes. The reaction mixture was cooled to –90 °C before the addition of cyclopropyl bromide (0.15 mL, 2.00 eq, 1.90 mmol) and followed by the addition of LiTMP (2 mL, 2.00 eq, 1.90 mmol) dropwise over 20 minutes. The reaction mixture was stirred for 10 minutes, quenched with MeOH (5 mL) and sat. $NaHCO_3$ solution (5 mL) then stirred for a further 16 hours. The products were extracted into diethyl ether (3 x 50 mL), the combined organic phases washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified using flash silica column chromatography (pentane) to yield the title compound, a clear colourless oil (70 mg, 46%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.51 (1H, dt, J = 15.3, 6.8 Hz, H_7), 4.97 (1H, ddt, J = 15.3, 8.5, 1.5 Hz, H_8), 1.97 (2H, q+fs, J = 6.8 Hz, H_6), 1.40–1.24 (9H, m, H_{2-5}, H_9),

0.89 (3H, t, J = 6.8 Hz, H_1), 0.67–0.63 (2H, m, H_{10} and H_{11}), 0.33–0.29 (2H, m, H_{10} and H_{11}) ppm.

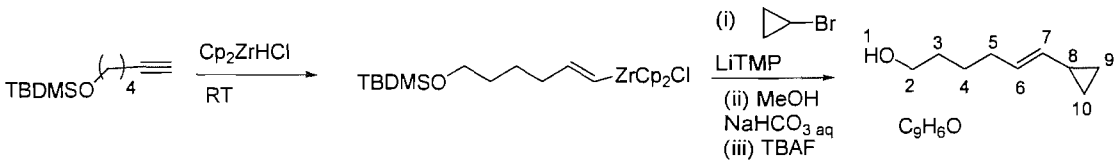
^{13}C NMR (100 MHz, $CDCl_3$): δ 133.72 (CH, C_8), 128.50 (CH, C_7), 32.68 (CH_2, C_6), 31.92 (CH_2), 29.85 (CH_2), 29.02 (CH_2), 22.79 (CH_2), 14.23 (CH_3, C_1), 13.62 (CH, C_9), 6.47 ($2CH_2$, C_{10} and C_{11}) ppm.

IR (film): 3079 (w), 3004 (w), 2955 (m), 2921 (s), 2852 (m), 1457 (m), 1043 (w), 1017 (w), 957 (s), 809 (m) cm^{-1}.

GCMS (CI) *m/z* (%): 170 ($(M+NH_4)^+$, 20), 152 ($(M)^+$, 54), 95 (40), 81 ($(M-C_5H_{11})^+$, 100), 67 ($(M-C_7H_{15})^+$, 70).

HRMS (ES)$^+$ for $C_{11}H_{20}$ $(M)^+$ calculated 152.1565, found 152.1565.

5.3.9 Preparation of (*E*)-6-cyclopropyl-hex-5-en-1-ol 601



A solution of *tert*-butyl(hex-5-ynyloxy)dimethylsilane (0.207 g, 1.00 eq, 0.98 mmol) in THF (1 mL) was added to a suspension of Cp_2ZrHCl (0.253 g, 1.00 eq, 1.00 mmol) in THF (5 mL) at room temperature. After stirring for 40 minutes the green solution was cooled to –90 °C before the addition of cyclopropyl bromide (0.16 mL, 2.00 eq, 1.96 mmol). This was followed by the dropwise addition of LiTMP (1.5 mL, 2.00 eq, 1.96 mmol) over 20 minutes. The reaction was stirred for 15 minutes, quenched with MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (5 mL) then stirred for a further 16 hours at room temperature. The product was extracted into diethyl ether (3 x 30 mL), the combined organic phases washed with HCl (50 mL, 2M aqueous solution), water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated *in-vacuo*. The crude product (0.204 g, 1.00 eq, 0.98 mmol) was dissolved in THF (5 mL) before the addition of TBAF (1M solution in THF) (2.00 mL, 2.04 eq, 2.00 mmol) and stirred for 18 hours. The reaction was quenched with water (20 mL) and the products were extracted as above. The product was purified using flash silica column

chromatography (hexane/ethyl acetate 3:1) to yield the title compound, a yellow oil (58 mg, 41%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.49 (1H, dt, J = 15.3, 6.9 Hz, H_6), 4.98 (1H, dd, J = 15.3, 8.2 Hz, H_7), 3.64 (2H, t, J = 6.7 Hz, H_2), 2.00 (2H, apparent q, J = 7.3 Hz, H_5), 1.61–1.54 (2H, m, H_3), 1.45–1.28 (4H, m, H_1, H_4 and H_8), 0.67–0.61 (2H, m, H_9 and H_{10}), 0.31–0.29 (2H, m, H_9 and H_{10}) ppm.

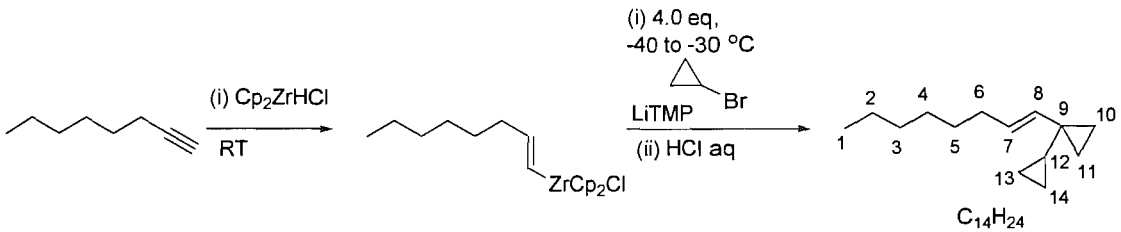
^{13}C NMR (100 MHz, $CDCl_3$): δ 134.30 (CH, C_7), 127.85 (CH, C_6), 63.04 (CH_2, C_2), 32.39 (CH_2, C_3 or C_5), 32.30 (CH_2, C_3 or C_5), 25.91 (CH_2, C_4), 13.59 (CH, C_8), 6.48 ($2CH_2$, C_9 and C_{10}) ppm.

IR (film): 3515–3110 broad (m), 3077 (w), 3001 (m), 2925 (s), 2855 (m), 1454 (m), 1259 (m), 1042 (s), 1015 (s), 958 (s), 808 (s) cm^{-1}.

GCMS (EI)$^+$ *m/z* (%): 140 ($(M+H)^+$, 8), 122 ($(M-H_2O)^+$, 10), 111 ($(M-C_2H_5)^+$, 36), 93 (64), 79 (100).

HRMS $(EI)^+$ for $C_9H_{16}O$ $(M)^+$ calculated 140.1201, found 140.1202.

5.3.10 Preparation of ((*E*)-1-oct-1-enyl)-bicyclopropyl 602



A solution of 1-octyne (0.121 g, 0.95 eq, 1.10 mmol) in THF (1 mL) was added to a suspension of zirconocene hydrogen chloride (0.298 g, 1.00 eq, 1.16 mmol) in THF (5 mL) at room temperature and stirred for 30 minutes. The reaction mixture was cooled to –40 °C before the addition of cyclopropyl bromide (0.37 mL, 4.00 eq, 4.26 mmol) and followed by the addition of LiTMP (4.20 mL, 4.00 eq, 4.26 mmol) dropwise over 35 minutes. It was warmed to –30 °C over 45 minutes, quenched with HCl (5 mL, 2M aqueous solution) and stirred for a further 1 hour. The products were extracted into diethyl ether (3 x 50 mL), the combined organic phases washed with water (50 mL)

and brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified using flash silica column chromatography (hexane) to yield the title compound, a clear coulourless oil (88 mg, 46 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.59 (1H, dt, J = 15.6, 6.8 Hz, H_7), 5.20 (1H, d, J = 15.6 Hz, H_8), 2.01 (2H, q+fs, J = 6.8 Hz, H_6), 1.40–1.22 (8H, m, H_{2-5}), 1.12 (1H, m, H_{12}), 0.89 (3H, t, J = 6.5 Hz, H_1), 0.42–0.34 (6H, m, H_{10}, H_{11}, $1H_{13}$ and $1H_{14}$), 0.00 (2H, apparent q, J = 5.1 Hz, H_{13}, H_{14}) ppm.

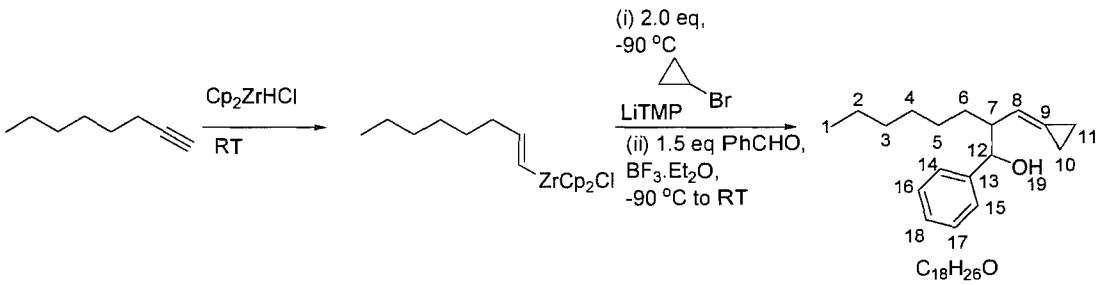
^{13}C NMR (100 MHz, $CDCl_3$): δ 136.84 (CH, C_8), 127.23 (CH, C_7), 32.79 (CH_2, C_6), 31.91 (CH_2), 29.93 (CH_2), 29.03 (CH_2), 22.79 (CH_2), 22.22 (C, C_9), 14.23 (CH_3, C_1), 14.15 (CH, C_{12}), 11.27 ($2CH_2$, C_{10} and C_{11}), 2.18 ($2CH_2$, C_{13} and C_{14}) ppm.

IR (film): 3077 (w), 3002 (m), 2956 (m), 2923 (s), 2853 (m), 1465 (w), 1016 (w), 962 (m) cm^{-1}.

GCMS (EI)$^+$ *m/z* (%): 193 ($(M+H)^+$, 66), 164 ($(M-C_2H_5)^+$, 6), 151 ($(M-C_3H_7+H)^+$, 10), 107 ($(M-C_6H_{13})^+$, 100), 95 (20).

HRMS $(ES)^+$ for $C_{14}H_{24}$ $(M)^+$ calculated 192.1877, found 192.1878.

5.3.11 Preparation of 2-cyclopropylidenemethyl-1-phenyl-octan-1-ol 604



A solution of 1-octyne (0.115g, 1.05 eq, 1.04 mmol) in THF (1 mL) was added to a suspension of zirconocene hydrogen chloride (0.257 g, 1.00 eq, 0.99 mmol) in THF (5 mL) at room temperature and stirred for 40 minutes. The reaction mixture was cooled to –90 °C before the addition of cyclopropyl bromide (0.15 mL, 2.50 eq, 1.98 mmol) and followed by the addition of LiTMP (2 mL, 2.00 eq, 1.98 mmol) dropwise over 20

minutes. After stirring for 10 minutes, benzaldehyde (0.15 mL, 1.50 eq, 1.49 mmol) and boron trifluoride-diethyl-etherate (0.19 mL, 1.50 eq, 1.49 mmol) were added to the mixture. The reaction mixture was warmed to room temperature over 8 hours, stirred at room temperature for a further 14 hours, quenched with sat. $NaHCO_3$ aqueous solution (5 mL) and MeOH (5 mL) then stirred for a further 6 hours. The products were extracted into ether (3 x 50 mL), the combined organic phases washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified using flash silica column chromatography (hexane/diethyl ether 4:1 - co-eluting benzaldehyde was removed under reduced pressure) to yield the title compound, a clear coulourless oil (47 mg, 18%). ((*E*)-Oct-1-enyl)-cyclopropane was recovered also recovered (44 mg, 0.29 mmol, 29%)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.24 (5H, m, H_{14-18}), 5.63 (1H, d, J = 9.0 Hz, H_8), 4.48 (1H, d, J = 7.5 Hz, H_{12}), 2.52 (1H, m, H_7), 2.11 (1H, s, H_{19}), 1.35–1.10 (10H, m, H_{2-6}), 1.05–0.92 (4H, m, H_{10} and H_{11}), 0.82 (3H, t, J = 7.0 Hz, H_1) ppm.

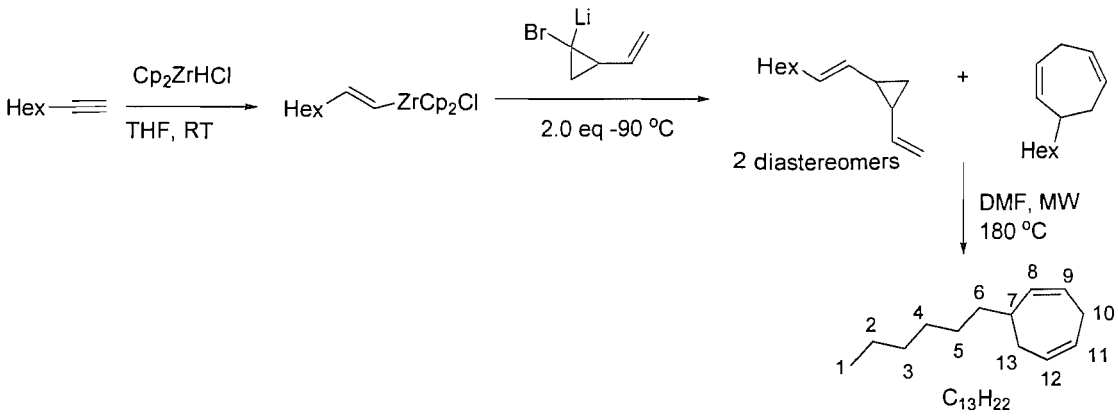
^{13}C NMR (100 MHz, $CDCl_3$): δ 143.16 (C, C_{13}), 128.26 (2CH, C_{16} and C_{17}), 127.56 (CH, C_{18}), 127.09 (2CH, C_{14} and C_{15}), 126.19 (C, C_9), 118.83 (CH, C_8), 77.62 (CH, C_{12}), 51.00 (CH, C_7), 31.91 (CH_2), 31.29 (CH_2), 29.32 (CH_2), 27.45 (CH_2), 22.72 (CH_2), 14.19 (CH_3, C_1), 2.91 (CH_2, C_{10} or C_{11}), 2.59 (CH_2, C_{10} or C_{11}) ppm.

IR (film): 3600–3190 broad (m), 3020 (w), 2953 (m), 2922 (s), 2853 (s), 1452 (m), 1377 (m), 1300 (w), 1260 (w), 1192 (w), 1024 (s), 966 (w), 935 (w), 909 (s) cm^{-1}.

GCMS (EI)$^+$ *m/z* (%): 258 ($(M)^+$, 4), 240 ($(M-H_2O)^+$, 28), 155 (70), 107 ($(C_6H_5CHOH)^+$, 100), 77 ($(C_6H_5)^+$, 83).

HRMS $(ES)^+$ for $C_{18}H_{26}O$ $(M)^+$ calculated 258.1984, found 258.1984.

5.3.12 Preparation of (1*Z*,4*Z*)-6-hexylcyclohepta-1,4-diene 617



A solution of 1-octyne (0.113 g, 1.00 eq, 1.02 mmol) in THF (1 mL) was added to a suspension of zirconocene hydrogen chloride (0.264 g, 1.00 eq, 1.02 mmol) in THF (4 mL) at room temperature. This was stirred for 1 hour before use.

A solution of 1,1-dibromo-2-vinylcyclopropane (0.300g, 1.30 eq, 1.33 mmol) in THF (5 mL) was cooled to –90 °C before the dropwise addition of *n*-BuLi (0.53 mL, 1.3 eq, 1.33 mmol) (2.5 M in hexanes) over 20 minutes. This was stirred for 15 minutes before the addition of the organochlorozirconocene complex (≈5 mL, 1.00 eq, 1.02 mmol) though an interconnected flask at the same temperature. It was stirred for 20 minutes, quenched with MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (5 mL) then stirred for 5 hours at room temperature. The products were extracted into diethyl ether (3 x 30 mL), the combined organic phases washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified using flash silica column chromatography (hexane) to yield a mixture of 2 diastereomers of the divinyl cyclopropane as well as some of the cycloheptadiene, as a clear colourless oil (32 mg, 19%). A sample of the inseparable mixture (20 mg, 1.00 eq, 0.11 mmol) was dissolved in DMF (2 mL) and heated in the microwave at 180 °C for 100 minutes in order to achieve complete cyclisation. The reaction mixture was poured onto water (10 mL) and extracted with pentane (10 x 10 mL), the combined organic phases were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was filtered using a silica plug (pentane), and resulted in the isolation of the title compound as a clear colourless oil (8 mg, this step 39% yield, overall 4%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.72 (1H, m, H_{12}), 5.66–5.78 (3H, m, H_8, H_9 and H_{11}), 2.96 (1H, d+fs, J = 19.6 Hz, H_{10}), 2.71 (1H, dt, J= 19.6, 5.4 Hz, H_{10}), 2.45 (1H, m,

H_7), 2.22 (1H, ddt, J = 15.5, 6.2, 3.1 Hz, H_{13}), 2.11 (1H, m, H_{13}), 1.41–1.22 (10H, m, H_{2-6}), 0.90 (3H, t, J = 6.8 Hz, H_1) ppm.

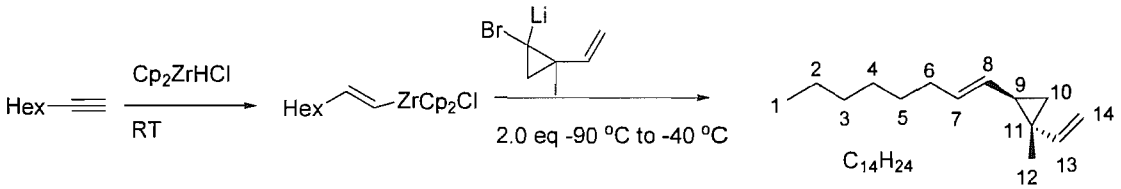
^{13}C NMR (100 MHz, $CDCl_3$): δ 137.03 (CH, C_8, C_9 or C_{11}), 130.08 (CH, C_8, C_9 or C_{11}), 128.30 (CH, C_{12}), 127.39 (CH, C_8, C_9 or C_{11}), 37.40 (CH, C_7), 36.51 (CH_2), 33.05 (CH_2, C_{13}), 32.03 (CH_2), 29.64 (CH_2), 28.53 (CH_2, C_{10}), 27.33 (CH_2), 22.81 (CH_2), 14.24 (CH_3, C_1) ppm.

IR (film): 3013 (w), 2956 (m), 2923 (s), 2854 (s), 2360 (s), 1466 (w), 683 (w), 642 (w) cm^{-1}.

GCMS (EI) *m/z* (%): 178 ($(M)^+$, 21), 163 ($(M\text{-}CH_3)^+$, 1), 121 ($(M\text{-}C_4H_9)^+$, 14), 107 ($(M\text{-}C_5H_{11})^+$, 26), 79 (100).

HRMS (EI) for $C_{13}H_{22}$ $(M)^+$ calculated 178.1722, found 178.1725.

5.3.13 Preparation of (1*R*,2*R*)-1-methyl-2-((E)-oct-1-enyl)-1-vinylcyclopropane 618



A solution of 1-octyne (0.224 g, 1.05 eq, 2.03 mmol) in THF (4 mL) was added to a suspension of zirconocene hydrogen chloride (0.501 g, 1.00 eq, 1.94 mmol) in THF (4 mL) at room temperature. This was stirred for 45 minutes before use.
A solution of 1,1-dibromo-2-methyl-2-vinylcyclopropane (1.103 g, 2.50 eq, 4.84 mmol) in THF (2 mL) was cooled to –90 °C before the dropwise addition of *n*-BuLi (2.5 M in hexanes) (1.94 mL, 2.50 eq, 4.84 mmol) over 20 minutes. This was stirred for 10 minutes before the dropwise addition of the organochlorozirconocene complex (≈8 mL, 1.00 eq, 0.94 mmol) over 40 minutes. The reaction was warmed to –40 °C over 6 hours, quenched with MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (5 mL) then stirred for a further 16 hours. The products were extracted into diethyl ether (3 x 30 mL), the combined organic phases washed with water (50 mL) and brine (50

mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified using flash silica column chromatography (pentane) to yield the title compound, a clear colourless oil (213 mg, 57%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.54 (1H, dt, J = 15.1, 6.9 Hz, H_7), 5.45 (1H, dd, J = 17.3, 10.5 Hz, H_{13}), 5.24 (1H, ddd, J = 15.1, 7.8, 1.1 Hz, H_8), 4.93 (1H, dd, J = 17.3, 1.3 Hz, H_{14} *trans*), 4.87 (1H, dd, J = 10.5, 1.3 Hz, H_{14} *cis*), 2.02 (2H, apparent q, J = 6.9 Hz, H_6), 1.47 (1H, apparent q, J = 7.6 Hz, H_9), 1.40–1.19 (8H, m, H_{2-5}), 1.14 (3H, s, H_{12}), 0.95 (1H, dd, J = 8.7, 4.7 Hz, H_{10}), 0.89 (3H, t, J = 6.8 Hz, H_1), 0.63 (1H, dd, J = 6.0, 4.7 Hz, H_{10}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.92 (CH, C_{13}), 132.10 (CH, C_7), 128.37 (CH, C_8), 109.34 (CH_2, C_{14}), 32.89 (CH_2, C_6), 31.90 (CH_2, C_3 or C_4 or C_5), 29.79 (CH_2, C_3 or C_4 or C_5), 28.99 (CH_2, C_3, C_4 or C_5), 28.92 (CH, C_9), 24.50 (C, C_{11}), 22.80 (CH_2, C_2), 21.47 (CH_2, C_{10}), 16.11 (CH_3, C_{12}), 14.24 (CH_3, C_1) ppm.

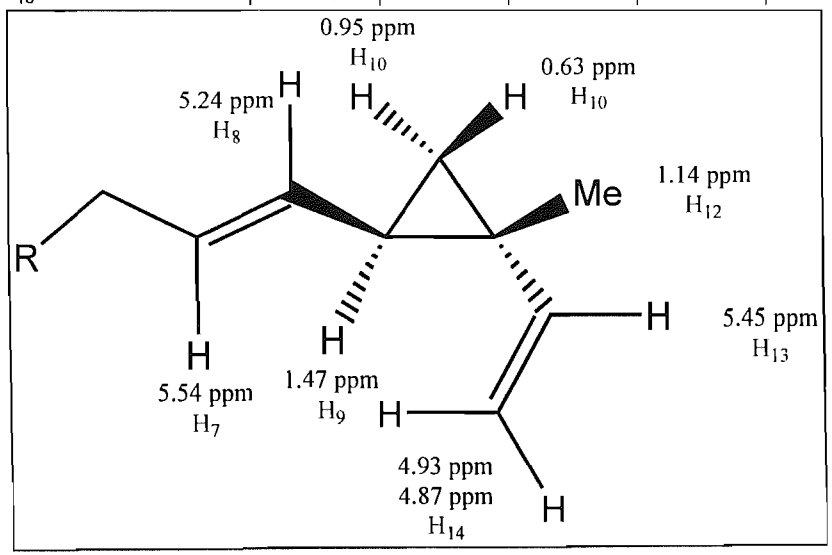
IR (film): 3064 (w), 2954 (m), 2922 (s), 2853 (m), 1633 (m), 1454 (m), 1377 (w), 1259 (s), 1089 (m), 1016 (s), 959 (s), 890 (s), 801 (s), 723 (w), 677 (w) cm^{-1}.

GCMS (EI)$^+$ *m/z* (%): 192 ($(M)^+$, 72), 177 ($(M\text{-}CH_3)^+$, 10), 163 ($(M\text{-}C_2H_5)^+$, 18), 149 ($(M\text{-}C_3H_7)^+$, 45), 107 (100).

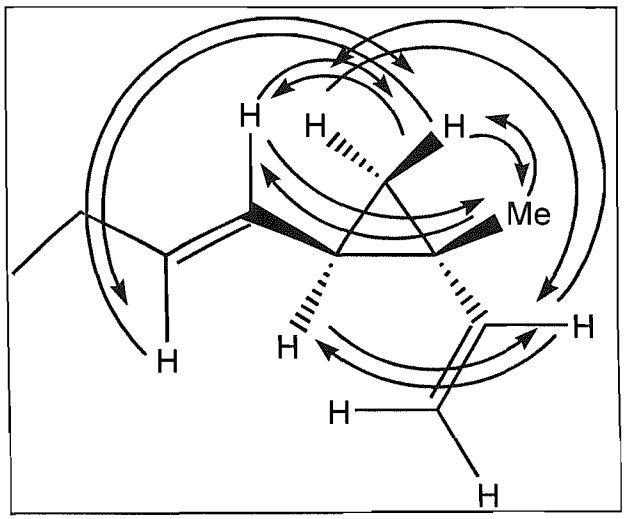
HRMS $(EI)^+$ for $C_{14}H_{24}$ $(M)^+$ calculated 192.1878, found 192.1876.

For NOE experiments used to assign the stereochemistry – see next page.

Proton		H_7	H_{13}	H_8	H_{14} *trans*	H_{14} *cis*	H_6	H_9	H_{12}	H_{10}	H_{10}
	ppm	5.54	5.45	5.24	4.93	4.87	2.02	1.47	1.14	0.95	0.63
H_7	5.54			-4.671			0.665	1.005			0.377
H_{13}	5.45							1.376	0.3	0.49	
H_8	5.24						1.04	0.62	1.23	0.43	0.75
H_{14} *trans*	4.93								0.88		
H_{14} *cis*	4.87										
H_6	2.02										
H_9	1.47	1.205	1.205	0.24	0.065	0.065					
H_{12}	1.14		0.064	0.318	0.398						0.228
H_{10}	0.95		0.4	0.04	0.11						2.85
H_{10}	0.63		0.61	0.6				1.18	0.66		

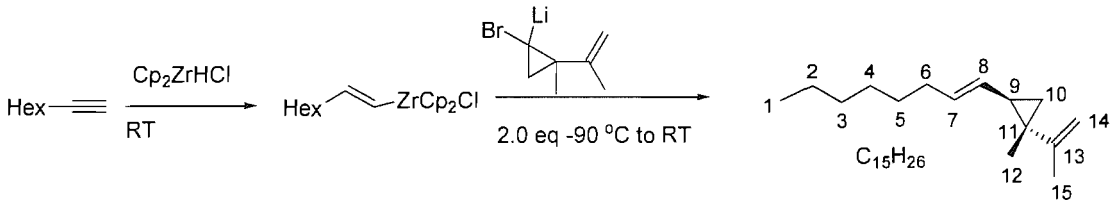


Map of relevant protons



Significant NOE interactions

5.3.14 Preparation of (1*S*,2*R*)-1-methyl-2-((*E*)-oct-1-enyl)-1-(prop-1-en-2-yl)cyclopropane 619



A solution of 1-octyne (0.113 g, 1.05 eq, 1.03 mmol) in THF (1 mL) was added to a suspension of zirconocene hydrogen chloride (0.254 g, 1.00 eq, 0.98 mmol) in THF (4 mL) at room temperature. This was stirred for 1 hour before use.

A solution of 1,1-dibromo-2-methyl-2-(prop-1-en-2-yl)cyclopropane (0.482 g, 2.00 eq, 1.96 mmol) in THF (2 mL) was cooled to –90 °C before the dropwise addition of *n*-BuLi (2.5 M in hexanes) (0.78 mL, 2.00 eq, 1.96 mmol) over 20 minutes. This was stirred for 15 minutes before the dropwise addition of the organochlorozirconocene complex (≈5 mL, 1.00 eq, 0.98 mmol) over 30 minutes. The reaction was warmed to room temperature over 5.5 hours, quenched with MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (5 mL) then stirred for a further 16 hours. The product was extracted into diethyl ether (3 x 30 mL), the combined organic phases washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified using flash silica column chromatography (pentane) to yield the title compound, a clear colourless oil (0.132 g, 65%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.54 (1H, dt, J = 15.0, 6.8 Hz, H_7), 5.27 (1H, dd, J = 15.0, 7.8 Hz, H_8), 4.73 (1H, broad s, H_{14}), 4.71 (1H, broad s, H_{14}), 2.03 (2H, apparent q, J = 6.8 Hz, H_6), 1.17 (3H, s, H_{15}), 1.49 (1H, apparent q, J = 7.6 Hz, H_9), 1.41–1.22 (8H, m, H_{2-5}), 1.15 (3H, s, H_{12}), 1.06 (1H, dd, J = 8.7, 4.6 Hz, H_{10}), 0.90 (3H, t, J = 6.5 Hz, H_1), 0.46 (1H, apparent t, J = 5.3 Hz, H_{10}) ppm.

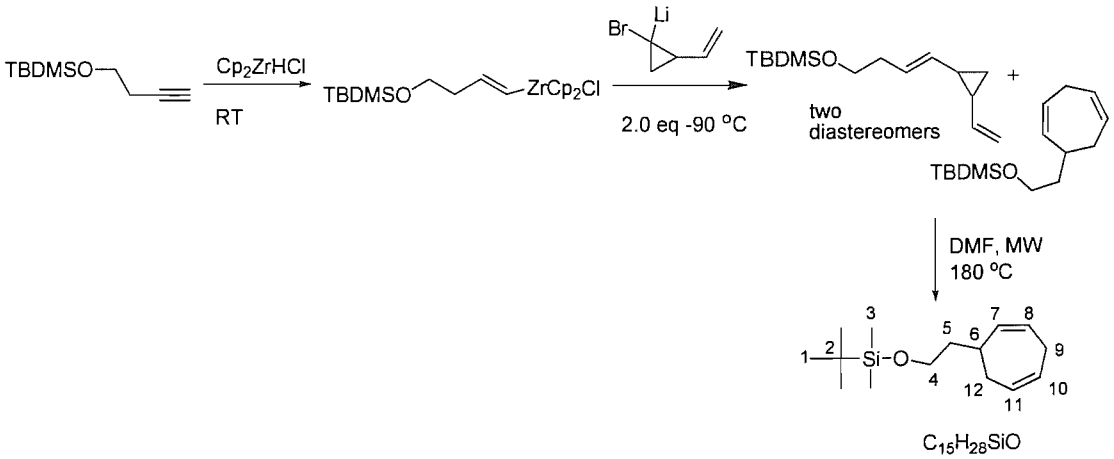
^{13}C NMR (100 MHz, $CDCl_3$): δ 150.43 (C, C_{13}), 131.77 (CH, C_7), 129.19 (CH, C_8), 108.92 (CH_2, C_{14}), 32.89 (CH_2, C_6), 31.91 (CH_2, C_3, C_4 or C_5), 29.83 (CH_2, C_3, C_4 or C_5), 29.01 (CH_2, C_3, C_4 or C_5), 27.78 (C, C_{11}), 26.96 (CH, C_9), 22.81 (CH_2, C_2), 20.23 (CH_3, C_{15}), 19.89 (CH_2, C_{10}), 18.63 (CH_3, C_{12}), 14.24 (CH_3, C_1) ppm.

IR (film): 3074 (w), 2954 (m), 2921 (s), 2852 (m), 1643 (w), 1452 (m), 1377 (w), 1176 (w), 860 (s), 890 (s), 875 (m), 723 (w) cm^{-1}.

GCMS (EI) *m/z* (%): 206 ($(M)^+$, 12), 191 ($(M\text{-}CH_3)^+$, 4), 135 ($(M\text{-}C_5H_{11})^+$, 8), 121 ($(M\text{-}C_6H_{13})^+$, 46).

HRMS (EI) for $C_{15}H_{26}$ $(M)^+$ calculated 206.20345, found 206.20314.

5.3.15 Preparation of (2-((2*Z*,5*Z*)-cyclohepta-2,5-dienyl)ethoxy)(tert-butyl)dimethylsilane 622



A solution of *tert*-butyl(but-3-ynyloxy)dimethylsilane (0.180 g, 1.00 eq, 0.98 mmol) in THF (1 mL) was added to a suspension of zirconocene hydrogen chloride (0.253 g, 1.00 eq, 0.98 mmol) in THF (4 mL) at room temperature. This was stirred for 1 hour before use.

A solution of 1,1-dibromo-2-vinylcyclopropane (0.288g, 1.30 eq, 1.27 mmol) in THF (5 mL) was cooled to –95 °C before the dropwise addition of *n*-BuLi (0.51 mL, 1.30 eq, 1.27 mmol) (2.5 M in hexanes) over 10 minutes. This was stirred for 15 minutes before the addition of the organochlorozirconocene complex (≈5 mL, 1.00 eq, 0.98 mmol) through an interconnected flask at the same temperature. The reaction was stirred for 20 min at –90 °C, quenched with MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (5 mL) then stirred for 20 hours. The products were extracted into diethyl ether (3 x 30 mL), the combined organic phases washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified using flash silica column chromatography (hexane) to yield a mixture of 2

diastereomers of the divinyl cyclopropane as well as some of the cycloheptadiene, as a clear colourless oil (96 mg, 38%). A sample of the inseparable mixture (70 mg, 1.00 eq, 0.28 mmol) was dissolved in DMF (2 mL) and heated in the microwave at 180 °C for 100 minutes in order to achieve complete cyclisation. The reaction mixture was poured onto water (10 mL) and extracted with pentane (10 x 10 mL), the combined organic phases were washed with water (20 mL) and brine (20 mL), before being dried over $MgSO_4$ and concentrated *in vacuo*. This resulted in the isolation of the title compound, a clear colourless oil (12 mg, this step 18% yield, overall 7%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.75–5.59 (4H, m, H_7, H_8, H_{10} and H_{11}), 3.67 (2H, td, J = 6.7, 1.2 Hz, H_4), 2.95 (1H, d, J = 19.2 Hz, H_9 or H_{12}), 2.70 (1H, m, J = 19.2 Hz, H_9 or H_{12}), 2.65 (1H, m, H_6), 2.24 (1H, m, H_9 or H_{12}), 2.15 (1H, m, H_9 or H_{12}), 1.70–1.54 (2H, m, H_5), 0.90 (9H, s, H_1), 0.06 (6H, s, H_3) ppm.

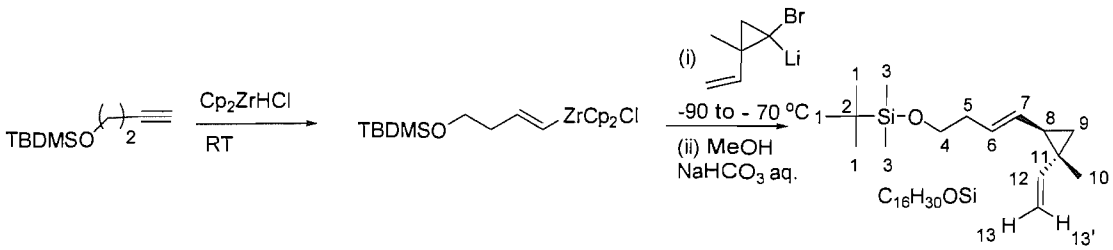
^{13}C NMR (75 MHz, $CDCl_3$): δ 136.41 (CH, C_7, C_8, C_{10} or C_{11}), 129.86 (CH, C_7, C_8, C_{10} or C_{11}), 128.39 (CH, C_7, C_8, C_{10} or C_{11}), 127.76 (CH, C_7, C_8, C_{10} or C_{11}), 61.37 (CH_2, C_4), 39.24 (CH_2, C_5), 34.02 (CH, C_6), 32.96 (CH_2, C_{12}), 28.55 (CH_2, C_9), 26.12 (CH_3, C_1), 18.50 (C, C_2), -5.14 (CH_3, C_3) ppm.

IR (film): 3014 (s), 2954 (m), 2928 (m), 2856 (m), 1650 (w), 1471 (m), 1388 (w), 1361 (w), 1255 (s), 1096 (s), 1006 (m), 939 (w), 833 (s), 807 (s), 773 (s), 679 (w), 690 (m) cm^{-1}.

GCMS (CI) *m/z* (%): 253 ($(M+H)^+$, 4), 195 ($(M-C(CH_3)_3)^+$, 78), 119 (54), 91 (100), 75 (68).

HRMS (EI) for $C_{11}H_{19}OSi$ $(M-C(CH_3)_3)^+$ calculated 195.1205, found 195.1207.

5.3.16 Preparation of ((*E*)-4-((1*R*,2*R*)-2-methyl-2-vinylcyclopropyl)but-3-enyloxy)(tert-butyl)dimethylsilane 623



A solution of *tert*-butyl(but-3-ynyloxy)dimethylsilane (0.185 g, 1.05 eq, 1.01 mmol) in THF (1 mL) was added to a suspension of zirconocene hydrogen chloride (0.248 g, 1.00 eq, 0.96 mmol) in THF (4 mL) at room temperature. This was stirred for 40 minutes before it was added to the carbenoid.

A solution of 1,1-dibromo-2-methyl-2-vinylcyclopropane (0.547 g, 2.50 eq, 2.4 mmol) in THF (2 mL) was cooled to –95 °C before the dropwise addition of *n*-BuLi (0.96 mL, 2.98 eq, 2.5 mmol) (2.5 M in hexanes) over 15 minutes. This was stirred for 10 minutes before the dropwise addition of the organochlorozirconocene complex (≈5 mL, 1.0 eq, 0.96 mmol) over 40 minutes. The reaction was stirred at –70 °C for 4.5 hours, quenched with MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (5 mL) then stirred for 16 hours at room temperature. The products were extracted into diethyl ether (3 x 30 mL), the combined organic phases washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified using flash silica column chromatography (hexane/diethyl ether 99:1) to yield the title compound, with two minor components - total 10%, believed to be minor isomers, a yellow oil (0.139 g, 52%).

^{1}H NMR (400 MHz, $CDCl_3$): **major** δ 5.53 (1H, dt, J = 15.2, 6.9 Hz, H_6), 5.44 (1H, dd, J = 17.3, 10.5 Hz, H_{12}), 5.31 (1H, ddt, J = 15.2, 8.0, 1.1 Hz, H_7), 4.93 (1H, dd, J = 17.3, 1.1 Hz, $H_{13'}$), 4.89 (1H, dd, J = 10.5, 1.1 Hz, H_{13}), 3.63 (2H, t, J = 6.9 Hz, H_4), 2.25 (2H, apparent qd, J = 6.9, 1.1 Hz, H_5), 1.48 (1H, apparent td, J = 8.3, 6.0 Hz, H_8), 1.15 (3H, s, H_{11}), 0.95 (1H, dd, J = 8.5, 4.6 Hz, H_9), 0.90 (9H, s, H_1), 0.64 (1H, dd, J = 6.0, 4.6 Hz, H_9), 0.06 (6H, s, H_3); 2 **minor** isomers – incomplete data and partial assignment δ 5.65 (1H, dd, J = 17.7, 10.2 Hz, H_6), 5.19 (1H, dd, J = 10.6, 9.1

Hz), 5.04 (1H, dd, J = 6.0, 1.5 Hz), 5.00 (1H, s), 3.65 – 3.62 (?1H, m), 2.37 (1H, m), 1.74 (1H, broad s, H_8), 1.23 (3H, s, H_{10}), 0.08 (6H, s, H_3) ppm.

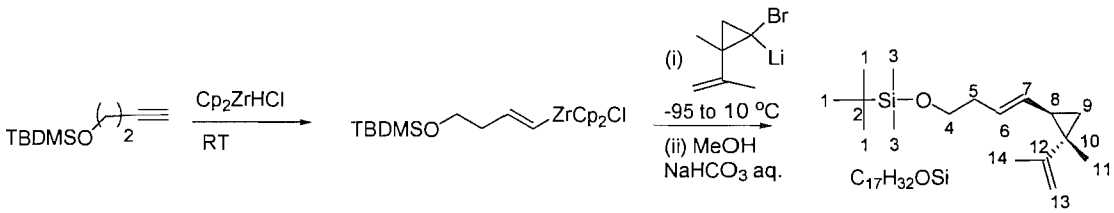
^{13}C NMR (100 MHz, $CDCl_3$): **major** δ 146.75 (CH, C_{12}), 130.68 (CH, C_7), 127.95 (CH, C_6), 109.48 (CH_2, C_{13}), 63.43 (CH_2, C_4), 36.58 (CH_2, C_5), 28.97 (CH, C_8), 26.18 ($3CH_3$, C_1), 24.51 (C, C_{11}), 21.50 (CH_2, C_9), 18.52 (C, C_2), 16.12 (CH_3, C_{10}), -5.08 ($2CH_3$, C_3); 2 **minor** isomers – incomplete data and partial assignments δ 142.26 (CH, C_{12}), 136.08 (CH), 131.12 (CH), 126.51 (CH), 126.38 (CH), 123.62 (CH), 112.36 (CH_2, C_{13}), 63.10 (CH_2, C_4), 61.33 (CH_2, C_4), 39.15 (CH_2), 33.93 (CH), 33.21 (CH_2), 32.05 (CH_2), 23.23 (CH_2), 22.70 (CH), 1.18 (CH_3) ppm.

IR (film): 2953 (s), 2928 (s), 2856 (s), 1741 (m), 1634 (m), 1257 (s), 1096 (s), 1017 (m), 843 (s), 807 (m), 775 (m) cm^{-1}.

GCMS (CI) *m/z* (%): 267 ($(M+H)^+$, 32), 209 ($(M-C_4H_9)^+$, 14), 135 ($(M-C_6H_{15}SiO)^+$, 100), 105 (12), 91 (16).

HRMS (EI) for $C_{16}H_{30}OSi$ $(M)^+$ calculated 266.2066, found 266.2075.

5.3.17 Preparation of ((E)-4-((1R,2S)-2-methyl-2-(prop-1-en-2-yl)cyclopropyl)but-3-enyloxy)(tert-butyl)dimethylsilane 624



A solution of *tert*-butyl(but-3-ynyloxy)dimethylsilane (0.162 g, 1.00 eq, 0.88 mmol) in THF (1 mL) was added to a suspension of zirconocene hydrogen chloride (0.258 g, 1.14 eq, 1.00 mmol) in THF (4 mL) at room temperature. This was stirred for 40 minutes before use.

A solution of 1,1-dibromo-2-methyl-2-(prop-1-en-2-yl)cyclopropane (0.492 g, 2.27 eq, 2.00 mmol) in THF (2 mL) was cooled to –95 °C before the dropwise addition of *n*-BuLi (0.80 mL, 2.27 eq, 2.0 mmol) (2.5 M in hexanes) over 20 minutes. This was

stirred for 15 minutes before the dropwise addition of the organochlorozirconocene complex (≈ 5 mL, 1.0 eq, 0.84 mmol) over 50 minutes. The reaction was warmed to 10 °C over 3 hours, quenched with MeOH (5 mL) and sat. $NaHCO_3$ solution (5 mL) then stirred vigorously for 12 hours at room temperature. The products were extracted into diethyl ether (3 x 30 mL), the combined organic phases washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified using flash silica column chromatography (hexane/diethyl ether 99.8:0.2 to 99.4:0.6) to yield the title compound, a clear colourless oil (122 mg, 50%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.52 (1H, dt, J = 15.3, 6.8 Hz, H_6), 5.33 (1H, ddt, J = 15.3, 8.0, 1.3 Hz, H_7), 4.72 (1H, s+fs, H_{13}), 4.70 (1H, s+fs, H_{13}), 3.63 (2H, t, J = 6.8 Hz, H_4), 2.26 (2H, qd, J = 6.8, 1.3 Hz, H_5), 1.70 (3H, s+fs, H_{14}), 1.48 (1H, m, H_8), 1.17 (3H, s, H_{11}), 1.08 (1H, dd, J = 8.8, 4.6 Hz, H_9), 0.90 (9H, s, H_1), 0.46 (1H, dd, J = 5.8, 4.6 Hz, H_9), 0.06 (6H, s, H_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.33 (C, C_{12}), 131.54 (CH, C_6), 127.64 (CH, C_7), 109.03 (CH_2, C_{13}), 63.50 (CH_2, C_4), 36.59 (CH_2, C_5), 27.91 (C, C_{10}), 27.07 (CH, C_8), 26.11 ($3CH_3$, C_1), 20.25 (CH_3, C_{14}), 19.98 (CH_2, C_9), 18.67 (CH_3, C_{11}), 18.52 (C, C_2), -5.07 ($2CH_3$, C_3) ppm.

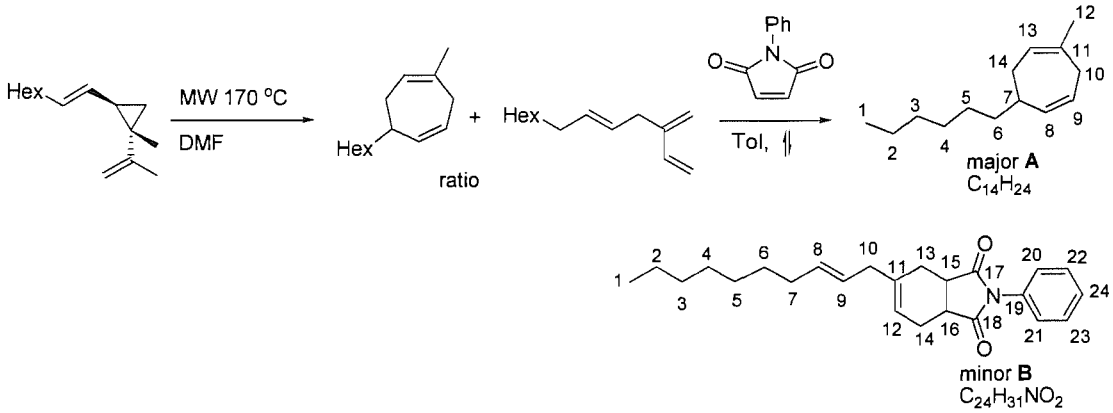
IR (film): 2952 (m), 2927 (m), 2892 (m), 2855 (m), 1643 (w), 1461 (w), 1379 (w), 1252 (m), 1092 (s), 961 (w), 936 (w), 891 (w), 831 (s), 771 (s), 661 (w) cm^{-1}.

GCMS (CI) *m/z* (%): 281 ($(M+H)^+$, 12), 223 ($(M-C(CH_3)_3)^+$, 10), 149 ($(M-C_6H_{15}SiO)^+$, 100), 91 (12), 74 (14).

MS (ES)$^+$ *m/z:* 303 ($(M+Na)^+$, 100%).

HRMS (ES)$^+$ for $C_{17}H_{32}OSi$ $(M+Na)^+$ calculated 303.2115, found 303.2118.

5.3.18 Preparation of 6-hexyl-2-methyl-cyclohepta-1,4-diene 625 and 5-((*E*)-dec-2-enyl)-2-phenyl-3a,4,7,7a-tetrahydro-isoindole-1,3-dione 628



A solution of (1*R*,2*R*)-1-methyl-2-((*E*)-oct-1-enyl)-1-vinylcyclopropane (90 mg, 1.00 eq, 0.47 mmol) in DMF (2 mL) was heated in the microwave for 1 hour at 170 °C. The reaction mixture was poured into water (10 mL) and extracted with hexane (10x20 mL), the combined organic phases were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The products were isolated as an 88:12 mixture of diene (1*Z*,4*Z*)-6-heptyl-2-methylcyclohepta-1,4-diene and triene (E)-3-methylenetrideca-1,5-diene (89 mg, 98%). The diene and triene mixture (60 mg, 1.00 eq, 0.29 mmol) and *N*-phenyl maleimide (10 mg, 0.12 eq, 0.05 mmol) in toluene (2 mL) were heated at 115 °C for 4 hours. The solvent was removed *in vacuo* and the products separated *via* column chromatography (hexane to hexane/ethyl acetate 3:1). The dione was purified further *via* radial chromatography to remove *N*-phenyl maleimide (hexane/diethyl ether 4:1). Two products were isolated: (1*Z*,4*Z*)-6-heptyl-2-methylcyclohepta-1,4-diene (clear colourless oil) (47 mg, 52%) and 5-((*E*)-dec-2-enyl)-3a,4,7,7a-tetrahydro-2-phenyl-2H-isoindole-1,3-dione (clear yellow oil) (11 mg, 6%).

Major **A**

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.62–5.55 (2H, m, H_8 and H_9), 5.50 (1H, t, J = 5.3 Hz, H_{13}), 2.83 (1H, d+fs, J = 17.4 Hz, H_{10}), 2.70 (1H, d+fs , J = 17.4 Hz, H_{10}), 2.30 (1H, m, H_7), 2.20–2.14 (2H, m, H_{14}), 1.72 (3H, s, H_{12}), 1.38–1.23 (10H, m, $H_{2\text{-}6}$), 0.89 (3H, t, J = 6.6 Hz, H_1) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.42 (C, C_{11}), 136.65 (CH, C_8), 126.06 (CH, C_9), 123.85 (CH, C_{13}), 37.33 (CH, C_7), 36.47 (CH_2, C_6), 33.25 (CH_2, C_{10}), 32.21 (CH_2), 32.04 (CH_2), 29.66 (CH_2), 27.27 (CH_2), 26.18 (CH_3, C_{12}), 22.81 (CH_2, C_2), 14.24 (CH_3, C_1) ppm.

IR (film): 3004 (w), 2954 (m), 2920 (s), 2851 (m), 1450 (m), 1376 (w), 1259 (w), 1090 (w), 1023 (w), 894 (w), 804 (w), 722 (w), 690 (w), 664 (w) cm^{-1}.

GCMS (CI) *m/z* (%): 193 ($(M+H)^+$, 100), 177 ($(M-CH_3)^+$, 2), 149 ($(M-C_3H_7)^+$, 4), 121 ($(M-C_5H_{11})^+$, 10), 107 ($(M-C_6H_{13})^+$, 32).

HRMS (EI) for $C_{14}H_{24}$ $(M)^+$ calculated 192.1878, found 192.1874.

Minor **B**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (2H, t, average J = 7.8 Hz, H_{22} and H_{23}), 7.41 (1H, d, J = 7.3 Hz, H_{24}), 7.22 (2H, d, J = 8.0 Hz, H_{20} and H_{21}), 5.65 (1H, m, H_{12}), 5.49 (1H, dt+fs, J = 18.1, 7.2 Hz, H_9), 5.30 (1H, dt+fs, J = 18.1, 7.3 Hz, H_8), 3.30–3.20 (2H, m, H_{15} and H_{16}), 2.79 (2H, d, J = 7.2 Hz, H_{10}), 2.70 (1H, ddd, J = 15.3, 6.8, 2.3 Hz, H_{14}), 2.62 (1H, dd, J = 15.3, 2.4 Hz, H_{13}), 2.34–2.26 (2H, m, H_{13} and H_{14}), 2.01 (2H, apparent q, J = 6.8 Hz, H_7), 1.40–1.19 (10H, m, H_{2-6}), 0.88 (3H, t, J = 6.9 Hz, H_1) ppm.

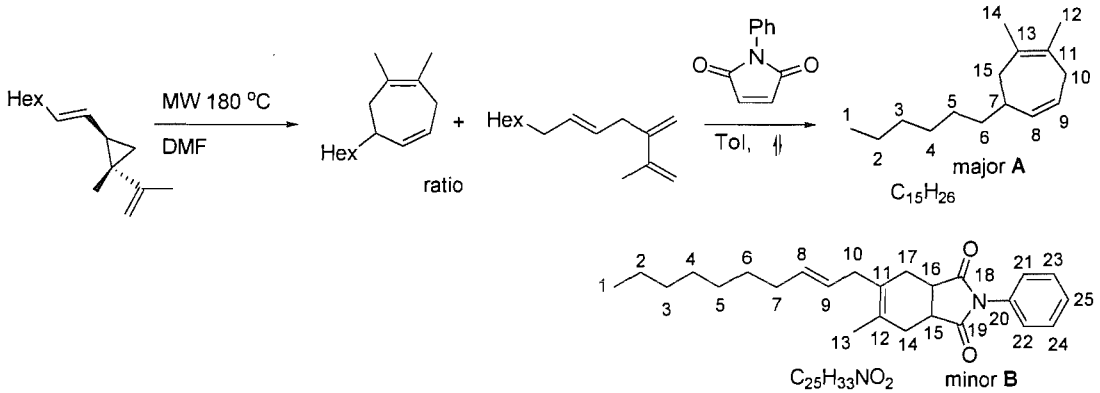
^{13}C NMR (100 MHz, $CDCl_3$): δ 179.44 (C, C_{17} or C_{18}), 179.17 (C, C_{17} or C_{18}), 139.54 (C, C_{11}), 132.44 (CH, C_9), 132.29 (C, C_{19}), 129.22 (2CH, C_{22} and C_{23}), 128.66 (CH, C_{24}), 126.56 (2CH, C_{20} and C_{21}), 125.38 (CH, C_8), 120.29 (CH, C_{12}), 39.97 (CH, C_{15} or C_{16}), 39.66 (CH, C_{15} or C_{16}), 35.12 (CH_2, C_{10}), 31.99 (CH_2), 29.75 (CH_2), 29.42 (CH_2), 29.33 (CH_2), 28.02 (CH_2), 27.32 (CH_2), 24.63 (CH_2), 22.79 (CH_2), 14.25 (CH_3, C_1) ppm.

IR (film): 2951 (w), 2921 (m), 2850 (m), 1705 (s), 1498 (m), 1454 (w), 1376 (s), 1312 (w), 1178 (s), 1156 (m), 765 (w), 726 (w), 690 (m), 618 (w), 583 (m) cm^{-1}.

GCMS (CI) *m/z* (%): 365 ($(M)^+$, 23), 280 ($(M-C_6H_{13})^+$, 10), 267 ($(M-C_6H_{13})^+$, 4), 241 ($(M-C_9H_{17}+H)^+$, 36), 91 ($(C_6H_5N)^+$, 100).

HRMS (**EI**) for $C_{24}H_{31}NO_2$ $(M)^+$ calculated 365.2355, found 365.2359.

5.3.19 Preparation of 6-hexyl-1,2-dimethyl-cyclohepta-1,4-diene 629 and 5-((*E*)-dec-2-enyl)-6-methyl-2-phenyl-3a,4,7,7a-tetrahydro-isoindole-1,3-dione 631



A solution of (1*S*,2*R*)-1-methyl-2-((*E*)-oct-1-enyl)-1-(prop-1-en-2-yl)cyclopropane (78 mg, 1.00 eq, 0.38 mmol) in DMF (2 mL) was heated in the microwave for 1 hour and 20 minutes at 180 °C. The reaction mixture was poured into water (10 mL) before being extracted into hexane (5 x 20 mL), the combined organic phases were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The products were isolated as a 3:1 mixture of diene (1*Z*,4*Z*)-6-hexyl-1,2-dimethylcyclohepta-1,4-diene and triene (*E*)-3-methylenetrideca-1,5-diene (66 mg, 85%). A portion of the mixture (60 mg, 1.0 eq, 0.29 mmol) was dissolved in toluene together with *N*-phenyl maleimide (25.2 mg, 0.50 eq, 0.15 mmol) and heated at 115 °C for 4 hours. The solvent was removed *in vacuo* and the product separated *via* flash colum chromatography (hexane to hexane/diethyl ether 1:1). Two products were isolated: (1*Z*,4*Z*)-6-hexyl-1,2-dimethylcyclohepta-1,4-diene (clear colourless oil) (22 mg, 37% - over 2 steps 31%) and 3a,4,7,7a-tetrahydro-5-methyl-2-phenyl-6-((*E*)-undec-2-enyl)-2H-isoindole-1,3-dione (24 mg, 22% - over 2 steps 19%).

Major **A**

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.61 (1H, dddd, J = 11.4, 6.2, 4.8, 2.3 Hz, H_9), 5.42 (1H, d+fs, J = 11.4 Hz, H_8), 2.88 (1H, d+fs, J = 17.6 Hz, H_{10}), 2.57 (1H, dd, J = 17.6, 6.2 Hz, H_{10}), 2.34 (1H, dd, J = 13.1, 10.0 Hz, H_{15}), 2.18 (1H, m, H_7), 2.11 (1H, dd, J = 13.1, 2.5 Hz, H_{15}), 1.71 (6H, s, H_{12} and H_{14}), 1.38–1.25 (10H, m, H_{2-6}), 0.89 (3H, t, J = 6.8 Hz, H_1) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.46 (CH, C_8), 131.21 (C, C_{11} or C_{13}), 129.54 (C, C_{11} or C_{13}), 126.45 (CH, C_9), 38.59 (CH_2, C_{15}), 36.82 (CH, C_7), 36.69 (CH_2), 34.03 (CH_2, C_{10}), 32.04 (CH_2) 29.71 (CH_2), 27.71 (CH_2), 22.82 (CH_2), 21.17 (CH_3, C_{12} or C_{14}), 20.72 (CH_3, C_{12} or C_{14}), 14.25 (CH_3, C_1) ppm.

IR (film): 2955 (m), 2921 (s), 2853 (m), 1445 (m), 1259 (m), 1093 (s), 1017 (s), 802 (s) cm^{-1}.

GCMS (EI) *m/z* (%): 206 ($(M)^+$, 40), 191 ($(M-CH_3)^+$, 4), 121 ($(M-C_6H_{13})^+$, 76), 107 (100), 93 (83).

HRMS (EI) for $C_{15}H_{26}$ $(M)^+$ calculated 206.2035, found 206.2031.

Minor

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (2H, t, J = 7.7 Hz, H_{23} and H_{24}), 7.38 (1H, t, J = 7.7 Hz, H_{25}), 7.20 (2H, d, J = 7.7 Hz, H_{21} and H_{22}), 5.41 (1H, m, H_8), 5.19 (1H, m, H_9), 3.21–3.20 (2H, m, H_{15} and H_{16}), 2.87 (1H, dd, J = 14.6, 7.3 Hz, H_{10}), 2.79 (1H, dd, J = 14.6, 7.3 Hz, H_{10}), 2.55 (2H, d, J = 13.3 Hz, H_{14} and H_{17}), 2.36–2.25 (2H, m, H_{14} and H_{17}), 2.08 (2H, q, J = 7.0 Hz, H_7), 1.77 (3H, s, H_{13}), 1.40–1.19 (10H, m, H_{2-6}), 0.89 (3H, t, J = 6.8 Hz, H_1) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 179.35 (C, C_{18} or C_{19}), 179.27 (C, C_{18} or C_{19}), 132.30 (C, C_{11} or C_{12} or C_{20}), 131.45 (CH, C_8), 130.30 (C, C_{11} or C_{12} or C_{20}), 129.21 (2CH, C_{23} and C_{24}), 128.62 (CH, C_{25}), 127.88 (C, C_{11} or C_{12} or C_{20}), 126.58 (2CH, C_{21} and C_{22}), 125.92 (CH, C_9), 40.33 (CH, C_{15} or C_{16}), 40.26 (CH, C_{15} or C_{16}), 31.98 (CH_2), 31.09 (CH_2), 31.01 (CH_2), 29.83 (CH_2), 29.45 (CH_2), 29.34 (CH_2), 29.27 (CH_2), 27.47 (CH_2, C_7), 22.79 (CH_2, C_2), 19.37 (CH_3, C_{13}), 14.24 (CH_3, C_1) ppm.

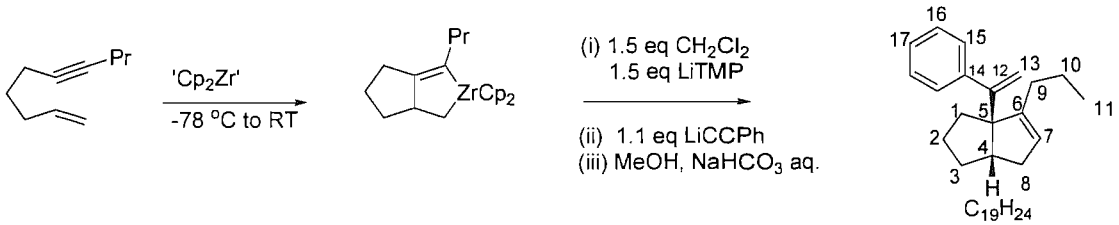
IR (film): 2922 (m), 2851 (m), 2362 (w), 1704 (s), 1498 (m), 1376 (s), 1184 (s), 909 (w), 732 (m), 690 (m) cm^{-1}.

GCMS (EI) *m/z* (%): 379 ($(M)^+$, 50), 267 ($(M- C_8H_{16})^+$, 94), 254 ($(M-C_9H_{17})^+$, 20), 91 ($(C_6H_5N)^+$, 90).

HRMS $(EI)^+$ for $C_{25}H_{33}NO_2$ $(M)^+$ calculated 379.2511, found 379.2507.

5.4 Experimental from Chapter 4

5.4.1 Preparation of 6-phenyl-6a-(1-phenylvinyl)-1,2,3,3a,4,6a-hexahydropentalene 738



A solution of *n*-BuLi (0.80 mL, 2.00 eq, 2.00 mmol)(2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) in THF (5 mL) at –78 °C. This was stirred for 10 minutes before the addition of dec-1-en-6-yne (0.136 g, 1.00 eq, 1.00 mmol) as a solution in THF (1 mL). The cool bath was removed and the reaction mixture was allowed to warm to room temperature over 2 hours.

The reaction mixture was cooled to –78 °C before the addition of dichloromethane (96 μL, 1.50 eq, 1.50 mmol) as a solution in THF (1.5 mL) and subsequently the dropwise addition of LiTMP (1.5 mL, 1.50 eq, 1.50 mmol) over 10 minutes. This was followed by the dropwise addition of lithiated phenyl acetylene (1.5 mL, 1.1 eq, 1.1 mmol) [made with phenyl acetylene (0.12 ml, 1.1 eq, 1.1 mmol), *n*-BuLi (0.44 mL, 1.1 eq, 1.1 mmol) and THF (1 mL), and stirred for 2 hours at 0 °C] over 15 minutes. The reaction mixture changed from orange to red, on addition of carbenoid, then to black on addition of the anion. The reaction was stirred for 20 minutes at –78 °C, quenched with MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (5 mL) and stirred vigorously overnight at room temperature. The product was extracted into diethyl ether (3 x 30 mL), the combined organic phases were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ before the solvent was removed *in vacuo*. The crude product was purified by flash silica column chromatography (petrol) to yield clear colourless oil, the title compound (130 mg, 52%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26–7.18 (5H, m, $H_{15\text{-}17}$), 5.42 (1H, m, H_7), 5.12 (1H, d, J = 1.6 Hz, H_{13}), 5.00 (1H, d, J = 1.6 Hz, H_{13}), 2.47 (1H, tt, J = 8.8, 2.4 Hz, H_4), 2.29 (1H, m, H_8), 1.98 (1H, m), 1.90–1.85 (2H, m, H_8 and other), 1.78 (2H, dd, J = 9.4, 5.1 Hz), 1.76 (1H, m), 1.63–1.55 (3H, m, H_{10} and other), 1.43 (1H, m), 1.31 (1H, m), 0.98 (3H, t, J = 7.3 Hz, H_{11}) ppm.

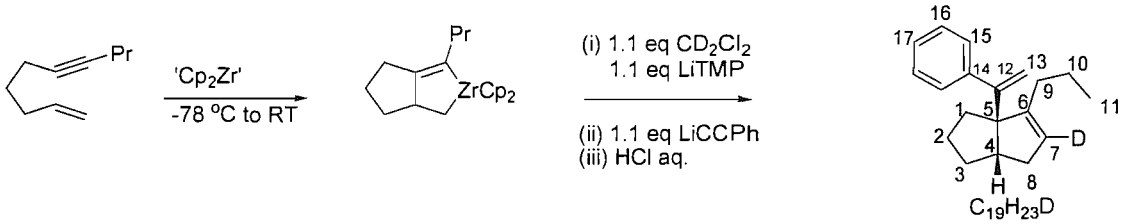
^{13}C NMR (100 MHz, $CDCl_3$): δ 155.33 (C, C_{12}), 146.67 (C, C_6 or C_{14}), 144.47 (C, C_6 or C_{14}), 127.98 (2CH, C_{15} or C_{16}), 127.58 (2CH, C_{15} or C_{16}), 126.49 (CH, C_{17}), 124.71 (CH, C_7), 113.71 (CH_2, C_{13}), 69.09 (C, C_5), 46.43 (CH, C_4), 40.79 (CH_2, C_8), 36.57 (CH_2), 35.68 (CH_2), 29.43 (CH_2), 25.66 (CH_2), 21.43 (CH_2), 14.59 (CH_3, C_{11}) ppm.

IR (film): 3079 (w), 3045 (w), 2949 (s), 2891 (m), 2866 (m) 2843 (m), 1619 (w), 1492 (m), 1449 (m), 1073 (w)1028 (w), 901 (s), 772 (s) cm^{-1}.

GCMS (CI) *m/z* (%): 253 ($(M+H)^+$, 100), 237 ($(M-CH_3)^+$, 5), 223 ($(M-C_2H_5)^+$, 15), 209 ($(M-C_3H_7)^+$, 10), 77 ($(C_6H_5)^+$, 12).

HRMS (EI) for $C_{19}H_{24}$ $(M)^+$, calculated 252.1878, found 252.1878.

5.4.2 Preparation of mono-deuterated 6-phenyl-6a-(1-phenylvinyl)-1,2,3,3a,4,6a-hexahydropentalene 739



A solution of *n*-BuLi (0.80 mL, 2.00 eq, 2.00 mmol)(2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) in THF (5 mL) at –78 °C. This was stirred for 10 minutes before the addition of dec-1-en-6-yne (0.136 g, 1.00 eq, 1.00 mmol) as a solution in THF (1 mL). The cool bath was removed and the reaction mixture was allowed to warm to room temperature over 2 hours.

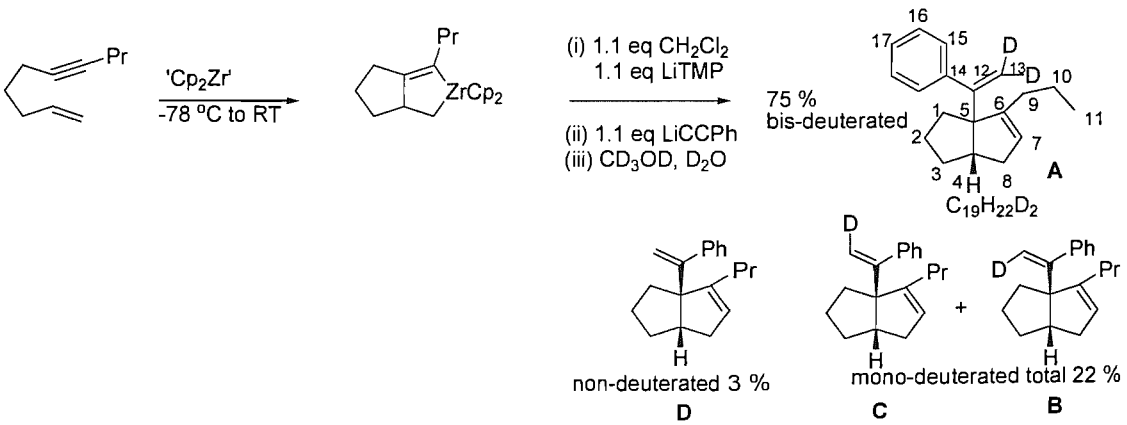
The reaction mixture was cooled to –78 °C before the addition of CD_2Cl_2 (70 μL, 1.10 eq, 1.10 mmol) as a solution in THF (1.5 mL) and subsequently the dropwise addition of LiTMP (1.5 mL, 1.50 eq, 1.50 mmol) over 10 minutes. This was followed by the dropwise addition of lithiated phenyl acetylene (1.5 mL, 1.10 eq, 1.10 mmol) [made with phenyl acetylene (0.12 ml, 1.10 eq, 1.10 mmol), *n*-BuLi (0.44 mL, 1.10 eq, 1.10 mmol) and THF (1 mL), and stirred for 2 hours at 0 °C] over 15 minutes. The reaction mixture changed from orange to red, on addition of carbenoid, then to black on

addition of the anion. The reaction was warmed to –50 °C over 2 hours, quenched with MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (5 mL) and stirred vigorously for 16 hours. The product was extracted into diethyl ether (3 x 30 mL), the combined organic phases were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash silica column chromatography (petrol) to yield a clear colourless oil, the title compound (108 mg, 43%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.21 (5H, m, $H_{15\text{-}17}$), 5.16 (1H, d, J = 1.7 Hz, H_{13}), 5.03 (1H, d, J = 1.7 Hz, H_{13}), 2.51 (1H, tt, J = 8.8, 2.2 Hz, H_4), 2.33 (1H, m, H_8), 2.07–1.75 (6H, m, H_8 and others), 1.68–1.58 (3H, m, H_{10} and other), 1.47 (1H, m), 1.36 (1H, m), 1.02 (3H, t, J = 7.3 Hz, H_{11}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.29 (C, C_{12}), 146.53 (C, C_6 or C_{14}), 144.47 (C, C_6 or C_{14}), 127.94 (2CH, C_{15} or C_{16}), 127.59 (2CH, C_{15} or C_{16}), 126.48 (CH, C_{17}), 124.43 (CD, t, J = 24.3 Hz, C_7), 113.73 (CH_2, C_{13}), 69.05 (C, C_5), 46.32 (CH, C_4), 40.72 (CH_2, C_8), 36.57 (CH_2), 35.67 (CH_2), 29.36 (CH_2), 25.64 (CH_2), 21.38 (CH_2, C_{10}), 14.59 (CH_3, C_{11}) ppm.

5.4.3 Preparation of bis-deuterated 6-phenyl-6a-(1-phenylvinyl)-1,2,3,3a,4,6a-hexahydropentalene 741



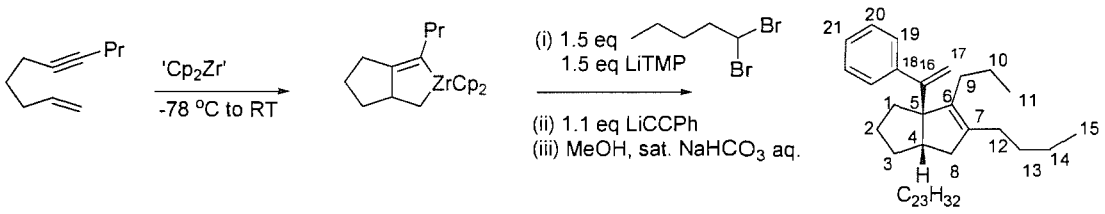
A solution of *n*-BuLi (0.80 mL, 2.00 eq, 2.00 mmol)(2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) in THF (5 mL) at –78 °C. This was stirred for 10 minutes before the addition of dec-1-en-6-yne (0.136 g, 1.00 eq, 1.00 mmol) as a solution in THF (1 mL). The cool bath was removed and the reaction mixture was allowed to warm to room temperature over 2 hours.

The reaction mixture was cooled to –78 °C before the addition of dichloromethane (70 μL, 1.10 eq, 1.10 mmol) as a solution in THF (1.5 mL) and subsequently the dropwise addition of LiTMP (1.5 mL, 1.50 eq, 1.50 mmol) over 10 minutes. This was followed by the dropwise addition of lithiated phenyl acetylene (1.5 mL, 1.10 eq, 1.10 mmol) [made with phenyl acetylene (0.12 ml, 1.10 eq, 1.10 mmol), *n*-BuLi (0.44 mL, 1.10 eq, 1.10 mmol) and THF (1 mL), and stirred for 2 hours at 0 °C] over 15 minutes. The reaction mixture changed from orange to red, on addition of carbenoid, then to black on addition of the anion. The reaction was warmed to –45 °C, over 2 hours, quenched with CD_3OD (1 mL) and D_2O (1 mL) and stirred vigorously for 1.5 hours. The product was extracted into diethyl ether (3 x 30 mL), the combined organic phases washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash silica column chromatography (petrol) to yield clear colourless oil, the title compound (92 mg, 36%), as an inseparable mixture of **A**, **B**, **C** and **D**.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25–7.18 (5H, m, $H_{15\text{-}17}$), 5.42 (1H, m, H_7), 5.12 (1H, d, J = 1.5 Hz, H_{13} minor non-deuterated), 5.11 (1H, s, H_{13} minor mono-deuterated), 4.99 (1H, d, J = 1.5 Hz, H_{13} minor non-deuterated), 4.98 (1H, s, H_{13} minor mono-deuterated), 2.47 (1H, tt, J = 8.8, 2.4 Hz, H_4), 2.29 (1H, m, H_8), 1.95 (1H, m), 1.89–1.85 (2H, m, H_8 and other), 1.78 (2H, dd, J = 9.5, 5.0 Hz), 1.76 (1H, m), 1.60–1.51 (3H, m, H_{10}), 1.43 (1H, m), 1.32 (1H, m), 0.98 (3H, t, J = 7.4 Hz, H_{11}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.25 (C, C_{12}), 155.17 (C, C_{12} deuterated), 146.68 (C, C_6 or C_{14}), 144.43 (C, C_6 or C_{14}), 127.99 (2CH, C_{15} or C_{16}), 127.56 (2CH, C_{15} or C_{16}), 126.49 (CH, C_{17}), 124.70 (CH, C_7), 113.71 (CD_2, t, J = 25.8 Hz, C_{13}), 69.07 (C, C_5), 69.03 (C, C_5 deuterated), 46.42 (CH, C_4), 40.79 (CH_2, C_8), 36.57 (CH_2), 35.69 (CH_2), 29.43 (CH_2), 25.66 (CH_2), 21.66 (CH_2), 14.59 (CH_3, C_{11}) ppm.

5.4.4 Preparation of 2-butyl-3a-(1-phenylvinyl)-3-propyl-1,3a,4,6,6a-hexahydropentalene 746



A solution of *n*-BuLi (0.80 mL, 2.00 eq, 2.00 mmol)(2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) in THF (5 mL) at –78 °C. This was stirred for 10 minutes before the addition of dec-1-en-6-yne (0.136 g, 1.00 eq, 1.00 mmol) as a solution in THF (1 mL). The cool bath was removed and the reaction mixture was allowed to warm to room temperature over 2 hours.

The reaction mixture was cooled to –78 °C before the addition of 1,1-dibromopentane (0.345 g, 1.50 eq, 1.50 mmol) as a solution in THF (1.5 mL) and subsequently the dropwise addition of LiTMP (1.5 mL, 1.50 eq, 1.50 mmol) over 10 minutes. This was followed by the dropwise addition of lithiated phenyl acetylene (1.5 mL, 1.10 eq, 1.10 mmol) [made with phenyl acetylene (0.12 ml, 1.10 eq, 1.10 mmol), *n*-BuLi (0.44 mL, 1.10 eq, 1.10 mmol) and THF (1 mL), and stirred for 2 hours at 0 °C] over 15 minutes. The reaction mixture changed from orange to red, on addition of carbenoid, then to black on addition of the anion. The reaction was warmed to –50 °C over 2 hours, quenched with MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (5 mL) and stirred vigorously for 16 hours. The product was extracted into diethyl ether (3 x 30 mL), the combined organic phases were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash silica column chromatography (petrol) to yield a clear colourless oil, the title compound (130 mg, 42%).

Alternative procedure:

For zirconacycle formation – see 5.4.1.

The reaction mixture was cooled to –78 °C before the addition of 1,1-dibromopentane (0.345 g, 1.50 eq, 1.50 mmol) as a solution in THF (1.5 mL) and subsequently the dropwise addition of LiTMP (1.5 mL, 1.50 eq, 1.50 mmol) over 10 minutes. This was followed by the dropwise addition of lithiated phenyl acetylene (3.00 mL, 3.00 eq, 3.00 mmol) [made with phenyl acetylene (0.33 ml, 3.0 eq, 3.00 mmol), *n*-BuLi (1.20 mL, 3.00 eq, 3.00 mmol) and THF (1 mL), and stirred for 2 hours at 0 °C]. The

reaction mixture changed from orange to red, on addition of carbenoid, then to black on addition of the anion. The reaction was warmed to –10 °C over 4 hours, quenched with MeOH (5 mL) and sat. $NaHCO_3$ solution (5 mL) and stirred vigorously for 16 hours. The product was extracted into diethyl ether (3 x 30 mL), the combined organic phases were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash silica column chromatography (petrol) to yield a clear colourless oil, the title compound (222 mg, 72%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24–7.17 (5H, m, $H_{19\text{-}21}$), 5.13 (1H, d, J = 1.8 Hz, H_{17}), 4.96 (1H, d, J = 1.8 Hz, H_{17}), 2.33 (1H, tt, J = 8.9, 2.2 Hz, H_4), 2.21 (1H, dd, J = 16.1, 8.9 Hz, H_8), 2.07 (2H, broad t, J = 7.8 Hz, H_9 or H_{12}), 1.97 (2H, t, J = 8.4 Hz, H_9 or H_{12}), 1.82–1.70 (4H, m, H_8 and others), 1.53 (1H, m), 1.47–1.39 (3H, m), 1.33–1.27 (5H, m), 0.93 (3H, t, J = 7.3 Hz, H_{11} or H_{15}), 0.92 (3H, t, J = 7.0 Hz, H_{11} or H_{15}) ppm.

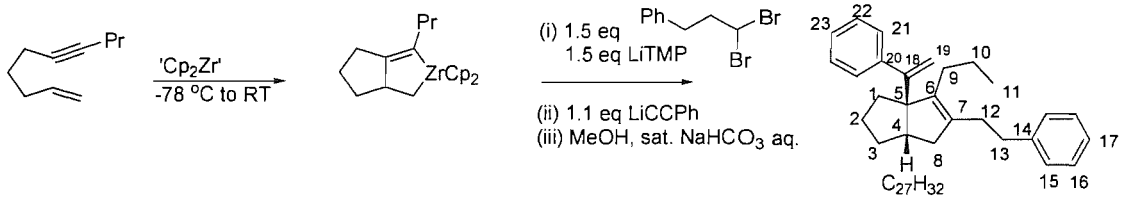
^{13}C NMR (100 MHz, $CDCl_3$): δ 156.24 (C, C_{16}), 144.69 (C, C_{18}), 139.41 (C, C_6 or C_7), 137.31 (C, C_6 or C_7), 128.08 (2CH, C_{19} or C_{20}), 127.46 (2CH, C_{19} or C_{20}), 126.39 (CH, C_{21}), 113.20 (CH_2, C_{17}), 70.55 (C, C_5), 44.14 (CH, C_4), 43.97 (CH_2, C_8), 36.73 (CH_2), 36.09 (CH_2), 30.21 (CH_2), 29.17 (CH_2), 29.08 (CH_2), 25.50 (CH_2), 23.92 (CH_2), 23.06 (CH_2), 15.25 (CH_3, C_{11} or C_{15}), 14.22 (CH_3, C_{11} or C_{15}) ppm.

IR (film): 3080 (w), 2952 (s), 2931 (s), 2868 (m), 2838 (m), 1619 (w), 1491 (w), 1464 (m), 1450 (m), 1377 (w), 1028 (m), 899 (s), 772 (s), 699 (s) cm^{-1}.

GCMS (CI) *m/z* (%): 309 ($(M+H)^+$, 75), 293 ($(M\text{-}CH_3)^+$, 10), 279 ($(M\text{-}C_2H_5)^+$, 45), 251 ($(M\text{-}C_4H_9)^+$, 18), 205 ($(M\text{-}C_6H_5CCH_2)^+$, 100).

HRMS (EI) $C_{23}H_{32}$ $(M)^+$ calculated 308.2504, found 308.2502.

5.4.5 Preparation of 5-phenethyl-3a-(1-phenylvinyl)-4-propyl-1,2,3,3a,6,6a-hexahydropentalene 744



A solution of *n*-BuLi (0.80 mL, 2.00 eq, 2.00 mmol)(2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) in THF (5 mL) at –78 °C. This was stirred for 10 minutes before the addition of dec-1-en-6-yne (0.136 g, 1.00 eq, 1.00 mmol) as a solution in THF (1 mL). The cool bath was removed and the reaction mixture was allowed to warm to room temperature over 2 hours.

The reaction mixture was cooled to –78 °C before the addition of (3,3-dibromo-propyl)-benzene (0.417 g, 1.50 eq, 1.50 mmol) as a solution in THF (1.0 mL) and subsequently the dropwise addition of LiTMP (2.0 mL, 1.50 eq, 1.50 mmol) over 15 minutes. This was followed by the dropwise addition of lithiated phenyl acetylene (1.5 mL, 1.10 eq, 1.10 mmol) [made with phenyl acetylene (0.12 ml, 1.10 eq, 1.10 mmol), *n*-BuLi (0.44 mL, 1.10 eq, 1.10 mmol) and THF (1 mL), and stirred for 2 hours at 0 °C] over 15 minutes. The reaction mixture changed from orange to dark red, on addition of carbenoid, then to black on addition of the anion. The reaction was stirred for 50 minutes at –78 °C, quenched with MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (5 mL) and stirred vigorously for 2 hours. The product was extracted into diethyl ether (3 x 30 mL), the combined organic phases washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash silica column chromatography (petrol) to yield a clear colourless oil, the title compound (191 mg, 54%).

^{1}H NMR (400 MHz, $CDCl_3$): 7.28–7.10 (10H, m, $H_{15\text{-}17}$ and $H_{21\text{-}23}$), 5.05 (1H, d, J = 1.8 Hz, H_{19}), 4.90 (1H, d, J = 1.8 Hz, H_{19}), 2.60 (2H, t, J = 7.9 Hz, H_{12} or H_{13}), 2.40–2.27 (3H, m, H_4 and, H_{12} or H_{13}), 2.20 (1H, dd, J = 16.0, 8.8 Hz, H_8), 1.90 (2H, dd, J = 10.4, 6.1 Hz), 1.82 (1H, d, J = 16.0 Hz, H_8), 1.76–1.67 (3H, m), 1.48 (1H, m), 1.41–1.23 (4H, m), 0.86 (3H, t, J = 7.3 Hz, H_{11}) ppm.

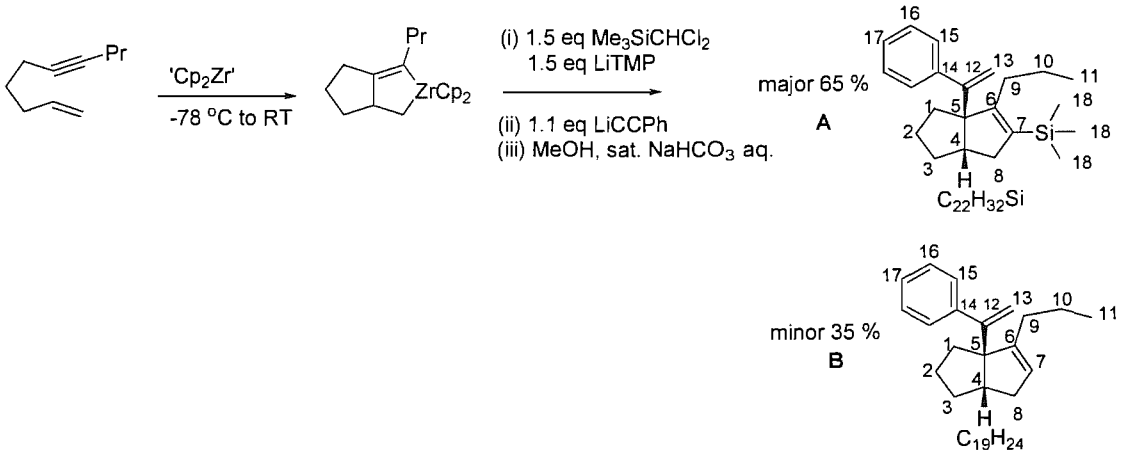
^{13}C NMR (100 MHz, $CDCl_3$): δ 155.98 (C, C_{18}), 144.56 (C, C_{20}), 142.71 (C, C_{14}), 138.34 (C, C_6 or C_7), 138.32 (C, C_6 or C_7), 128.45 (2CH), 128.43 (2CH), 128.05 (2CH), 127.48 (2CH), 126.43 (CH, C_{17} or C_{23}), 125.91 (CH, C_{17} or C_{23}), 113.33 (CH_2, C_{19}), 70.53 (C, C_5), 44.17 (CH, C_4), 43.94 (CH_2, C_8), 36.65 (CH_2), 35.97 (CH_2), 34.38 (CH_2, C_{12} or C_{13}), 31.60 (CH_2, C_{12} or C_{13}), 29.07 (CH_2), 25.49 (CH_2), 23.87 (CH_2, C_{10}), 15.25 (CH_3, C_{11}) ppm.

IR (film): 3083 (w), 3025 (w), 2945 (m), 2865 (w), 2837 (w), 1601 (w), 1452 (m), 1072 (w), 1029 (w), 900 (m), 773 (m), 746 (m), 697 (s) cm^{-1}.

GCMS (CI) *m/z* (%): 357 ($(M+H)^+$, 100), 253 ($(M-C_6H_5CCH_2)^+$, 30), 91 ($(C_6H_5)^+$, 78), 77 ($(C_6H_5)^+$, 6).

HRMS (EI) for $C_{27}H_{32}$ $(M)^+$ calculated 356.2504, found 356.2505.

5.4.6 Preparation of an inseparable mixture of trimethyl (3a-(1-phenylvinyl)-3-propyl-1,3a,4,5,6,6a-hexahydropentalen-2-yl) silane (major) 748 and 3a-(1-phenyvinyl)4-propyl-1,2,3,3a,6,6a-hexahydropentalene (minor) 738



A solution of *n*-BuLi (0.80 mL, 2.00 eq, 2.00 mmol)(2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) in THF (5 mL) at –78 °C. This was stirred for 10 minutes before the addition of dec-1-en-6-yne (0.136 g, 1.00 eq, 1.00 mmol) as a solution in THF (1 mL). The cool bath was removed and the reaction mixture was allowed to warm to room temperature over 2 hours.

The reaction mixture was cooled to –78 °C before the addition of dichloromethyl trimethylsilane (0.23 mL, 1.50 eq, 1.50 mmol) as a solution in THF (1.5 mL) and subsequently the dropwise addition of LiTMP (1.5 mL, 1.50 eq, 1.50 mmol) over 10 minutes. This was followed by the dropwise addition of lithiated phenyl acetylene (1.5 mL, 1.10 eq, 1.10 mmol) [made with phenyl acetylene (0.12 ml, 1.10 eq, 1.10 mmol), *n*-BuLi (0.44 mL, 1.10 eq, 1.10 mmol) and THF (1 mL), and stirred for 2 hours at 0 °C] over 10 minutes. The reaction mixture changed from orange to red, on addition of carbenoid, then to black on addition of the anion. The reaction was warmed to –60 °C over 2 hours, quenched with MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (5 mL) and stirred vigorously for 16 hours. The product was extracted into diethyl ether (3 x 30 mL), the combined organic phases were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash silica column chromatography (petrol) to yield a clear colourless oil, an inseparable mixture of the silylated and desilylated title compounds (162 mg, overall 55%, molar ratio of silylated: non-silylated compound 65:35).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24–7.17 (5H, m, $H_{15\text{-}17}$), 5.42 (1H, m, H_7 minor), 5.16 (1H, d, J = 1.7 Hz, H_{13} major), 5.13 (1H, d, J = 1.7 Hz, H_{13} minor), 5.00 (1H, d, J = 1.7 Hz, H_{13} minor), 4.99 (1H, d, J = 1.7 Hz, H_{13} major), 2.47 (1H, tt, J = 8.8, 2.4 Hz, H_4 minor), 2.37–2.22 (2H, m), 1.96–1.76 (4H, m), 1.59–1.33 (5H, m), 0.98 (3H, t, J = 7.4 Hz, H_{11} minor), 0.93 (3H, t, J = 7.3 Hz, H_{11} major), 0.10 (9H, s, H_{18} major) ppm.

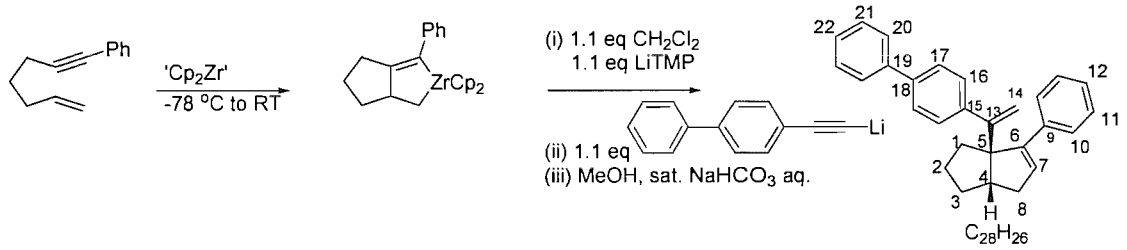
^{13}C NMR (75 MHz, $CDCl_3$): δ 155.56 (C, C_{12} major), 155.33 (C, C_{12} minor), 146.63 (C, C_6), 144.46 (C, C_{14}), 137.82 (C, C_7 major), 128.02 (2CH, C_{15} or C_{16} major), 127.94 (2CH, C_{15} or C_{16} minor), 127.58 (2CH, C_{15} or C_{16} minor), 127.43 (2CH, C_{15} or C_{16} major), 126.48 (CH, C_{17}), 124.70 (CH, C_7 minor), 113.73 (CH_2, C_{13} minor), 113.34 (CH_2, C_{13} major), 73.27 (C, C_5 major), 69.05 (C, C_5 minor), 46.36 (CH_2, C_8 major), 46.32 (CH, C_4 minor), 45.54 (CH, C_4 major), 40.83 (CH_2, C_8 minor), 36.82 (CH_2, major), 36.57 (CH_2, minor), 36.30 (CH_2, major), 35.68 (CH_2, minor), 31.43 (CH_2, major), 29.38 (CH_2, minor), 25.80(CH_2, major), 25.64 (CH_2, minor), 25.51

(CH_2, major), 21.40 (CH_2, C_{10} minor), 15.12 (CH_3, C_{11} major), 14.62 (CH_3, C_{11} minor), –0.65 (CH_3, C_{18} major) ppm.

Major (A) GCMS (CI) *m/z* (%): 325 ($(M+H)^+$, 50), 295 ($(M-C_2H_5)^+$, 10), 221 ($(M-C_6H_5CCH_2)^+$, 45), 103 ($(C_6H_5CCH_2)^+$, 18), 73 ($(SiMe_3)^+$, 100).

Minor (B) GCMS (CI) *m/z* (%): 253 ($(M+H)^+$, 100), 237 ($(M-CH_3)^+$, 10), 223 ($(M-C_2H_5)^+$, 30), 209 ($(M-C_3H_7)^+$, 15), 77 ($(C_6H_5)^+$,12)

5.4.7 Preparation of 4-[1-(4-phenyl-2,3,6,6a-tetrahydro-1H-pentalen-3a-yl)-vinyl]-biphenyl 752



A solution of *n*-BuLi (0.80 mL, 2.00 eq, 2.00 mmol) (2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) in THF (5 mL) at –78 °C. This was stirred for 10 minutes before the addition of hept-6-en-1-ynyl-benzene (0.170 g, 1.00 eq, 1.00 mmol) as a solution in THF (1 mL). The cool bath was then removed and the reaction mixture was allowed to warm to room temperature over 2 hours.

The reaction mixture was cooled to –78 °C before the addition of dichloromethane (70 μL, 1.10 eq, 1.10 mmol) as a solution in THF (1.5 mL) and subsequently the dropwise addition of LiTMP (1.1 mL, 1.10 eq, 1.10 mmol) over 10 minutes. After 5 minutes a solution of lithiated 4-ethynyl-biphenyl (1.5 mL, 1.10 eq, 1.10 mmol) [made with 4-ethynyl-biphenyl (0.178 g, 1.10 eq, 1.10 mmol), *n*-BuLi (0.44 mL, 1.10 eq, 1.10 mmol) and THF (1 mL), and stirred for 2 hours at 0 °C] was added dropwise over 15 minutes. The reaction was warmed to –15 °C over 1.5 hours, quenched with HCl (5 mL, 2 M aqueous solution) and stirred for 1 hour at room temperature. The product was extracted into diethyl ether (3 x 30 mL), the combined organic phases were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and

concentrated *in vacuo*. The crude product was purified by radial chromatography (petrol) to yield a clear colourless oil, the title compound (157 mg, 43%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53–7.50 (4H, m), 7.43–7.35 (4H, m), 7.26–7.13 (6H, m), 6.07 (1H, t, J = 2.3 Hz, H_7), 5.22 (1H, d, J = 1.5 Hz, H_{14}), 4.99 (1H, d, J = 1.5 Hz, H_{14}), 2.62 (1H, td, J = 8.1, 6.0 Hz, H_4), 2.35 (1H, ddd, J = 17.5, 8.1, 2.3 Hz, H_8), 2.09–1.98 (2H, m, H_1 and H_8), 1.87 (1H, m, H_3), 1.71 (1H, m, H_1), 1.51–1.42 (2H, m, H_2), 1.29 (1H, m, H_3) ppm.

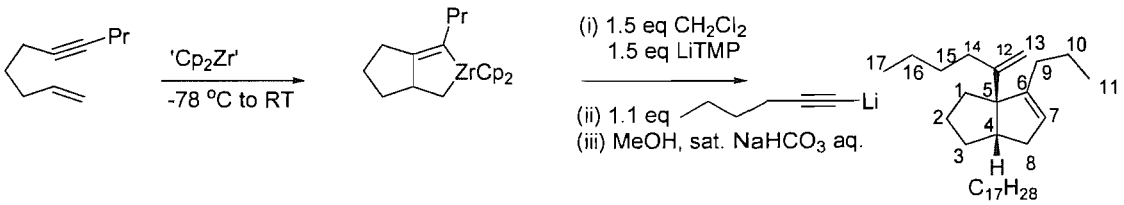
^{13}C NMR (75 MHz, $CDCl_3$): δ 154.58 (C), 146.08 (C), 142.55 (C), 141.01 (C), 139.44 (C), 136.55 (C), 128.97 (2CH), 128.86 (2CH), 128.74 (CH), 128.18 (2CH), 127.42 (2CH), 127.26 (CH), 127.10 (2CH), 126.87 (CH), 126.26 (2CH), 113.84 (CH_2, C_{14}), 67.27 (C, C_5), 50.27 (CH, C_4), 39.10 (CH_2, C_8), 35.92 (CH_2, C_3), 35.23 (CH_2, C_1), 26.82 (CH_2, C_2) ppm.

IR (film): 3079 (w), 3054 (w), 3029 (w), 2945 (m), 2864 (w), 1599 (w), 1485 (m), 1445 (m), 1115 (m), 842 (m), 768 (m), 756 (s), 738 (s), 693 (s) cm^{-1}.

GCMS (CI) *m/z* (%): 363 ($(M+H)^+$, 4), 337 ($(M-C_2H_5)^+$, 2), 179 ($(PhCCH_2)^+$, 40), 154 ($(C_6H_5C_6H_5)^+$, 85), 77 ($(C_6H_5)^+$, 100).

HRMS (EI) for $C_{28}H_{26}$ $(M)^+$ calculated 362.2035, found 362.2032.

5.4.8 Preparation of 3a-(hex-1-en-2-yl)-4-propyl-1,2,3,3a,6,6a-hexahydropentalene 754



A solution of *n*-BuLi (0.80 mL, 2.00 eq, 2.00 mmol)(2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) in THF (5 mL) at –78 °C. This was stirred for 10 minutes before the addition of dec-1-en-6-yne (0.136 g, 1.00 eq, 1.00 mmol) as a solution in THF (1 mL). The cool bath was removed and the reaction mixture was allowed to warm to room temperature over 2 hours.

The reaction mixture was cooled to –78 °C before the addition of dichloromethane (96 μL, 1.50 eq, 1.50 mmol) as a solution in THF (1.5 mL) and subsequently the dropwise addition of LiTMP (2.0 mL, 1.50 eq, 1.50 mmol) over 15 minutes. This was followed by the dropwise addition of lithiated 1-hexyne (1.5 mL, 1.10 eq, 1.10 mmol) [made with 1-hexyne (0.13 ml, 1.10 eq, 1.10 mmol), *n*-BuLi (0.44 mL, 1.10 eq, 1.10 mmol) and THF (1 mL) at 0 °C] over 10 minutes. The reaction was stirred at –78 °C for 1.5 hours, quenched with MeOH (5 mL) and sat. $NaHCO_3$ aqueous solution (5 mL) and stirred vigorously for 16 hours. The product was extracted into diethyl ether (3 x 30 mL), the combined organic phases were washed with sat. $NaHCO_3$ aqueous solution (30 mL), water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash silica column chromatography (petrol) to yield a clear colourless oil, the title compound (109 mg, 47%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.38 (1H, t, J = 2.1 Hz, H_7), 4.85 (1H, d, J = 1.5 Hz, H_{13}), 4.77 (1H, d, J = 1.5 Hz, H_{13}), 2.64 (1H, ddq, J = 16.5, 8.6, 2.1 Hz, H_8), 2.41 (1H, tt, J = 8.6, 2.1 Hz, H_4), 1.98 (1H, dt, J = 16.5, 2.1 Hz, H_8), 1.91–1.65 (5H, m), 1.64–1.25 (11H, m), 0.91 (3H, t, J = 7.3 Hz, H_{11} or H_{17}), 0.90 (3H, t, J = 7.2 Hz, H_{11} or H_{17}) ppm.

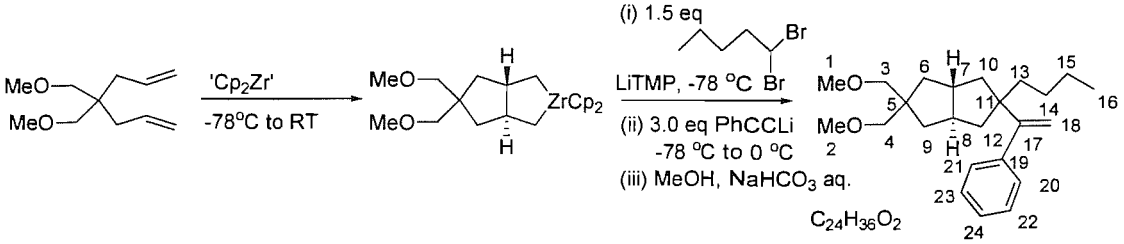
^{13}C NMR (75 MHz, $CDCl_3$): δ 154.50 (C, C_{12}), 147.18 (C, C_6), 123.47 (CH, C_7), 106.65 (CH_2, C_{13}), 69.68 (C, C_5), 46.24 (CH, C_4), 41.24 (CH_2, C_8), 36.85 (CH_2), 33.73 (CH_2), 31.88 (CH_2), 30.98 (CH_2), 29.32 (CH_2), 25.71 (CH_2), 23.02 (CH_2), 21.34 (CH_2), 14.52 (CH_2, C_{11} or C_{17}), 14.31 (CH_2, C_{11} or C_{17}) ppm.

IR (film): 2951 (s), 2932 (s), 2865 (m), 2844 (m), 1631 (w), 1452 (m), 1377 (m), 886 (s), 789 (m) cm^{-1}.

GCMS (CI) *m/z* (%): 233 ($(M+H)^+$, 100), 217 ($(M-CH_3)^+$, 8), 203 ($(M-C_2H_5)^+$, 25), 189 ($(M-C_3H_7)^+$, 40), 175 ($(M-C_4H_9)^+$, 90).

HRMS $(ES)^+$ for $C_{17}H_{28}$ $(M)^+$, calculated 232.2191, found 232.2192.

5.4.9 Preparation of rac-(1*S*, 5*S*)-7-butyl-7-(1-phenylvinyl)-3,3-bis(methoxymethyl)-bicyclo[3.3.0]octane 769



A solution of n-BuLi (0.80 mL, 2.00 eq, 2.00 mmol)(2.5 M in hexanes) was added to a solution of zirconocene dichloride (0.292 g, 1.00 eq, 1.00 mmol) in THF (5 mL) at –78 °C. This was stirred for 10 min before the addition of 4,4-bis-methoxymethyl-hepta-1,6-diene (0.184 g, 1.00 eq, 1.00 mmol) as a solution in THF (1 mL). The cool bath was removed and the reaction mixture was allowed to warm to room temperature over 2 hours.

The reaction mixture was cooled to –78 °C before the addition of 1,1-dibromopentane (0.345 g, 1.50 eq, 1.50 mmol) in THF (1 mL) and followed by the dropwise addition of LiTMP (1.5 mL, 1.50 eq, 1.50 mmol) over 15 minutes. A solution of lithiated phenylacetylene (2.5 mL, 3.00 eq, 3.00 mmol) [freshly made from phenyl acetylene (0.33 mL, 3.00 eq, 3.00 mmol), THF (2 mL) and *n*-BuLi (1.20 mL, 3.00 eq, 3.00 mmol), stirred for 2 hours at 0 °C] was then added to the reaction mixture, dropwise, over 20 minutes. It was warmed to 0°C over 4 hours, quenched with MeOH (5 mL), and sat. $NaHCO_3$ aqueous solution (5 mL) and stirred vigorously for 16 hours. The product was extracted into diethyl ether (3 x 30 mL), the combined organic phases were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash silica column chromatography (hexane/diethyl ether 9:1) to yield a clear colourless colourless oil, the title product (0.276 g, 77%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.18 (5H, m, H_{20-24}), 5.13 (1H, d, J = 1.4 Hz, H_{18}), 4.94 (1H, d, J = 1.4 Hz, H_{18}), 3.33 (3H, s, H_1 or H_2), 3.32 (3H, s, H_1 or H_2), 3.25–3.22 (4H, m, H_3 and H_4), 2.12 (1H, dd, J = 12.6, 5.8 Hz, H_6 or H_9 or H_{10} or H_{12}), 1.82 (1H, m, H_7 or H_8), 1.76 (1H, m, H_7 or H_8), 1.68 (1H, dd, J = 11.7, 5.6 Hz, H_6 or H_9 or H_{10} or H_{12}), 1.60–1.41 (5H, m), 1.24–1.10 (4H, m, H_{14} and H_{15}), 1.05 (1H,

apparent t, J = 12.1 Hz, H_6 or H_9 or H_{10} or H_{12}), 0.95 (2H, apparent t, J = 11.7 Hz, H_6 or H_8 or H_{10} or H_{12}), 0.79 (3H, t, J = 6.9 Hz, H_{16}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.16 (C, C_{17}), 144.17 (C, C_{19}), 128.35 (2CH, C_{20} and C_{21}, or C_{22} and C_{23}), 127.67 (2CH, C_{20} and C_{21}, or C_{22} and C_{23}), 126.51 (CH, C_{24}), 113.21 (CH_2, C_{18}), 78.23 ($2CH_2$, C_3 and C_4), 59.36 (CH_3, C_1 or C_2), 59.33 (CH_3, C_1 or C_2), 58.52 (C, C_5 or C_{11}), 54.33 (C, C_5 or C_{11}), 51.22 (CH, C_7 or C_8), 50.95 (CH, C_7 or C_8), 42.78 (CH_2, C_6 or C_9 or C_{10} or C_{12}), 42.64 (CH_2, C_6 or C_9 or C_{10} or C_{12}), 39.18 (CH_2, C_{13}), 34.88 (CH_2, C_6 or C_9 or C_{10} or C_{12}), 34.84 (CH_2, C_6, C_9, C_{10} or C_{12}), 27.30 (CH_2, C_{14} or C_{15}), 23.27 (CH_2, C_{14} or C_{15}), 14.17 (CH_3, C_{16}) ppm.

IR (film): 2927 (m), 2869 (m), 2823 (m), 1491 (w), 1455 (m), 1387 (w), 1198 (m), 1105 (s), 1029 (w), 963 (m), 889 (m), 775 (m), 702 (m) cm^{-1}.

GCMS (EI) *m/z* (%): 356 ($(M)^+$, 6), 299 ($(M-C_4H_9)^+$, 36), 279 ($(M-C_6H_5)^+$, 105 (100), 103 ($(C_8H_7)^+$, 43), 77 ($(C_6H_5)^+$, 39).

HRMS (EI) for $C_{24}H_{36}O_2$ $(M)^+$ calculated 356.2715, found 356.2710.

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