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The Synthesis of Novel Chiral Transition Metal Complexes

A thesis submitted for the degree of

Doctor of Philosophy

By

David Michael Dossett B. Sc.

Department of Chemistry
University of Southampton

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UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF SCIENCE

CHEMISTRY

Doctor of Philosophy

THE SYNTHESIS OF NOVEL CHIRAL TRANSITION METAL COMPLEXES

by David Michael Dossett

The synthesis of a variety of novel chiral annulated and C_2-symmetric cyclopentadienyl ligands and the formation of a novel titanocene complex is described. Chapter 1 provides an introduction to the research, outlining the methodology and stating the aims of the project. A literature review of chiral annulated Cyclopentadienyl ligands and the use of Group IV metallocenes as chiral catalysts is in asymmetric synthesis is discussed. Chapter two deals with the development of a chiral double Michael addition reaction, via the synthesis of 4-substituted chiral cyclopentenones, the products of which are intended for use as chiral Cyclopentadienyl ligands. Chapter three introduces a novel C_2-symmetric ligand design, and the synthesis thereof, whilst chapter 4 presents the complexation of the novel C_2-symmetric ligand to form a titanocene complex. Experimental details are given in chapter 5.

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For Nicky and my parents.

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Outside of work I would like to thank all the residents of 9 Crofton Close over the last 4 years, especially Dan Merckel and Steve Jones for regular battles on the oche, in the nets, on the roads and on the golf course and Sam Bardwell for reminding me that things could be worse. Thanks also to Chris and Tamara for their hospitality before my viva.

Cheers to all my brothers and sisters and their respective children for regular free meals and much amusement, also John, Liza and Sam Rogers and Flavia Griggs for their hospitality.

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DAVE DOSSETT
September 2003
Sudbury, UK.

Abbreviations.

Ar – aryl group

APCI – atmospheric pressure chemical ionisation (relating to mass spectrometry)

b – broad (relating to NMR, IR data)

bu – n butyl group

CAN – ceric ammonium nitrate

$_cC_6H_{11}$ – cyclohexyl

°C - degrees celcius

CI - chemical ionisation (relating to mass spectrometry)

Cp – Cyclopentadienyl

Cp* - pentamethylcyclopentadienyl

d – doublet (relating to IR data)

DCM – dichloromethane

DIBAL-H – diisobutylaluminium lithium hydride

DMAP- dimethylaminopridine

DME – dimethoxy ethane

DMF – dimethylformamide

e.e. - enantiomeric excess

ebthi – ethylene-bistetrahydroindenyl

EI electron impact (relating to mass spectrometry)

Et – ethyl group

ether, – diethyl ether

g – gram(s)

GC – gas chromatography

h – hour(s)

Hz – hertz(s)

HPLC – high performance liquid chromatography

HRMS - high resolution mass spectrometry

iBu – isobutyl group

IPA – isopropyl alcohol

iPr – isopropyl group

IR – infrared

J – coupling constant in hertz (relating to NMR)

LDA – lithium isopropylamide

LiHMDS – lithium hexamethyldisilazide

LRMS – low-resolution mass spectrometry

m – medium (relating to IR data)

m – multiplet (relating to NMR data)

M – molarity in moles per litre

Me – methyl group

meso - mesomeric

mg – milligram(s)

mL – millilitre(s)

min – minute(s)

mmol – millimole(s)

M. Pt. - Melting Point

Ms - mesyl group

MS – mass spectrometry

nBuLi – *n*-butyl lithium

nm – nanometre(s)

(+) or **(-) NME** – (+) or (-)- N,N-dimethylephedrine

NMR – nuclear magnetic resonance

o – ortho

p – para

piv - pivaloyl

Ph – phenyl group

PMA – phosphomolybdic acid

ppm – parts per million

q – quartet relating to NMR data

R - general organic aliphatic or aromatic substituent

rac - racemic

s - singlet (relating to NMR data)

s - strong (relating to IR data)

^{t}Bu – tertiary butyl

t – triplet

TEAF – triethylamine/formic acid azeotrope

THF – tetrahydrofuran

TBS or **TBDMS** – tertiary butyl dimethylsilyl group

TsDPhEN - toluenesulphonyl diphenylethylene diamine

TLC – thin layer chromatography

uv – ultraviolet

w- weak (relating to IR data)

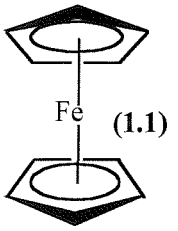
α[D]298 - (optical rotation at 298K and sodium D line)

λ – wavelength (nm)

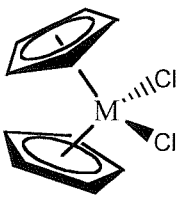
1. Introduction to Cyclopentadienyl Ligands and Their Complexes.

1.1 Metallocenes.

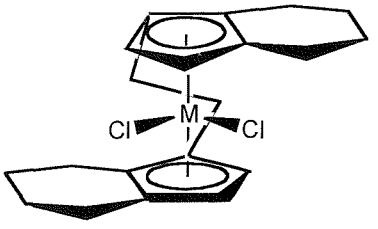
The discovery of ferrocene **(1.1)** in 1951 was highly significant in the development of modern organometallic chemistry: It was the starting point in a chain of development and progression that would lead from stoichiometric reagents to the development of highly active catalysts for one of the most important requirements in modern synthetic chemistry, the production of compounds with high enantiomeric and diastereomeric excess.[1,2,3,4,5] With this requirement in mind, it can be said that organometallic complexes are potentially ideal candidates. A metal centre for catalysis and a chiral organic framework to provide enantiocontrol around the active site. Furthermore when designing such catalysts, η^5 chiral cyclopentadienes would seem to be suitable ligands for trying to synthesise highly active chiral organometallic complexes: The strength of bonding can be as high as 495 KJ mol^{-1}, a wide variation in the number of elaborations of the Cp ring are known, and a number of synthetic routes are available for their formation. Two such cyclopentadiene ligands bound to the transition metal centre, as shown in ferrocene, are called metallocenes and are described as having a sandwich structure. Metal centres with only one Cp ligand are known as half sandwich monocyclopentadienyl complexes. It is the former that will be discussed here.



(1.1)



M = Ti, Zr, Hf



M = Ti (**1.2**)
M = Zr (**1.3**)

Scheme 1.1

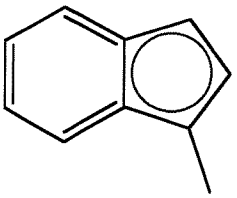
Group IV metallocenes of Titanium, Zirconium and Hafnium are commercially available; relatively air stable solids, and their derivatives have many applications in polymer

chemistry. Of those developed so far, the ethylene bridged C_2-symmetric tetrahydroindenyl complexes (**1.2**, **1.3**), first reported by Brintzinger, have proved to be the most successful metallocenes. The use of **1.3,** and other structurally similar complexes to control the stereoregularity of olefin polymerisation is now an area of chemistry with enormous commercial significance.[6,7] Of greater significance to this project, the application of **1.2** and **1.3** to catalytic enantioselective carbometallations, hydrosilylations and hydrogenation reactions has resulted in materials with very high levels of optical purity.[8]

However the success of these catalysts serves to highlight the challenge facing the synthetic chemist in this area: No truly chiral commercially viable cyclopentadienyl organometallic complexes exist. Brintzinger's designs published 20 years ago, the outstanding successes in the field, are not formed as optically pure materials, but rather as racemates, which require resolution.[9] In addition they are difficult and expensive to make and so when designing new complexes the ideal should be to improve upon these areas whilst retaining the enantioselectivity.[9]

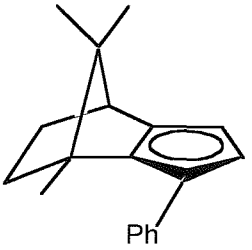
1.1.1 Different Types of Chirality in η^5-chiral Cyclopentadienyl Metal Complexes.

It is possible to distinguish three approaches to ligand design that could exhibit such optical activity, based on the relationship between the two faces of the Cp ring. Cp's with homotopic faces, where the two faces are related by C_2-symmetry, so that complexation to either face results in same compound. Cp's with enantiotopic faces, where a mirror plane relates the two faces and gives rise to enantiomeric complexes following metallation to non-chiral metal fragments. Finally Cp's with diastereotopic faces, in which the faces are unrelated by symmetry and give rise to a mixture of diastereiosomers upon complexation to a metal. Examples of this type of isomerism are shown below.[10,11]



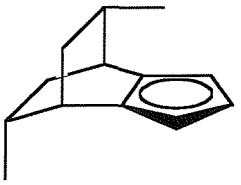
ENANTIOTOPIC

(1.5)



DIASTEREOTOPIC

(1.6)



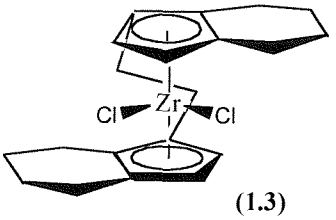
HOMOTOPIC

(1.7)

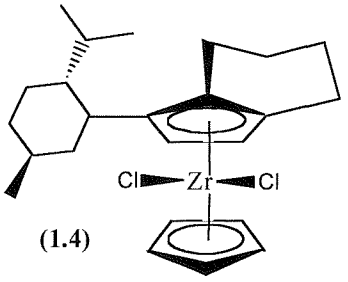
Scheme 1.3

1.1.2 Chiral Induction by Design.

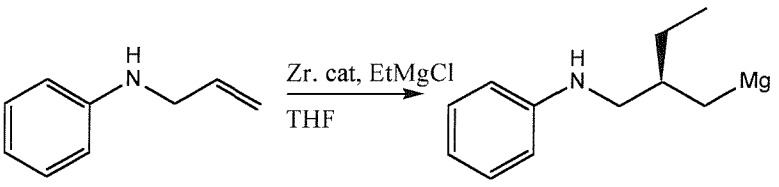
As stated above C_2-symmetric ligands with homotopic faces are often used in catalyst design because upon complexation only one compound can be formed. In addition they are perceived to be potentially useful as chiral catalysts, as the chiral "information" is often close to the metal centre. Paradoxically however this in itself can be a potential problem as in addition to the often problematic syntheses, C_2-symmetric systems often have low turnover numbers, i.e. they are un-reactive, and this is often attributable to steric crowding of the metal centre. In 1995 Whitby and co-workers published a non-C_2-symmetric zirconocene **1.4**, which in the ethylmagnesiation reaction proved to be highly efficient, providing results comparable to and often better than those achieved with **1.3**. [9,12]



(1.3)



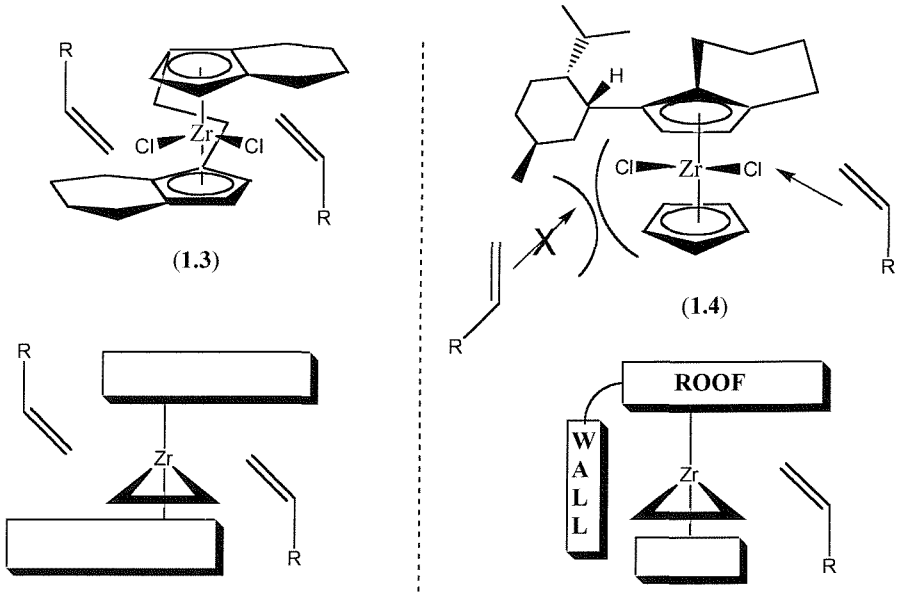
(1.4)



cat.	ee %
(1.3)	30
(1.4)	75

Scheme 1.4

The origin of of stereocontrol in the two complexes is compared in the schematic below. Although the two designs are very different, the way in which chiral information is imparted to substrates is very similar. Both use the architecture of the chiral ligand to ensure that the substrate has to approach the metal centre in a specific orientation. In the case of **1.3** the alkene substrate must approach the ligand with its bulkiest group way from the tetrahydroindene group, and as the complex is C_2-symmetric, approach from either side is enantiomerically identical. In **1.4** the chiral menthyl molecule is large enough to ensure that the substrate can only approach the metal centre from one side, effectively acting as a blocking "wall". The tetrahydroindene moiety again forces the substrate to adopt a specific orientation in order to bond, forming a "roof" and as only one Cp ring is substituted the metal centre is relatively unhindered and so the steric problems mentioned above are avoided, making the complex highly active. Furthermore the menthyl moiety is from a naturally occurring molecule and so makes the complex inexpensive to make.

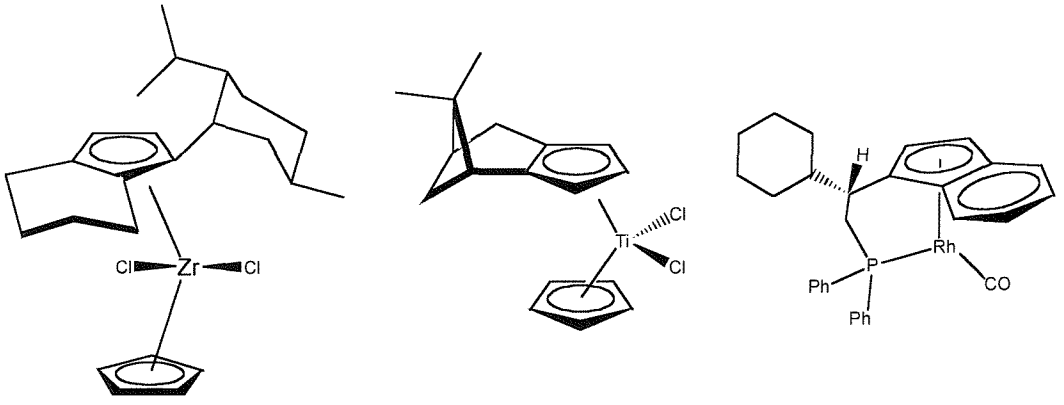


Scheme 1.5.

Incorporating this "roof" and "wall" approach is an important concept in most ligand design within the Whitby group.

1.1.3 The Induction of Planar Chirality.

Section 1.1.2 described how ligands with diastereotopic Cp faces gave rise to diasteromeric complexes, and the pendant menthyl group of **1.4** renders the two faces of this ligand diastereotopic. This means that diastereomers will be formed upon complexation, and although this is an advantage over the enantiomer formation that occurs when Brintzinger's ligand is complexed, as diastereomers can often be separated by recrystallisation or column chromatography, it is still rather inefficient. However in the case of zirconocene **1.4,** complexation gives a 6:1 ratio of diastereoisomers with the desired compound formed as a single enantiomer. This occurs because the design employs the induction of planar chirality in order to influence upon which face of the Cp ring complexation will occur. The diastereotopic nature of the ligand results in different energy barriers that have to be overcome to bond to each face of the Cp. In the case of **1.4** the presence of the menthyl group ensures the ligand induces planar chirality upon complexation, and combined with the "roof" and "wall" approach these ideas can be developed further in order to produce successful transition metal complexes. Below are shown three C_1 symmetric complexes and each is representative of one of three types of stereocontrol employed to induce planar chirality.



Type 1: (1.4)
Favoured rotomer

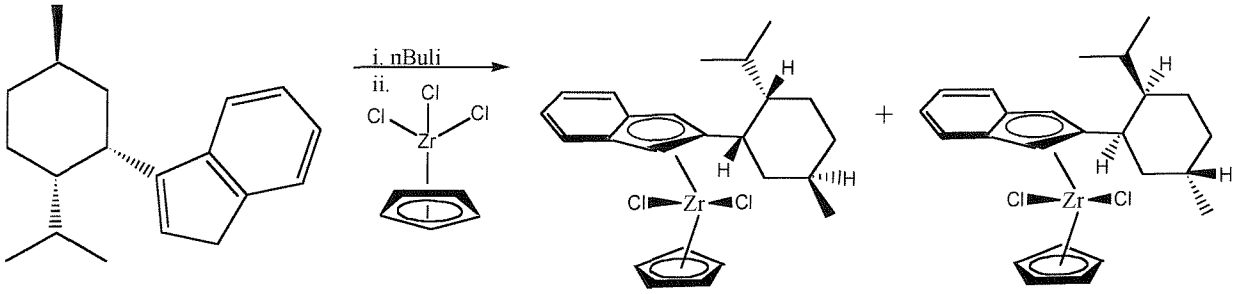
Type 2: (1.8)
Steric control

Type3 (1.9)
Co-ordination

Scheme 1.6

1.1.3.1 Favoured Rotomer.

Synthesis of **1.4** relies on control from a favoured rotomer. Following deprotonation of the neomenthylindene ligand **1.10** with n-BuLi, addition to a solution of $ZrCpCl_3$ in THF gives a 6:1 selectivity of isomers **1.11** and **1.12** (Scheme **1.7**). Hydrogenation of the indene ring then leads to **1.4** and the required orientation of the chiral ligand is maintained by interactions with the unsubstituted Cp.[12]

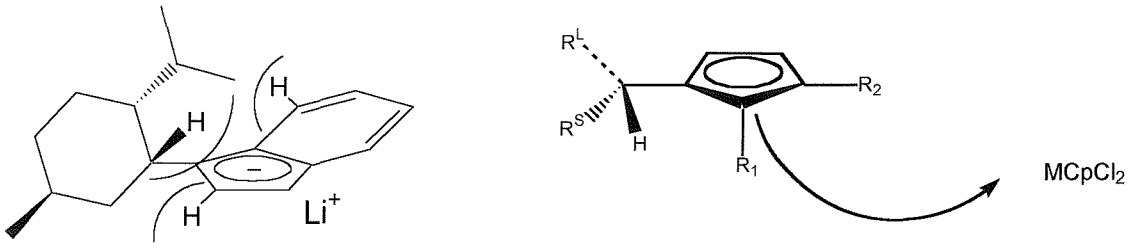


6:1

(1.10) **(1.11)** **(1.12)**

Scheme 1.7

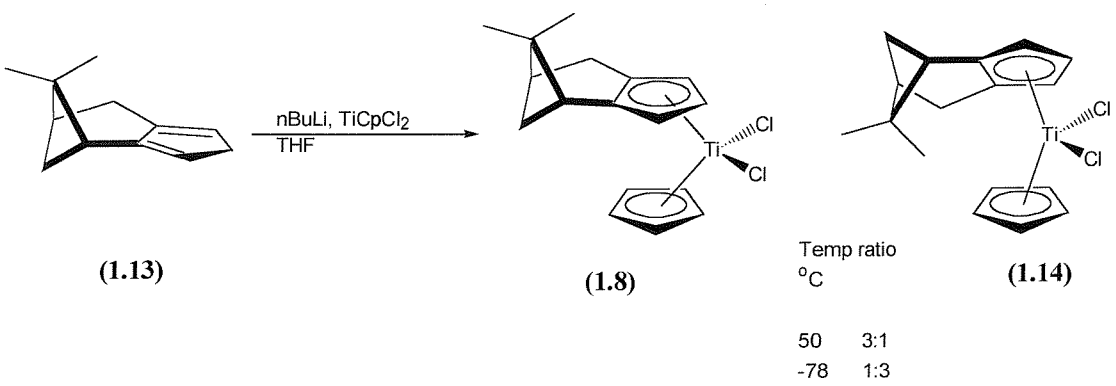
That facial selectivity is dominated by rotational conformation of the menthyl group is shown in the following diagram. Here the hydrogen is placed closest to the indene ring R_1 so that the ^{i}Pr group, designated LR, of the menthyl blocks one face of the Cp ring mediating complexation of the metal to the other less sterically hindered face.[13]



Scheme 1.8

1.1.3.2 Steric Control.

Annulated provide are good examples of the use of stereochemistry to direct facial control. Paquette has illustrated this with several systems such as the one below.[14] This system shows that if one face of the Cp is significantly more hindered than the other, then the facial preference is for the less congested face opposite the methylene bridges.

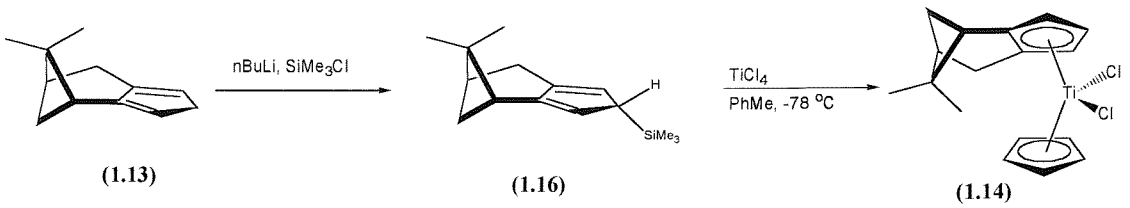


(1.13) **(1.8)** **(1.14)**

Scheme 1.9

However the steric effects are not the only driving force in this example. At 50°C metallation produces the expected 3:1 ratio of **1.8** to **1.14**, with the least hindered face favoured, but when the complexation is carried out at -78°C the selectivity is reversed. It is postulated that this is attributable to aggregation of the lithium anion, which then hinders complexation from the bottom face.

Further work on this system by Paquette demonstrated that silylation of the anion allowed diatereoselective control to produce exclusive formation of **1.15**.[15] Steric preference upon complexation is reversed as silation of the anion is strongly affected by steric effects, giving an 8:1 ratio of the *endo* silane **1.16**. The endo and exo isomers of **1.16** can then be separated by column chromatography, and treatment with the metal halide results in electrophilic capture of the silane with inversion of configuration, leading to the exclusive generation of **1.14.**

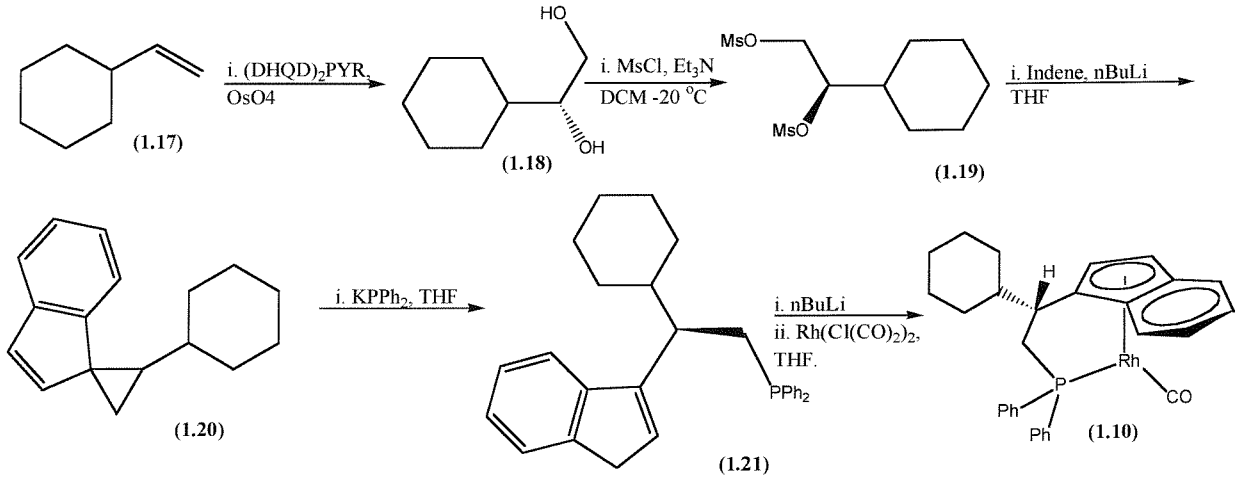


(1.13) **(1.16)** **(1.14)**

Scheme 1.10

1.1.3.3 Coordination Control.

Cp-phosphine metal complexes with chiral linkages have recently been reviewed, however none have been synthesised with the objective of inducing planar chirality via coordination.[16] However Harrison and Whitby have recently published indenyl systems with the aim of inducing planar chirality by the use of a chiral linking group to direct metallation.[17] The complex itself is synthesised in a 61% overall yield from vinylcyclohexane in 5 steps. The key step was the ring opening of a spirocyclopropane-1,1-indene with potassium diphenylphosphide. Complex **1.10** was formed as a 3:1 ratio of diastereoisomers, separable via flash column chromatography. The desired diastereoisomer only is shown below.



Scheme 1.11

1.1.4 Project Aims.

The basis of this project was to develop novel ligand systems combining the design principles established above. Any new design should be

- Highly active
- Inexpensive

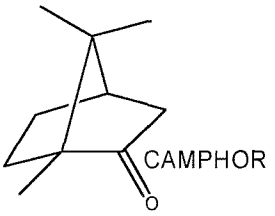
- Structurally Adaptable
- Induce Planar Chirality

With this in mind a non-C_2-symmetric system of annulated ligands and a new series of C_2-symmetric ligands were investigated

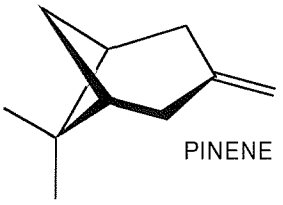
1.2 Synthesis of Chiral Annulated Cp Ligands and Metallocenes.

1.2.1 Ligands and Metallocenes Derived from Naturally Occurring Materials.

The chiral pool contains several compounds that are ideal candidates for the synthesis of homochiral Cp ligands: Camphor, verbenone and pinene are particularly suited to further investigation and have been widely studied over the years.[3]



(1.22)



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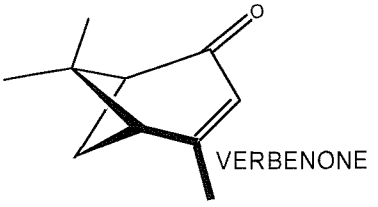
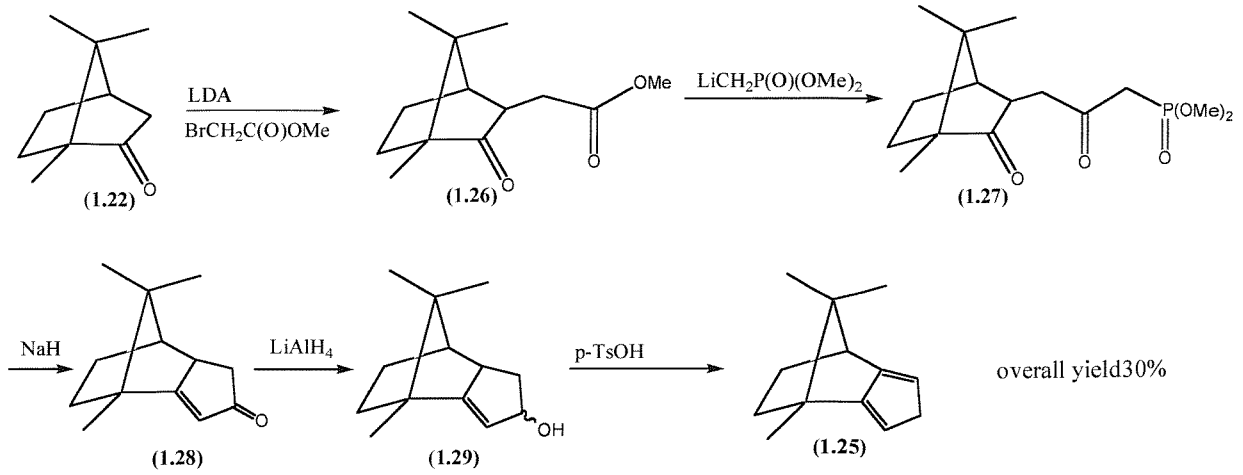


(1.24)

Scheme 1.12

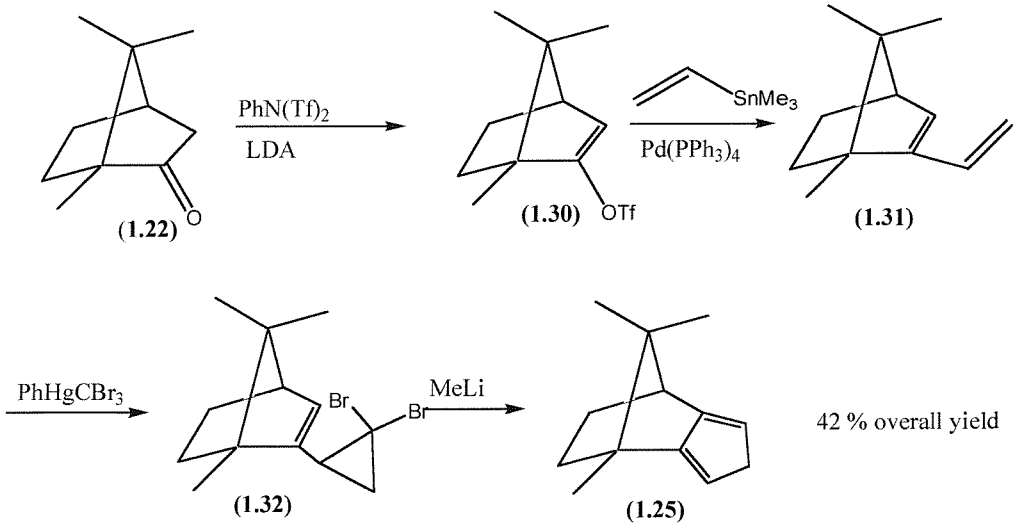
1.2.1.1 Disubstituted Ligands Derived from Camphor.

Halterman and Vollhardt published the first useful synthesis of a camphor derived Cp ligand in 1986.[18] The five step synthesis afforded ligand **1.25** in an overall yield of 30% and consisted of the addition of a three-carbon fragment to camphor **1.22** followed by base catalysed ring closure.



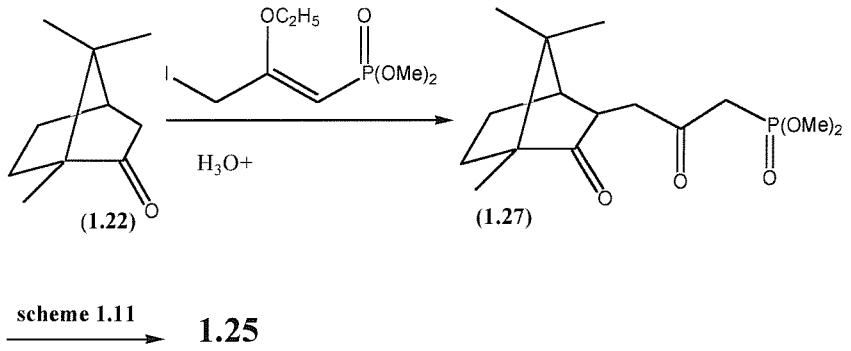
Scheme 1.13

Paquette and co-workers published in an alternative route also in 1986, utilising a Skatterböl rearrangement which provided **1.25** in 42 % over 4 steps.[19]



Scheme 1.14

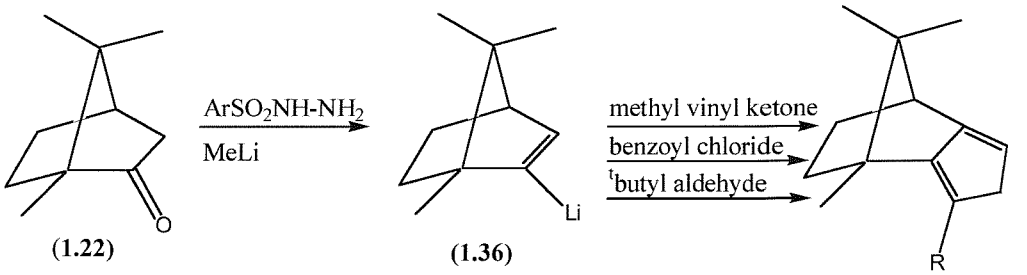
The increased efficiency of this route was compromised by the high costs associated with some of the reagents involved and so a modification of Vollhardt's original method by Paquette has been found to be the most practical. In this modified route the formation of the Wadsworth-Emmons-type compound **1.27** occurred in one step rather than two. After that the route is the same as scheme **1.13**.[20]



Scheme 1.15

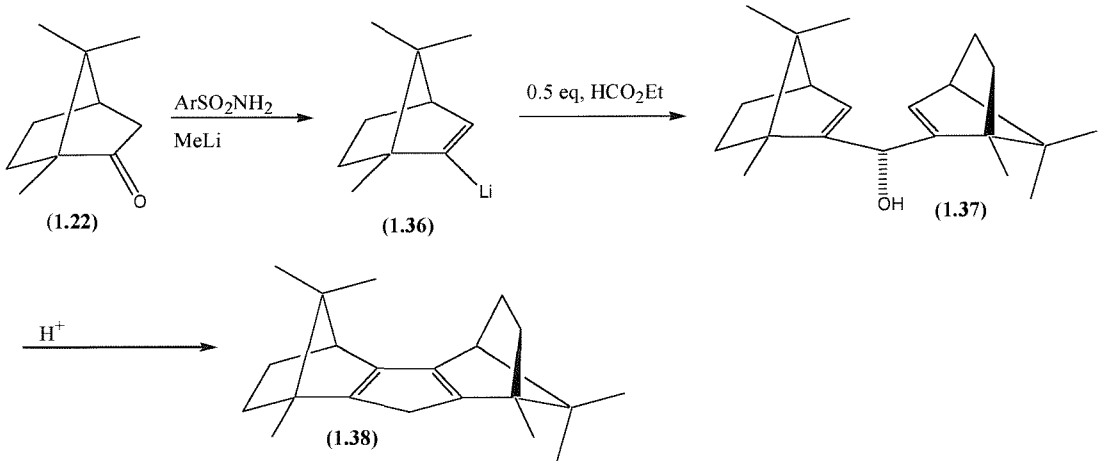
1.2.1.2 Camphor Derived Cp's with a Higher Degree of Substitution.

Ligand **1.25** is effectively a disubstituted cyclopentadiene and is unlikely to induce high enantioselectivities upon complexation. Therefore further substitution is necessary and further developing his own work with Vollhardt, Halterman reported the synthesis of three trisubstituted Cp's.[10] This was achieved by lithiation of **1.22** to afford vinyl lithium **1.36** which was then treated with a variety of enone derivatives to afford ligands **1.33**, **1.34** and **1.35**.



Scheme 1.16

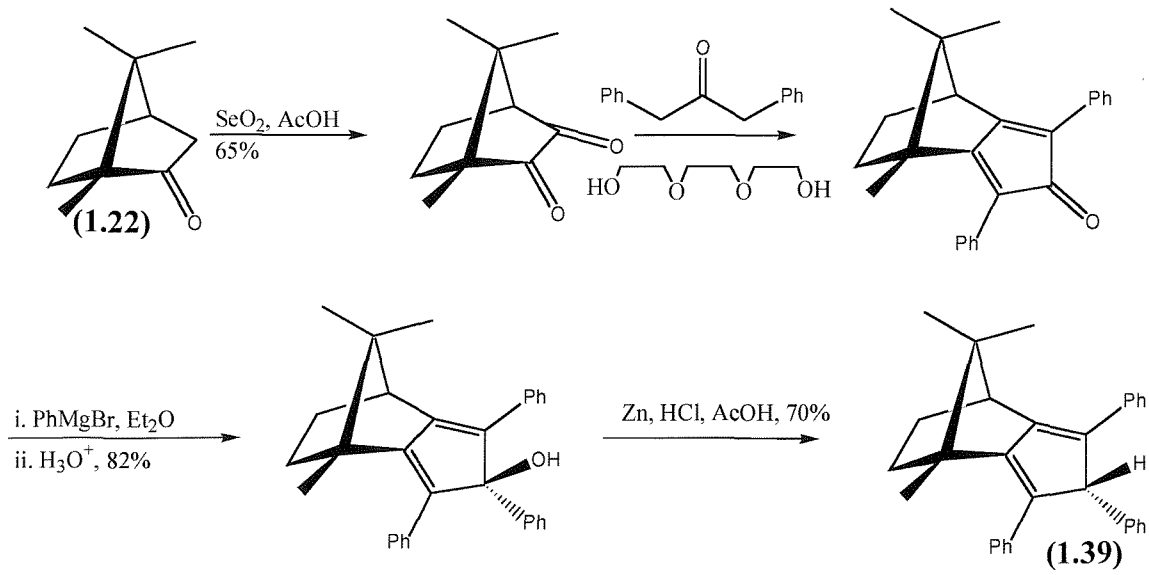
Erker has also reported the synthesis of a camphor-derived ligand with a higher degree of substitution, and its synthesis also makes use of vinyl lithium species **1.36**.[21] In this case dibornacyclopentadiene ligand **1.38** was prepared in a high yield (80%), by first treating the lithium species with half an equivalent of ethyl formate and then exposing it to forcing Nazarov cyclisation conditions to effect ring closure.



Scheme 1.17

The advantage of Cp **1.38** is that it has homotopic faces so upon complexation it would give rise to a single diastereoisomer only. The disadvantage however is that when complexation was attempted only the half sandwich monocyclopentadienyl zirconium species could be formed, probably as a result of the severe steric congestion.[21,22]

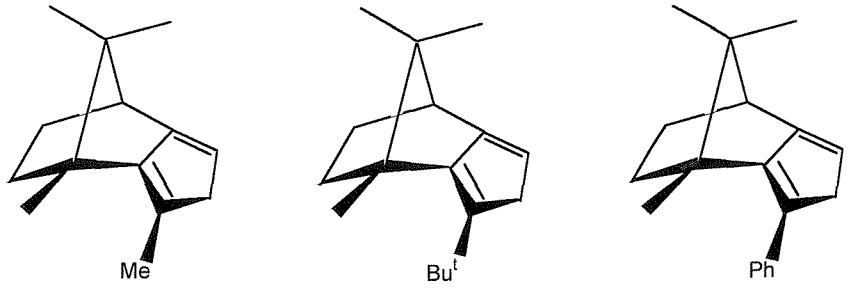
A penta-substituted camphor based system has been synthesised by White and has been complexed to rhodium. Cp **1.39** is synthesised from camphor in an overall yield of 20%.[23]



Scheme 1.18

1.2.1.3 Synthesis of Metallocenes Based on Camphor.

Halterman has reported the complexation of ligands **1.33, 1.34** and **1.8** to zirconium and titanium.[10]

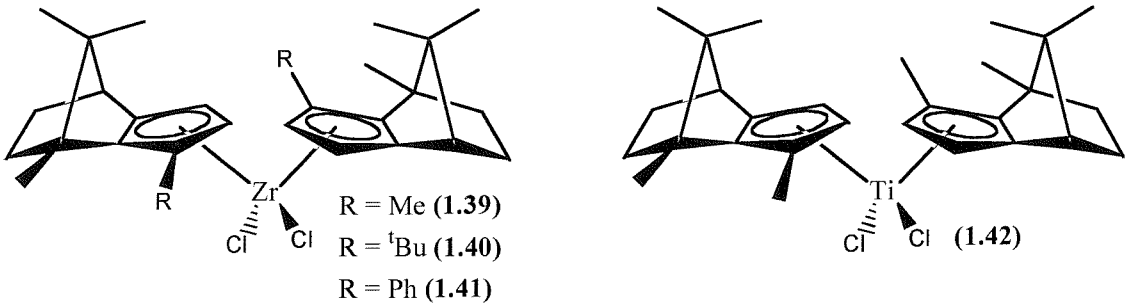


(1.33) **(1.34)** **(1.8)**

Scheme 1.19

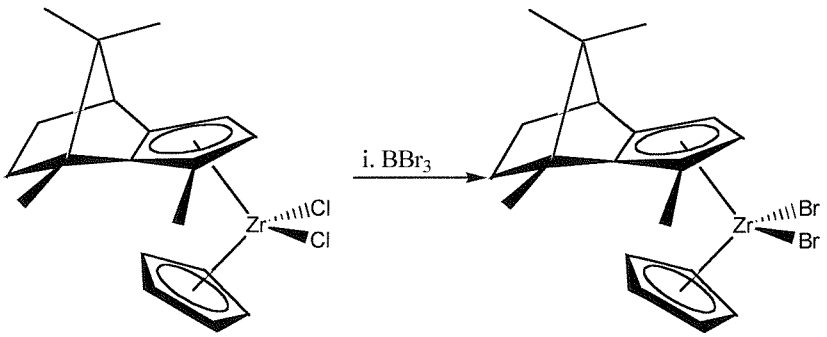
With all three ligands, successful formation of C_2-symmetric zirconium complexes **1.39**, **1.40** and **1.41** was reported. Zirconium complex **1.39** was formed as a single diastereoiosmer. Cp-butyl complex **1.40** was formed as a mixture of compounds and was isolated in a low yield after tritruation in hexane. Finally Cp-phenyl complex **1.41** was formed as a 6:1 mixture of diastereoisomers again in low yield. Attempts to form the corresponding titanium complexes were less successful, with **1.33** successfully converted to

the corresponding titanocene **1.42,** as 9:1 ratio of the C_1- and C_2-symmetric compounds, separable via recrystallisation in hexane.



Scheme 1.20

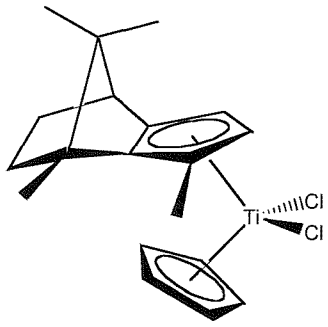
Green and Whitby have recently investigated C_1-symmetric metallocenes, synthesised by successfully reacting **1.33**, **1.34** and **1.38** with $CpTiCl_3$ and $CpZrCl_3$, for use as enantioselective catalysts.[24] Cp-methyl complex **1.43** was synthesised in 55% yield as a 4:1 mixture of diastereomers that were inseparable by recrystallisation. It was assumed that co-crystallisation of the diastereomers was occurring, so in order to encourage differentiation by recrystallisation, the corresponding dibromide complex **1.44** was also synthesised by reacting **1.43** with boron tribromide. Resulting complex **1.44** was formed as a 20:1 mixture of diastereomers with enrichment occurring without recrystallisation. This ratio was not improved when **1.44** was recrystallised, suggesting that co-crystallisation was still occurring. The overall yield for the formation of **1.44** was 40%.



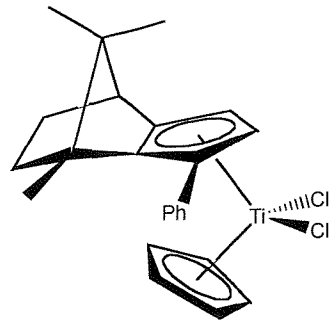
(1.43) **(1.44)**

Scheme 1.21

Ligands **1.32** and **1.34** were complexed to $CpTiCl_3$ according to the protocol developed by Paquette.[20] Phenyl titanium Complex **1.45** was formed as a 10:1 mixture of diastereoisomers in a 23% isolated yield and methyl titanium complex **1.46** as a single diastereoisomer in 20 % yield. Instead of recrystallisation, column chromatography on silica proved to be the best way of isolating analytically pure material. In both cases the endo-isomer given below was the major constituent.



(1.45)



(1.46)

Scheme 1.22

1.2.1.4 Catalytic Screening Results.

Complexes **1.43, 1.44, 1.45 and 1.46** have all been screened by Green and Whitby as to their efficacy as catalysts in ethylmagnesiation reactions, hydrogenation and hydrosilylation reactions. The best results are summarised below.[24]

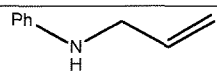
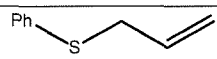
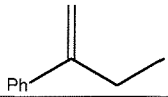
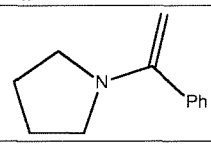
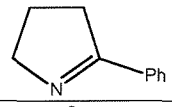
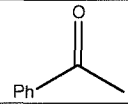
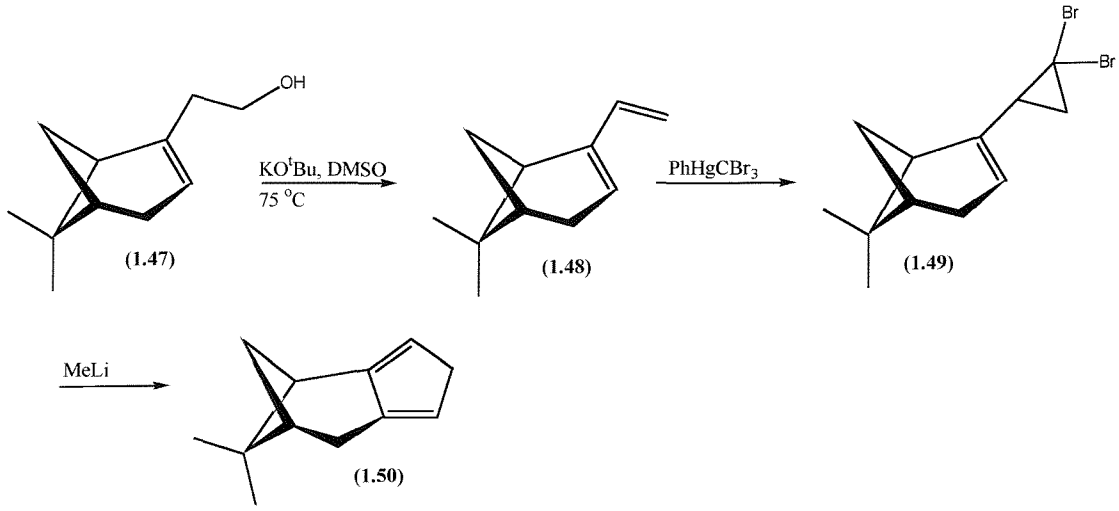
Reaction	Substrate	Highest e.e. %	Complex
ethlymagnesiation		30	**1.43**
ethlymagnesiation		17	**L.43**
hydrogenation		18	**1.46**
hydrogenation		34	**1.45**
hydrogenation		0	N/A
hydrosilylation		0	N/A

Table 1.1

1.2.1.5 Disubstituted Ligands Derived from Pinene.

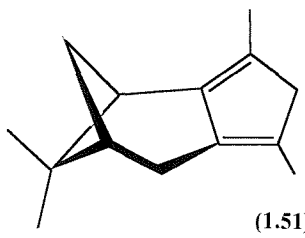
Paquette has reported the synthesis of pinene **1.23**[19] and verbenone-derived **1.24** ligands.[25] Pinene derived ligand **1.50** is synthesised from commercially available (1*R*)-(-)-nopol **1.47**. Formation of nopadiene **1.48** is then followed by cyclopropanation of the least substituted double bond to afford intermediate **1.49**, and this is then set up for the Skatterbol rearrangement by the addition of MeLi, to provide Cp **1.50**, in an 80% overall yield from nopadiene **1.48**.



(1.47) (1.48) (1.49) (1.50)

Scheme 1.23.

1.2.1.6 Pinene Derived Cp's with a Higher Degree of Substitution.



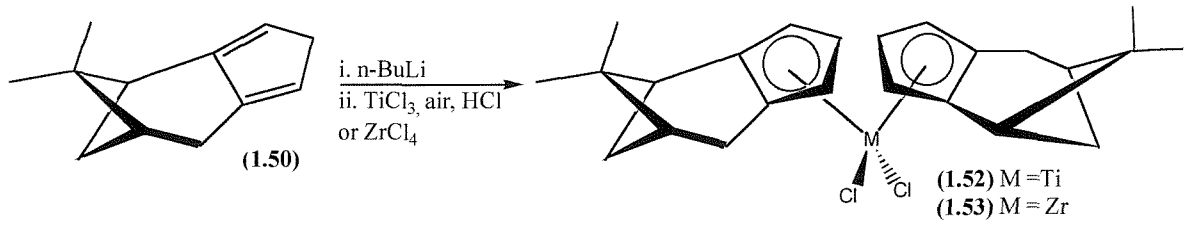
(1.51)

Other variations of pinene ligands have also been synthesised: Negishi and co-workers produced bis methyl Cp **1.51**, in five steps from pinene.[26]

1.2.1.7 Metallocenes from Pinene Derived Ligands.

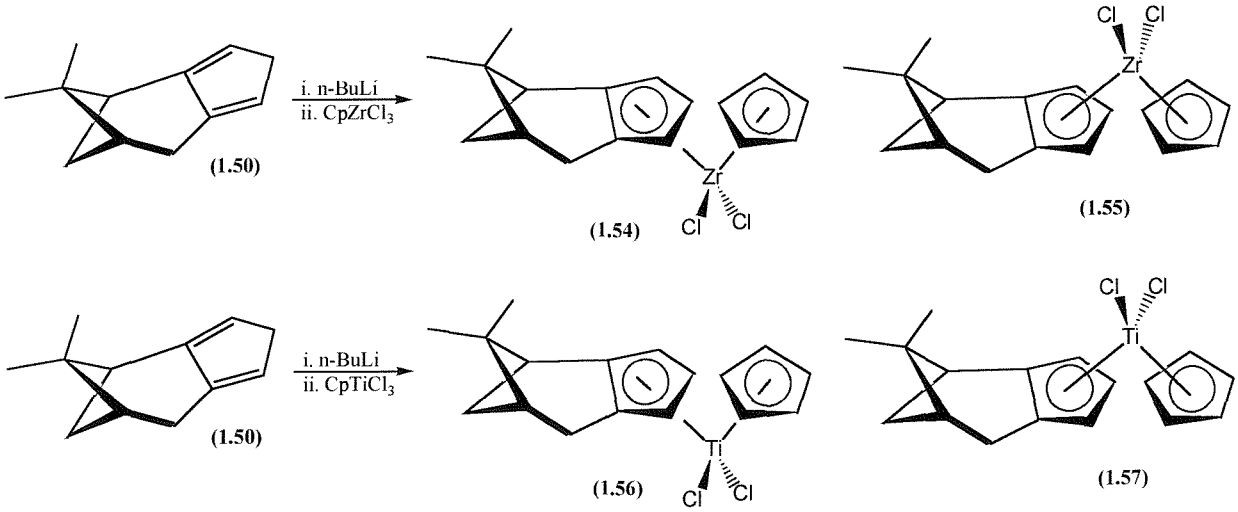
Paquette and co-workers performed extensive studies into the complexation of ligand **1.50** to a variety of metal sources and in particular into how facial selectivity could be controlled

by varying the temperature of the metallation reaction. When complexed to $TiCl_3$, $ZrCl_4$ or $TiCl_4$ complexation was exclusively to the bottom face irrespective of temperature, giving rise to metallocenes **1.52** and **1.56**.[19,20]



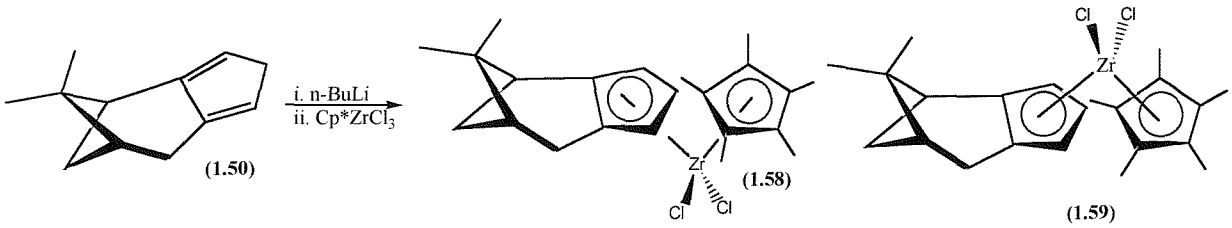
Scheme 1.24

Reaction of the ligand with $CpZrCl_3$ at –78 °C followed by heating at 60°C also lead to complexation exclusively from the bottom face to give complex **1.54**, but when the initial mixing of reagents was carried out at room temperature instead, selectivity was reversed with a ratio of 1:3.5 in favour of **1.55,** the product formed as a result of complexation from the top face. The opposite effect was observed when metallation with $CpTiCl_3$ was carried out. Using the low temperature protocol a 1:5 ratio of **1.56** to **1.57** was seen, but this was reversed to a 3:1 ratio when room temperature conditions were used.[20]



Scheme 1.25

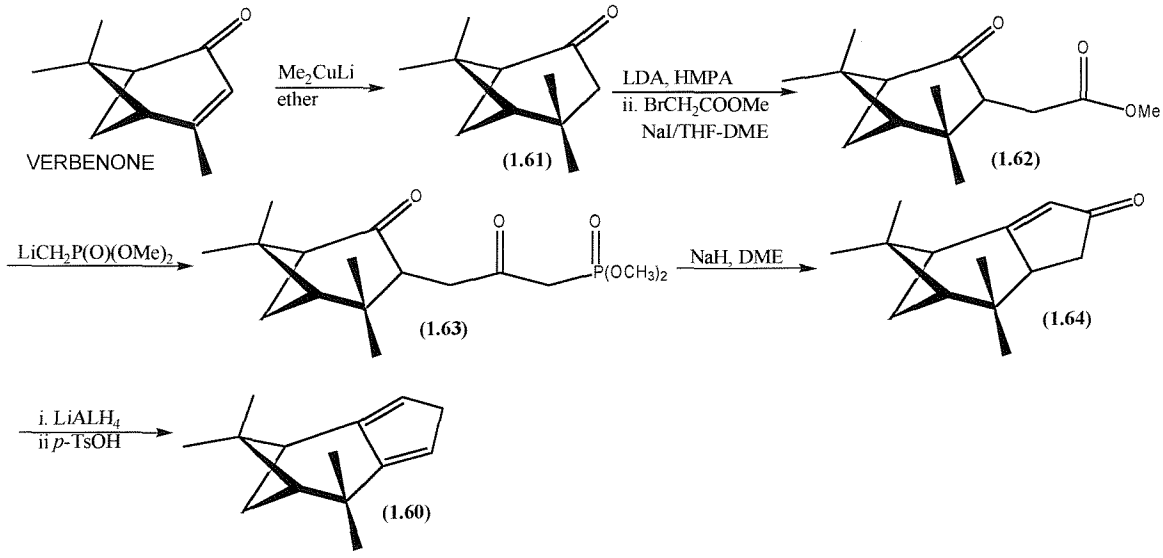
When Cp^*ZrCl_3 was employed in this reaction the ratio of products was the same regardless of the reaction conditions, with the reaction affording a 2:1 ratio of **1.58** and **1.59**.[19]



Scheme 1.26

1.2.1.8 Disubstituted Ligands Derived from verbenone.

The verbenone-derived ligand **1.60** was prepared by the conjugate addition of a methyl group to enantiomerically enriched verbenone **1.24**.[25] The same cyclopentanulation procedure as shown in scheme **1.13** was employed to provide the desired Cp ligand.

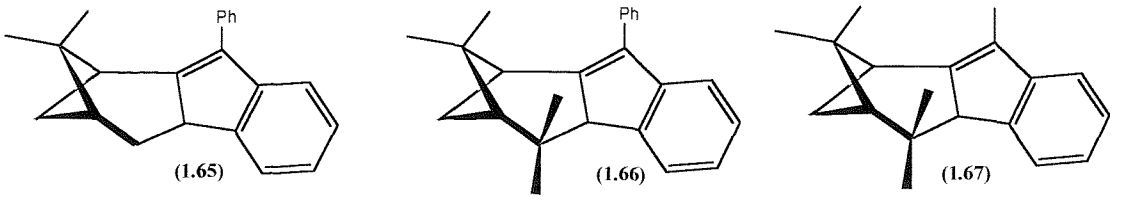


Scheme 1.27.

1.2.1.9 Verbenone Derived Cp's with a Higher Degree of Cp Substitution.

Sowa and Liu have further elaborated the verbenone systems to produce several indenyl systems, again utilising Shapiro and Nazarov methodologies as developed by Haltermann, to accomplish the synthesis of the desired Cp ligand products. The hydrazones of verbenone, and nopinone were prepared and then condensed with acetophenone or

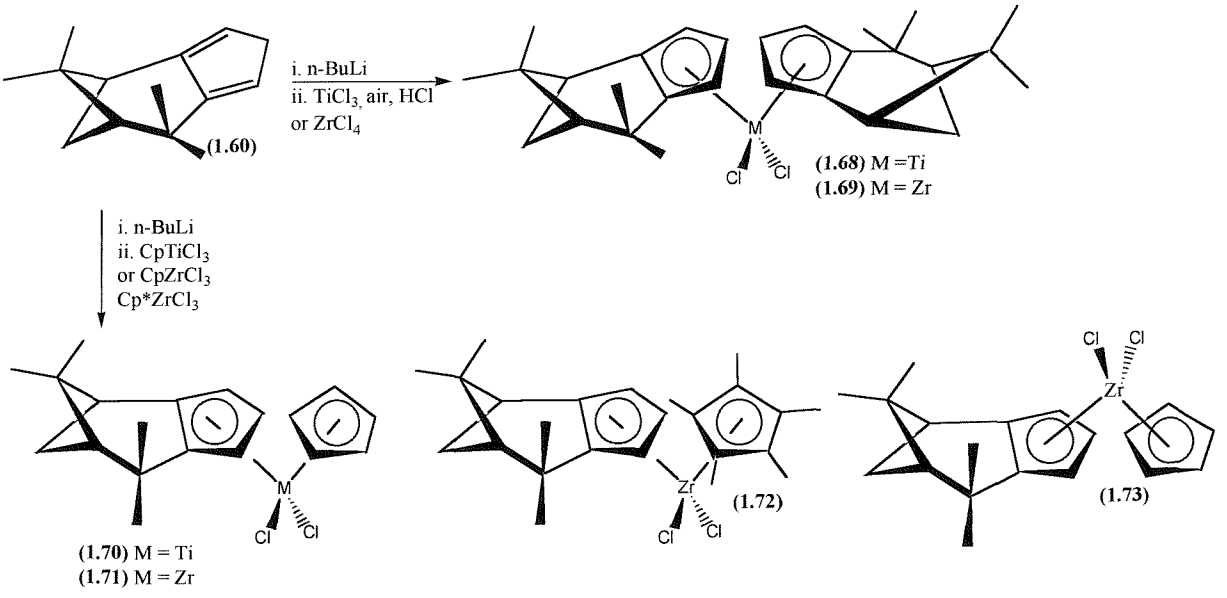
benzophenone to afford the dienol products. Electrocyclisation under acidic conditions furnished the indenyl ligands **1.65, 1.66** and **1.67** in good yields.[27]



Scheme 1.28.

1.2.2.10 Metallocenes from Verbenone Derived Ligands.

Verbenone ligand **1.60** was complexed to $TiCl_3$, $ZrCl_4$, $CpZrCl_3$, $CpTiCl_3$ and $(Me_5Cp)ZrCl_3$. In all but the case of $CpZrCl_3$ where a mixture of isomers was formed, metallation was exclusive to the bottom face, giving rise to metallocenes **1.68 – 1.73**.[25]

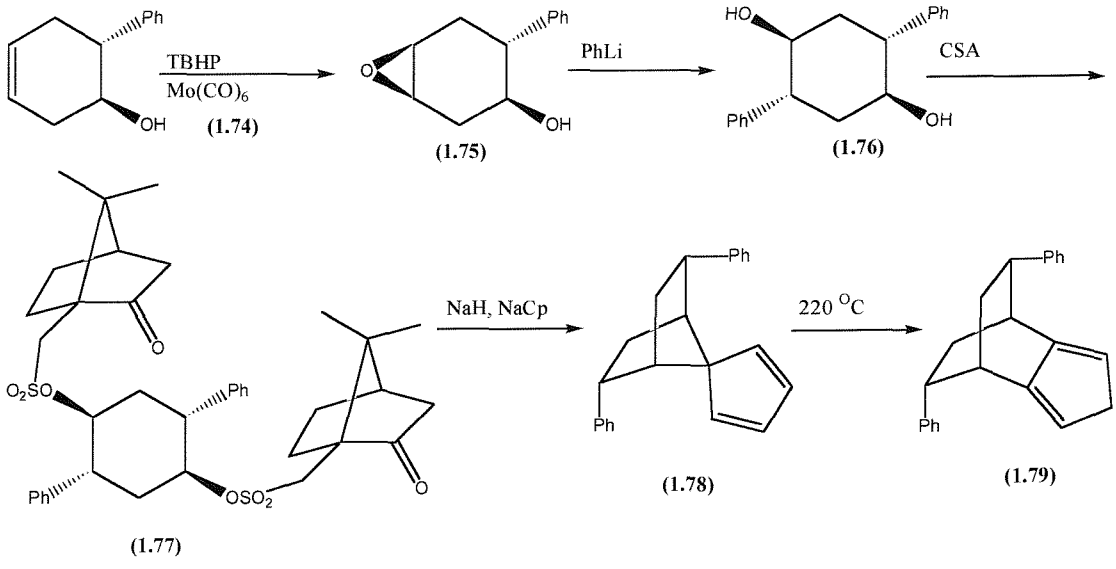


Scheme1.29

1.2.2 Chiral Ligands and Metallocenes Based on Unnatural Starting Materials.

1.2.2.1 C_2-symmetric Ligands Based on Bicyclo[2.2.2]octane.

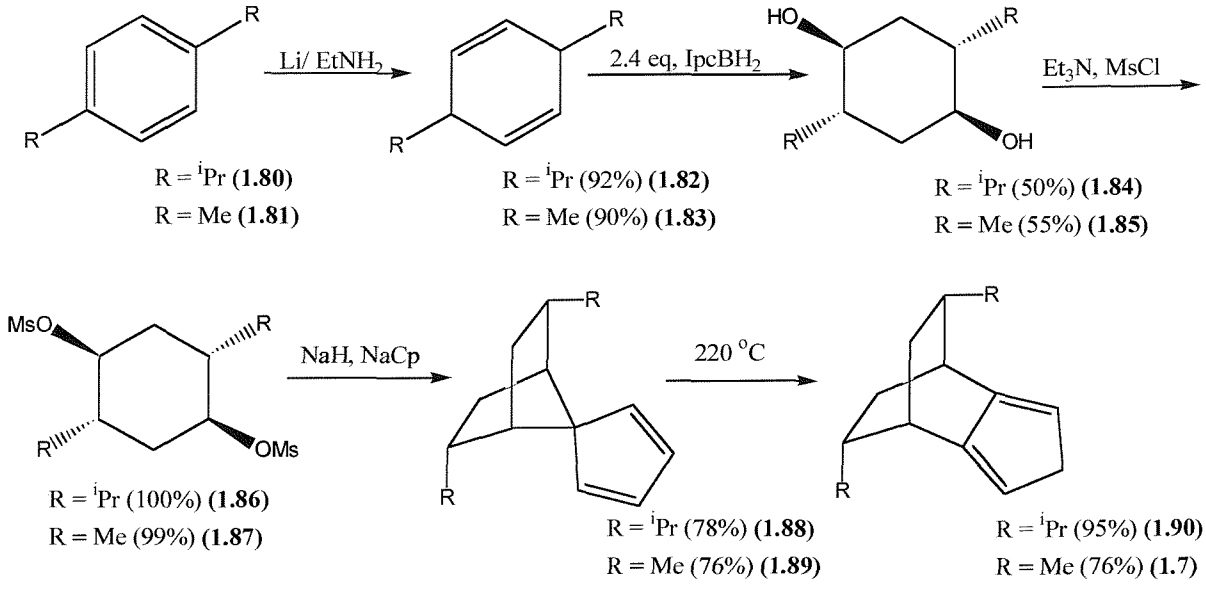
Halterman has developed a class of enantiomerically pure C_2-symmetric annulated Cp ligands with homotopic faces, from achiral starting materials unknown in nature, with chiral information held close to the Cp ring.[11,28,29] Unfortunately the synthetic route to these compounds is demanding and is not suitable for large-scale synthesis. First, cyclohexenol **1.74** was epoxidised to afford epoxide **1.75**, which was then regeoselectively opened to afford key intermediate cyclohexadiol **1.76**. Conversion of **1.77** to the bis camphor sulphonate ester **1.78** gave a mixture of two diastereoisomers that required resolution by column chromatography. The enriched (+) or (-) sulphonate ester was then deprotonated with sodium hydride and quenched with sodium cyclopentadienide to provide the corresponding spirocycle **1.78**, which underwent a thermal sigmatropic rearrangement at 220 °C to produce desired Cp ligand **1.79**.[28]



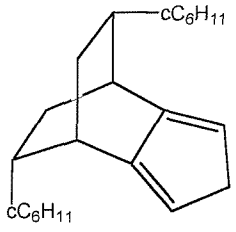
Scheme 1.30

A different route enabled the synthesis of the methyl **1.7** and isopropyl (**1.90**) analogues of **1.79**.[11,29] The avoidance of purification by separation of diastereiosmers is a highly advantageous aspect of this approach. By establishing asymmetry early in the route, the key intermediates were formed with e.e.'s often in excess of 95%, and thus a high degree of chiral purity was passed down the route: A modified Birch reduction of the 1,4-diisopropyl and 1,4- dimethylbenzenes **1.80** and **1.81** is followed by exposure to pinene based monoisopinocamphenylborane to afford bis diols **1.84** and **1.85**, which are then mesylated.

The two mesylate groups on each variant were then displaced by a single equivalent of sodium cyclopentadienide in the presence of excess base to give spiro compounds **1.88** and **1.89.** Thermal sigmatropic rearrangement of the spirocycles afforded the corresponding desired Cp's **1.90** and **1.7** in overall yields of 34% and 28% respectively.



Scheme 1.31

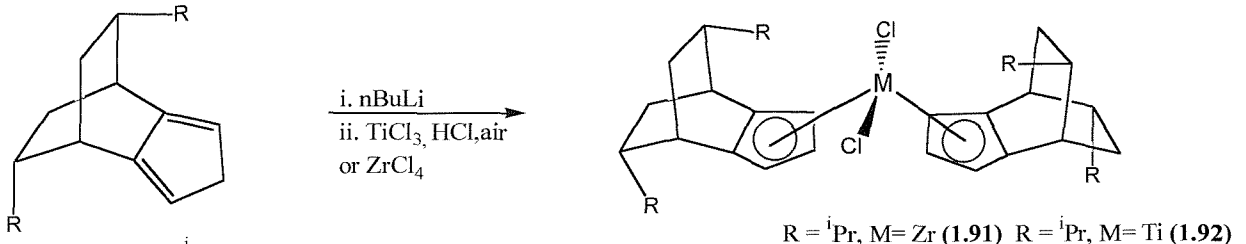


(1.91)

Gathergood and Whitby have prepared cyclohexyl derivative **1.91** on a large scale by modifying Halterman's approach, although separation of diastereoisomers by column chromatography is still required to achieve purification.[30]

1.2.2.2 Metallocenes from Bicyclo[2.2.2]octane Derived Ligands.

Halterman has used **1.79**, **1.90** and **1.7** as ligands in the synthesis of a variety of novel metallocenes, with the C_2-symmetric titanocenes and zirconocenes being the most relevant to this project. Each was synthesised by treating the anion of the ligand with either $TiCl_3$ followed by HCl/air oxidation of the product or with $ZrCl_4$.[11,28,29]



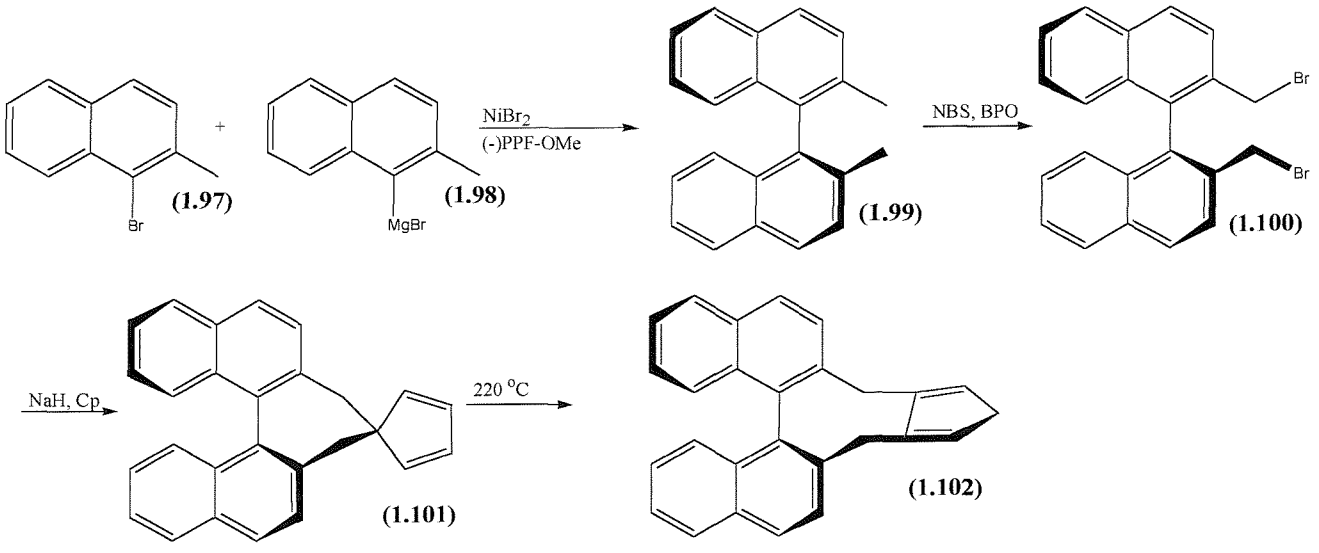
R = ^{i}Pr (**1.90**)
R = Me (**1.7**)
R = Ph (**1.79**)

R = ^{i}Pr, M= Zr (**1.91**) R = ^{i}Pr, M= Ti (**1.92**)
R = Ph, M= Zr (**1.93**) R = Ph, M= Ti (**1.94**)
R = Me, M= Zr (**1.95**) R = Me, M= Ti (**1.96**)

Scheme 1.32

1.2.2.3 C_2-symmetric Ligands Based on a Binapthyl System.

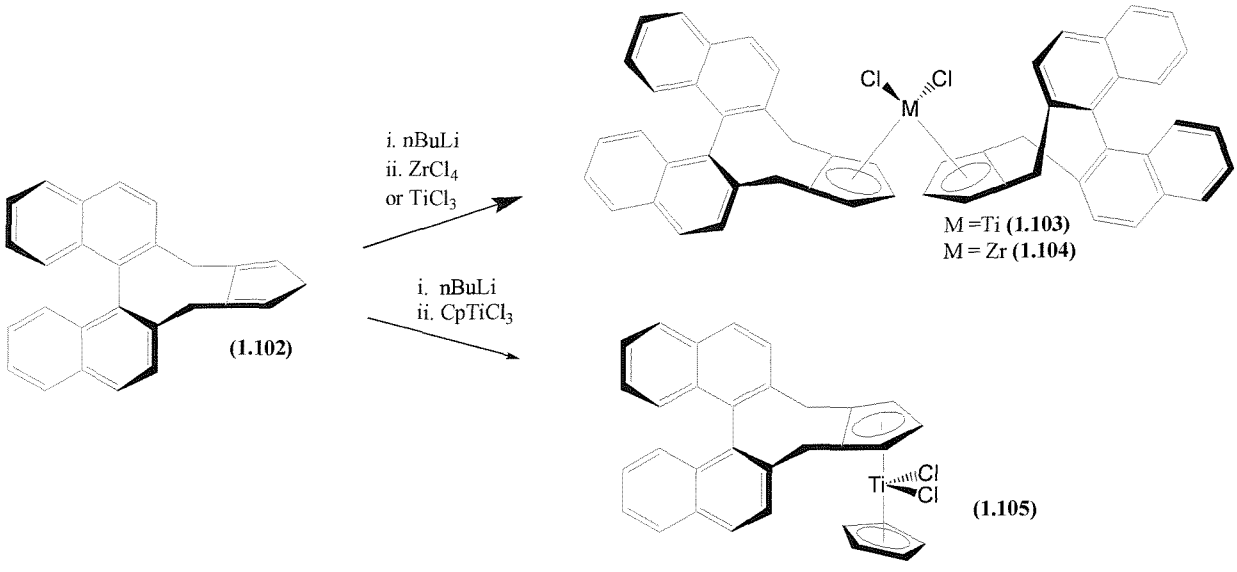
Halterman has also developed a binapthyl-based system.[31] The most efficient route to this compound was based on a highly enantioselective nickel-catalysed coupling of 1-bromo-2-methylnaphthalene **1.97** to its Grignard derivative **1.98** in the presence of chiral phosphine PPF-OMe.[32] Dibromide **1.100** was prepared by NBS bromination of dimethyl compound **1.99** and was then itself alkylated by displacement of both bromide moieties by a single Cp to afford spirocycle **1.101**. This spirocycle was then thermolysed at 220 °C to effect the same sigmatropic rearrangement as shown in schemes **1.23** and **1.24**, to furnish Cp **1.102** in an overall yield of 30% from **1.99**.



Scheme 1.33

1.2.2.4 Metallocenes from the Binaphthyl Derived System.

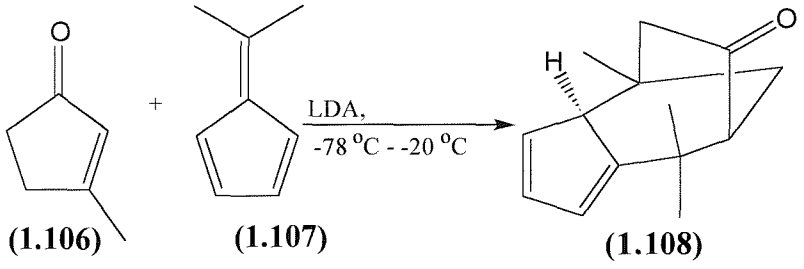
The binapthyldimethylenecyclopentadiene ligand **1.102** first published by Halterman has been used to form titanocene and zirconocene dichlorides.[31,33] Treatment of the anion with either $TiCl_3$ followed by an HCl/air oxidative work up or $ZrCl_4$ gave the corresponding metallocene dichlorides **1.103** and **1.104** as single C_2-symmetric isomers. Treatment with $CpTiCl_3$ gave a titanocene with one chiral Cp ligand attached **1.105.**



Scheme 1.34

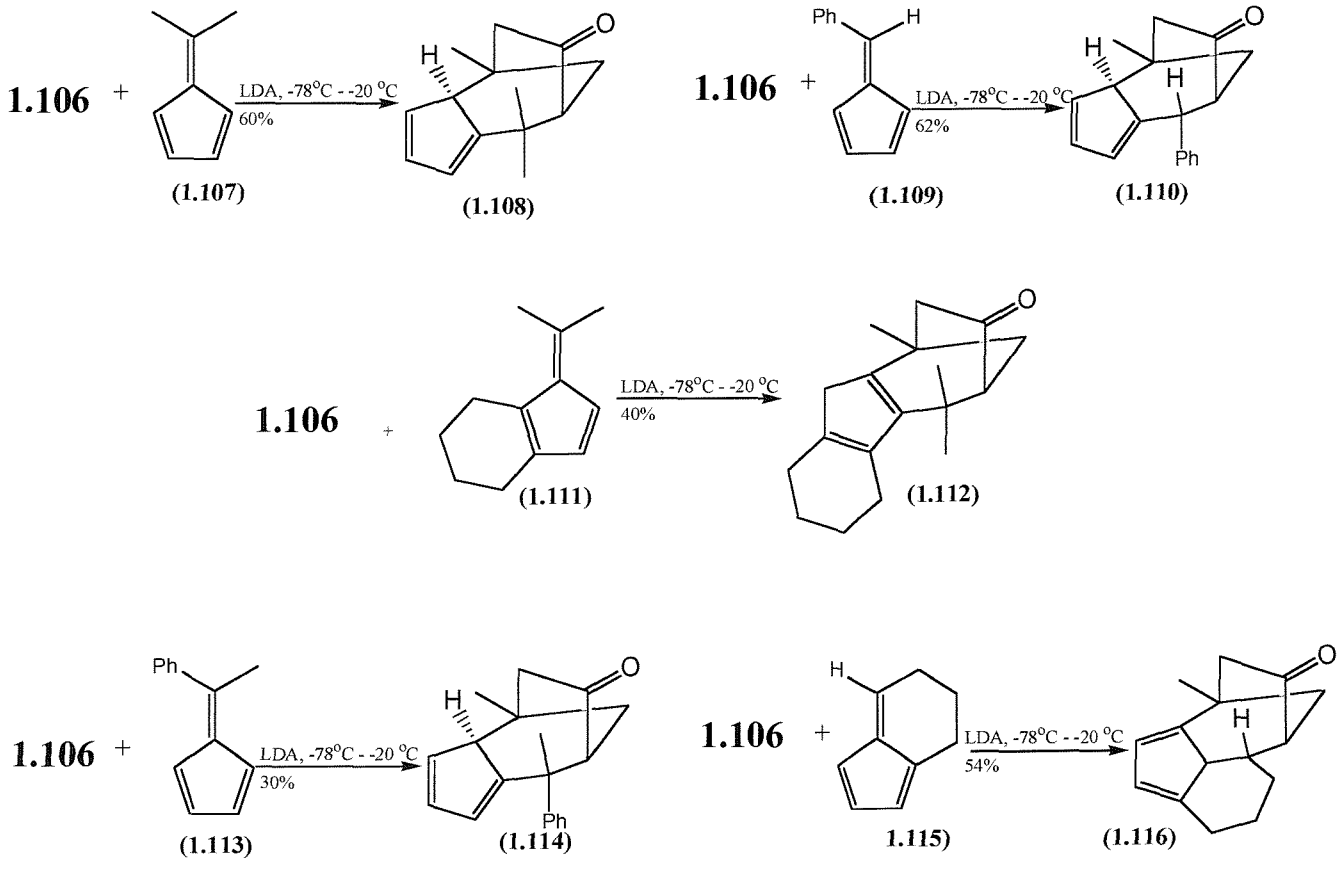
1.2.2.5 A Non-C_2-symmetric Ligand System Based on Unnatural Starting Materials.

Hong and Hong have published a series of Cp compounds based on the double Michael reaction reaction between dimethylfulvene and a variety of cyclopentenones. In the example below 3-methylcyclopentenone **1.106** is reacted with fulvene **1.107** to provide the resulting Cp ligand **1.108** diastereomerically pure, but as a mixture of enantiomers.[34]



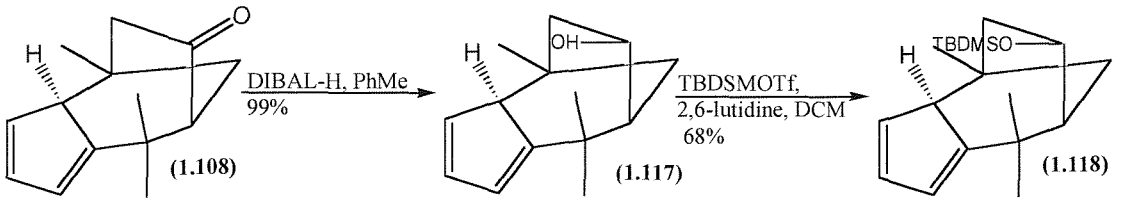
Scheme 1.35

Green and Whitby further developed this series of Cp ligands by varying the fulvene component of the reaction.[24] Scheme **1.36** shows some of the results: The fulvenes were generally prepared from freshly cracked cyclopentadiene and a variety of aldehydes and ketones prepared according to the method of Stone and Little.[35]



Scheme 1.36

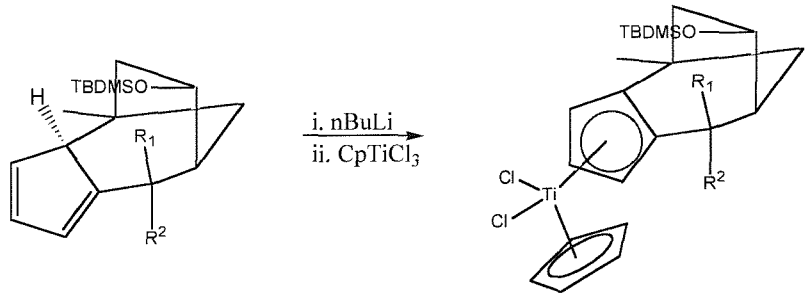
Although suitable for complexation with rhodium trichloride, the ketone functionality of the above ligands is not tolerated during complexation to titanium and zirconium and so further derivatisation was required before this could be attempted. In each case diastereoselective reduction of the ketone with Dibal-H was performed to give the corresponding alcohol, which was then silylated with TBDMSOTf in the presence of 2,6-lutidine. Scheme **1.37** shows a simple example.[24]



Scheme 1.37

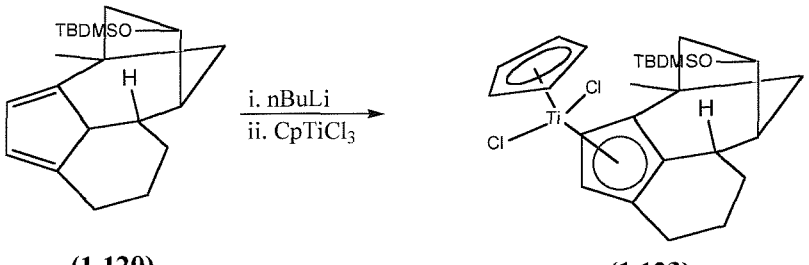
1.2.2.6 Metallocenes Based on the Double Michael Derived System.

Green and Whitby have complexed a number of the above double Michael derived Cp ligands to titanium, zirconium and rhodium. Titanocenes **1.121**, **1.122** and **1.123** were all generated from the reaction between the Cp anion of the silylated Cp ligands **1.118**, **1.119** and **1.120** and cyclopentadienyl titanium trichloride.[24]



R_1 = Me, R_2 = Me **(1.118)**
R_2 = H, R_2 = Ph, **(1.117)**

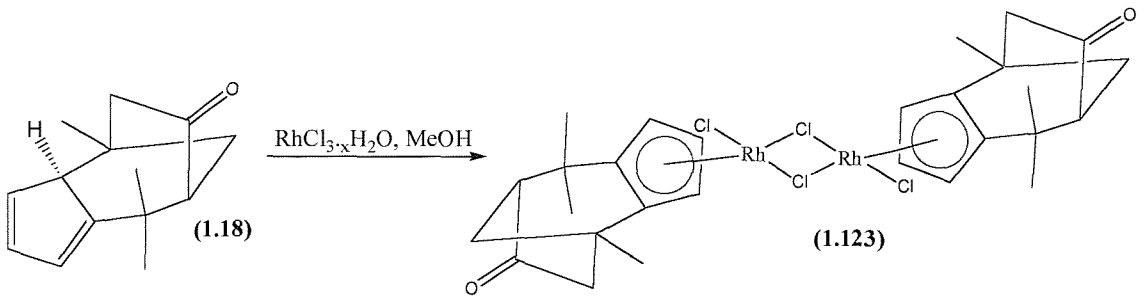
R_1 = Me, R_2 = Me, 20%, **(1.121)**
R_2 = H, R_2 = Ph, 26% **(1.122)**



(1.120) **(1.123)**

Scheme 1.38

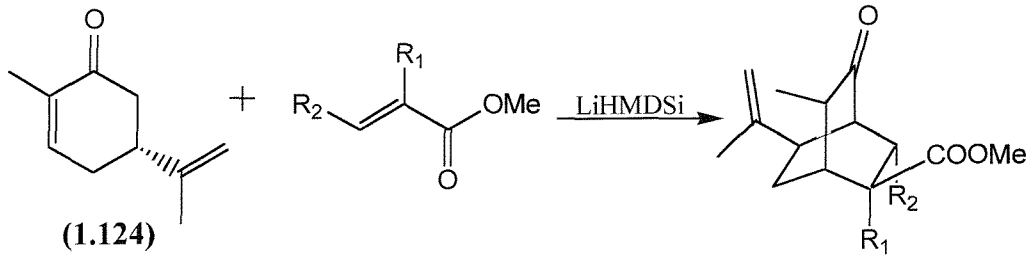
Refluxing ligand **1.118** with hydrated rhodium trichloride in the presence of MeOH gave rhodium complex **1.123** in a 63% yield.[24]



Scheme 1.39

1.2.2.7 Developing Enantiomerically Pure Ligands Based on the Double Michael Derived System.

Although potentially useful, this ligand system was handicapped by the lack of enantio-control necessarily arising from two achiral starting materials Developing enantiomerically pure ligands based on this double Michael reaction was originally investigated by Whitby and Green. In 1990 Wu and co-workers prepared a series of bicyclo[2.2.2]octane derivatives with high diastereoselectivity from the double Michael addition reaction of carvone **1.124** with α,β-unsaturated esters. This allowed facile access to enantio-pure compounds such as **1.125** and was subsequently applied to the chiral synthesis of natural products.[36,37]

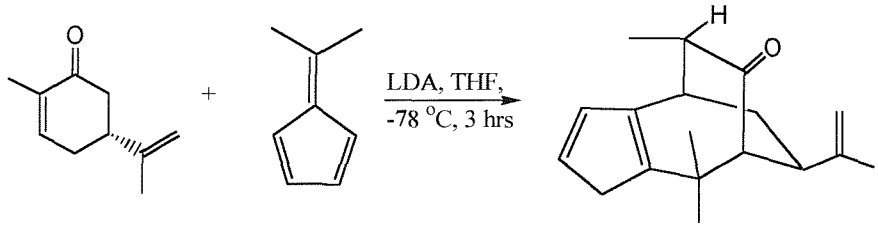


(1.125)

Scheme 1.40

By applying carvone, a naturally occurring chiral 6-membered cyclopentenone, instead of flat 5-membered cyclopentenone **1.106** to Hong's double Michael reaction Green and Whitby hoped that the outcome would be a Cp ligand with a degree of enantiocontrol similar to that observed by Wu and co-workers.

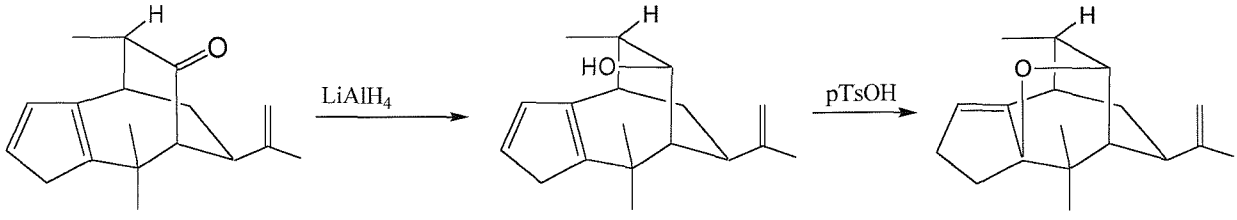
Treatment of carvone, **1.124**, with LDA followed by addition of 6,6-dimethylfulvene, **1.107**, furnished the desired product as a mixture of two Cp double bond isomers, which converted to a single thermodynamically stable isomer **1.126** during storage at 5 °C.



(1.124) **(1.107)** **(1.126)**

Scheme1.41

Thus a novel enantiomerically pure Cp ligand containing 3 new chiral centres was prepared from cheap commercially available starting materials in one step. In common with racemic ligands **1.108**, **1.118**, **1.112**, **1.114**, and **1.116,** ketone **1.126** was reduced to alcohol **1.127.** During preparation of alcohol **1.127** decomposition product **1.128** was discovered to have formed after **1.127** was left in an NMR tube for 5 days. Further investigation revealed **1.128** to be a furan formed by the acid catalysed ring closure of alcohol **1.127**. The formation of this product has been repeated deliberately, using p-TsOH as the catalyst.[24]

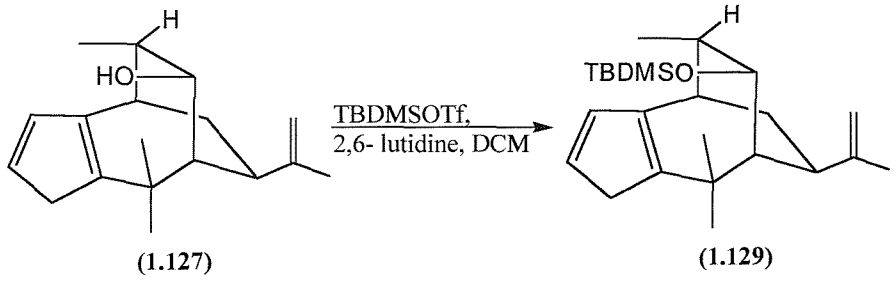


(1.126) **(1.127)** **(1.128)**

Scheme 1.42

Storage of alcohol **1.127** in base washed glassware was found to sufficient to prevent furan formation, enabling TBDMS ether **1.129** to be successfully prepared using the conditions shown in scheme **1.40**. As stated earlier the formation of the TBDMS ether is necessary to allow the formation of titanocene and zirconocene complexes, as the presence of ketone

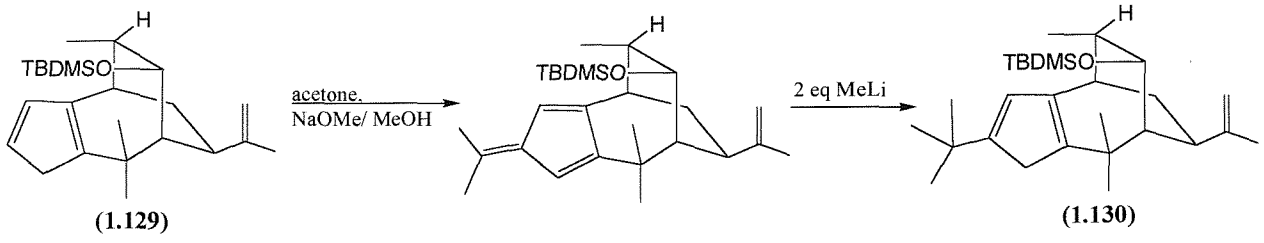
and alcohol moieties in Cp ligands is not tolerated for complexation to titanium and zirconium.



(1.127) (1.129)

Scheme 1.43

Although the above Cp ligands were produced enantiomerically pure and very efficiently, in terms of the design concepts discussed on page 7, it was highly unlikely that with so much steric bulk concentrated on one half of the molecule that complexes derived directly from **1.129**, would lead to catalysts capable of inducing high e.e.'s. With this in mind, ligand **1.130** was prepared from **1.129** in an overall yield of 65%.[24]



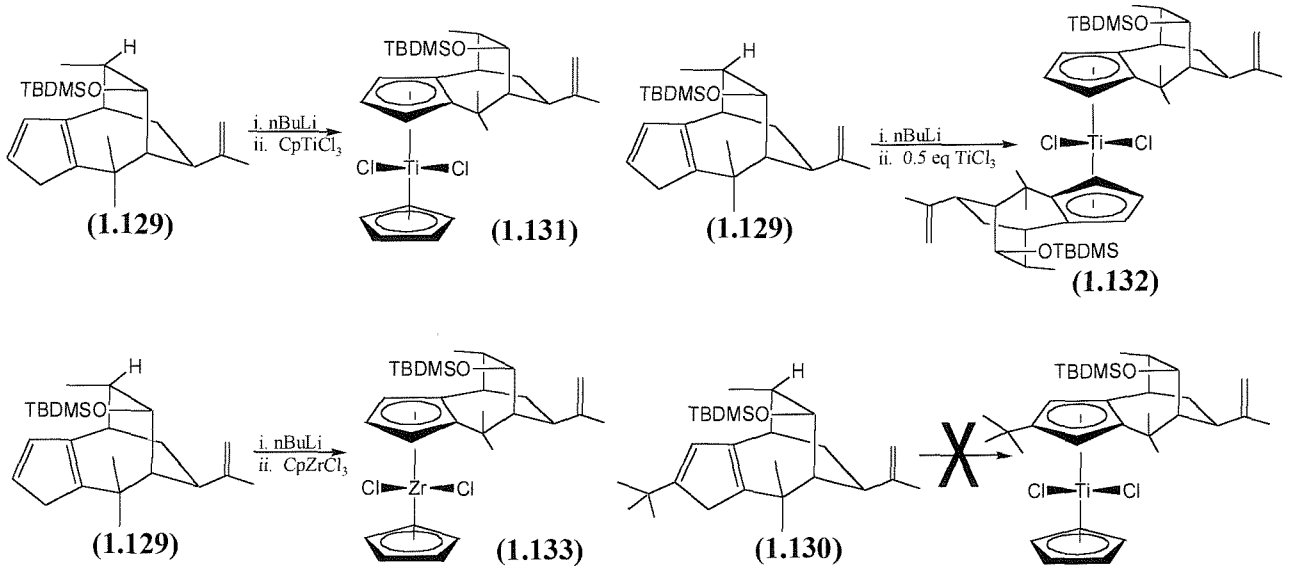
(1.129) (1.130)

Scheme 1.44

Section **1.2.2.3** showed how Green and Whitby had successfully extended the double Michael methodology to use variety of fulvenes resulting in the preparation of a number of novel Cp's. However attempts to apply this to the condensation of carvone with the fulvenes, **1.109**, **1.111**, **1.113** and **1.115** was unsuccessful with the disubstituted fulvenes **1.111** and **1.115** resulting in no products at all whilst the reaction between carvone and fulvenes **1.109** and **1.113** led to complex mixtures of products.

1.2.2.8 Complexation of Carvone Derived Ligands to Transition Metals.

Ligand **1.129** was successfully complexed to $CpTiCl_3$, $TiCl_3$ and $CpZrCl_3.2THF$ to afford metallocene compounds **1.131**, **1.132** and **1.133** with purified yields of 46%, 10% and 3% respectively. Attempts to complex ligand **1.130** were unsuccessful.[24]



Scheme 1.45

Further investigation into solving the problems of substitution and enantio-control is reported in chapter 3.

1.3 Chiral Cyclopentadienyl Metal Complexes as Catalysts.

Some applications and results have already been reported in table **1**.

1.3.1 Introduction.

The number of reactions to which chiral transition metal catalysts can be applied is ever increasing with regards to both novel enantioselective reactions and to existing reactions currently mediated under non-chiral conditions. Polymerisations,[7] carbometallations,[11,38] hydrosilation, hydroborations,[39] epoxidation, Pauson-Khand,[40] ketone reduction and aldol condensations[3,8], are typical of the processes that have been catalysed by chiral Cp

complexes. Hydrogenation, hydrosilation and carbometallation will be described below, as some of the most significant developments in chiral metallocene catalysed reactions have been concerned with these processes. In addition ketone reduction will be touched upon as this is of significance to this project.

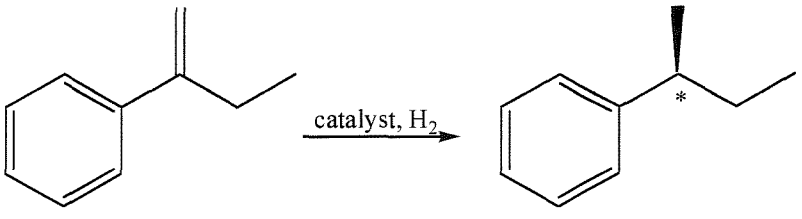
1.3.2 Hydrogenation.

This itself can be further subdivided dependant on the functional group involved:

- Hydrogenation of unfunctionalised alkenes
- Reduction of imines
- Hydrogenation of enamines

1.3.2.1 Hydrogenation of Unfunctionalised Alkenes.

Alkyl lithium/alkyl aluminium reduced Cp_2TiCl_2 is an active catalyst for the hydrogenation of alkenes.[41] In 1978 Kagan and Cesarotti developed the first enantioselctive variant of this reduction using homochiral menthyl and neomenthyl substituted titanocenes to reduce 2-phenyl-1-butene, a reaction now defined as the standard test for the evaluation of novel catalyst designs.[42,43]



Scheme 1.46

The 28% ee obtained with complex **1.134** set the benchmark for this reaction and gave rise to research into more complex annulated Cp ligands derived from natural starting materials. However the results obtained with nopol derived complex **1.52** and camphor-based complex **1.135** were disappointing with e.e's 7% and 34 % respectively. It was not until 1995 that e.e.'s of 69% and 53% respectively by were reported by Paquette using titanium complex **1.68** and its zirconium equivalent **1.69** for the reduction of 2-phenyl-1-butene.[44]

The differences between the results for titanium and zirconium are a general observation: zirconium complexes are, for the most part, less active for hydrogenation than titanium analogoues.[44,45] Another general rule is that C_2-symmetric complexes gave better enantioselectivities than C_1-symmetric analogues, and this is shown in the remarkable enantioselectivities observed by Halterman using complex **1.94**.[28,31] At room temperature a 68% e.e. was measured for the hydrogenation of 2-phenyl-1-butene, but when the reaction was repeated at –75 °C the e.e. rose to 95%.

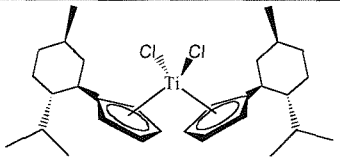
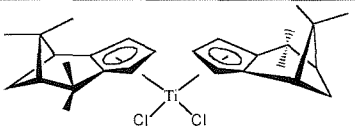
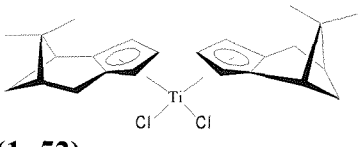
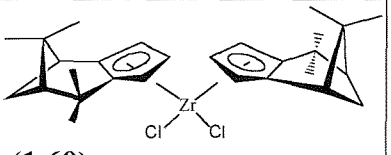
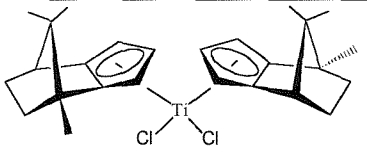
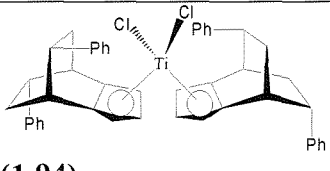
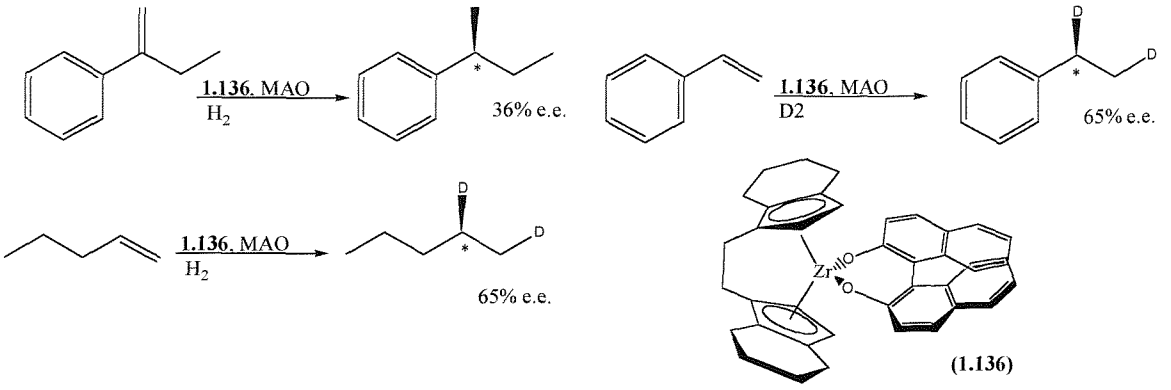
Complex	e.e.	Complex	e.e.
 **(1.134)**	28%	 **(1.68)**	69%
 **(1. 52)**	7%	 **(1.69)**	53%
 **(1.135)**	34%	 **(1.94)**	95% at –75 °C

Table 1.2

The application of complexes derived from Brintzingers original ethylene-bistetrahydroindenyl complexes to enantioselective hydrogenantion has also had great success: Waymouth and Pino have reported an e.e. of 36% for the reductive hydrogenation of 2-phenyl-1-butene, 65% ee for the deuteration of styrene and 65% for the deuteration of 1-pentene using resolved binaptholate derivative of ansa-bis(tetrahydroindenyl)zirconium dichloride **1.136** activated by methyl aluminium oxame (MAO).[7]



Scheme 1.47

Buchwald achieved the most notable success in this area with activated titanium complex **1.137**, reducing trisubstituted alkenes with observed e.e.'s ranging from 92% to >99%. However it should be noted that in each substrate the alkene is attached to a phenyl ring, i.e. the substrates most likely to give the highest e.e. due to the differing steric environments found at each end of such an olefin. A degree of functionality is tolerated with allylic amines and alcohol functionalities present in some of the substrates.[46]

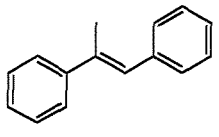
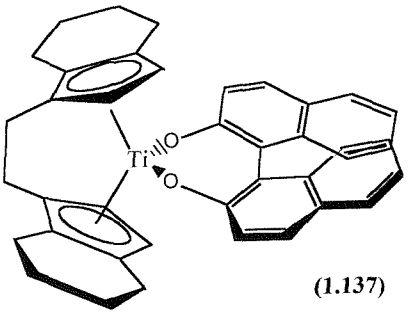
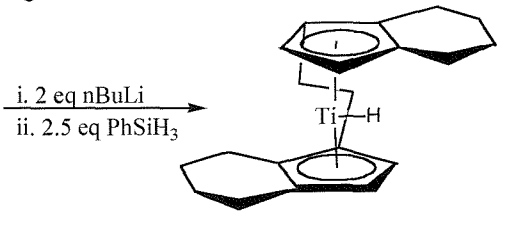
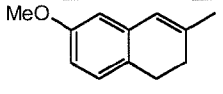
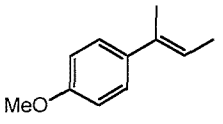
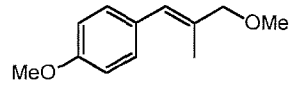
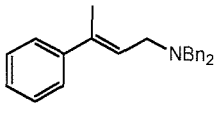
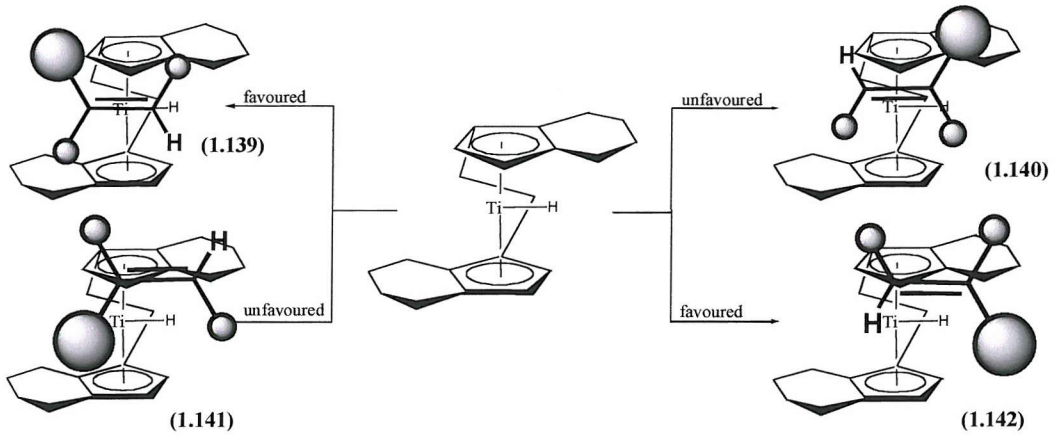
Substrate	e.e. %	Active Catalyst
	99	 (1.137)  (1.138)
	92	
	95	
	94	
	95	

Table 1.3

Buchwald found that Z-alkenes were reduced much more slowly than E-alkenes, and postulated transition states based on steric interactions in order to explain this and the high e.e.'s.



Scheme 1.48

As Scheme **1.46** shows, a steric clash occurs when the largest substituent, in this case always a phenyl ring, is orientated so that it is closest to the tetrahydroindenyl ligand as in **1.140** and **1.141**. However no such interaction occurs in **1.139** and **1.142** and therefore these approach orientations are very much favoured leading to reduction from a single enantioface and therefore high e.e.'s. The nature of the steric interaction is also altered depending on whether an *E* or *Z* alkene is present, and this explains the differing reactivity's observed for the *E* and *Z* alkenes.[46]

1.3.2.2 Reduction of Imines.

In 1992 Buchwald and Willoughby published the first early transition metal catalyst for the asymmetric hydrogenation of imines.[47] The results for such a catalyst for this function were remarkable, with chiral amines of e.e.'s up to 98% achieved using 5 mol% of resolved binaptholate titanocene **1.137** under a H_2 atmosphere of 2000 psi. Buchwald showed that cyclic imines reacted faster and generally produced amines with higher e.e.'s than acyclic imines. This is thought to be due to the acyclic imines used often being mixtures of E and Z isomers, which would tend to be reduced from opposite enantiofaces resulting in the

lower e.e.'s. Furthermore, a detailed mechanistic study by the authors has shown that the rate-determining step of the catalytic cycle for the reduction of imines with **1.137** is the hydrogenolysis of the Ti-N bond, and it has been postulated that in the case of cyclic imines this bond is more accessible to the hydrogenolysis step.[48] This would explain therefore the difference in reactivity between the cyclic and acylic imines. As a result of these findings it was discovered that cyclic imines could be reduced under a much lower pressure hydrogen atmosphere of 50 psi, with a catalyst loading of 1%.[49,50]

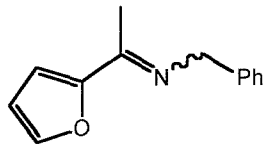
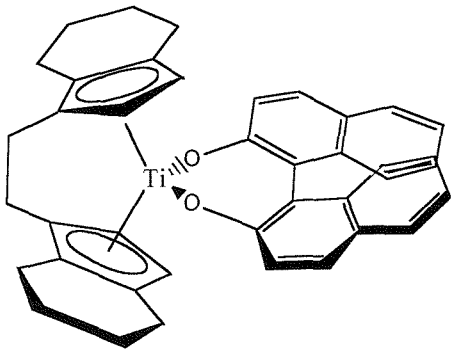
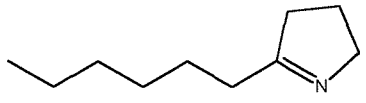
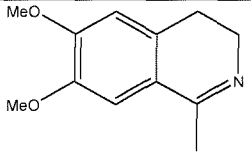
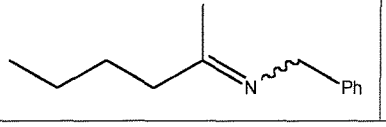
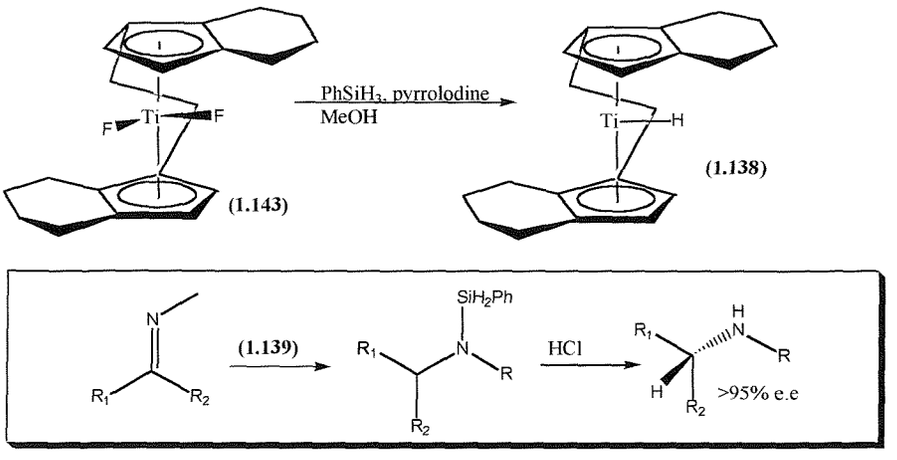
Substrate	**e.e.**	**catalyst**
	53%	
	98%	
	98%	
	58%	**(1.137)**

Table1.4

This strategy has enabled chiral amines to be produced in very high yields, both in terms of turnover and optical purity and has been futher improved by Buchwald and co-workers with the publication of a titanocene catalysed hydrosilation based imine reduction reaction.[51] The authors found that the addition of $PhSiH_3$ to ebthi-titanocene difluoride complex **1.143**, generated an active hydrosilation catalyst at room temperature, which afforded remarkable e.e.'s of 95-99% when introduced to a range of acyclic and cyclic imines for 12 hours under an argon atmosphere with loadings sometimes as low 0.02-0.1 mol%. Perhaps the most significant feature of this process is that acyclic amines are formed with enantiomeric purities on a par with those observed for cyclic examples. This is despite the acyclic imines used existing as mixtures of *E,Z* isomers, which led to a

considerable fall in the e.e.'s observed for hydrogenation catalyst **1.137.** At present there is no explanation for these results.



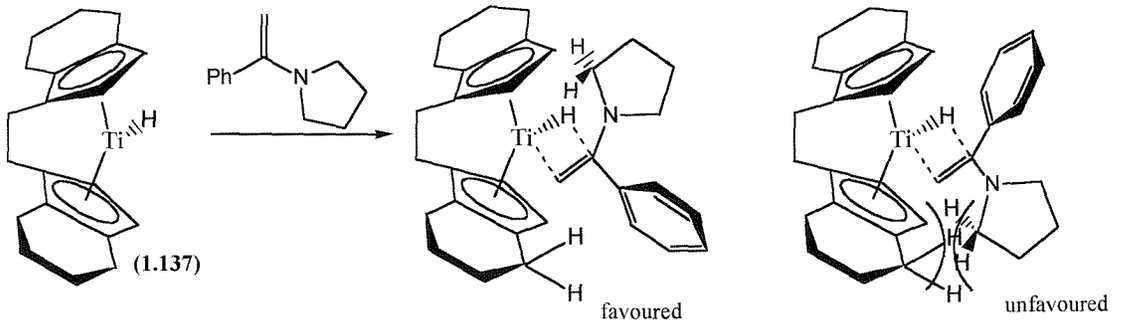
Scheme 1.49

The mechanistic cycles of both the hydrogenation and the hydrosilation catalysts are proposed to be very similar, with the origin of the stereoselectivity arising from insertion of the imine into the Ti-H bond and the rate determining step again proposed to be the hydrogenolysis of the Ti-N bond. As result of these findings Buchwald proposed that adding a nucleophilic reagent to the reaction mixture would result in an increased reaction rate. This was found to be the case when slow addition of a primary amine to the reaction mixture allowed hitherto unreactive sterically encumbered imines to be completely hydrosilated in 2 hours.[52]

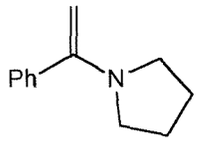
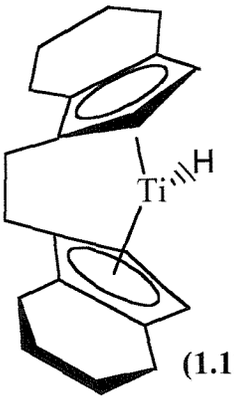
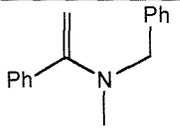
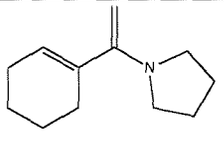
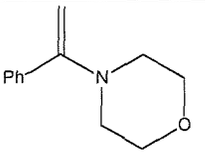
1.3.2.3 Hydrogenation of Enamines.

Buchwald and Lee have also applied titanium complex **1.137** to the asymmetric reduction of enamines, observing very high e.e.'s for the hydrogenation of prochiral α-phenyl enamines.[53] Up to 5 mol % of the catalyst is used, at 80 psi for more hindered substrates and 15 psi for other examples. For this reaction it was postulated that the origin of stereoselctivity is derived from the conformation adopted by the α-phenyl group in the proposed transition state. Buchwald suggests that the phenyl group of the substrates is

twisted out of conjugation with the alkene whilst the lone pair on the nitrogen atom remains conjugated. This leads to energy differences between the two possible transition states. In one, the most stable, a steric clash between the N,N-dialkyl substituent of the substrate and one of the tetrahydroindenyl moieties on the ligand is avoided but this clash is present in the other. This results in the favoured orientation being adopted by the substrate during each cycle and therefore hydrogenation from one enantioface.



Scheme 1.50

Substrate	e.e.	catalyst
	92%	
	96%	
	95%	
	91%	

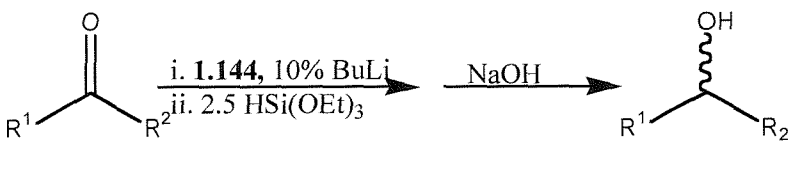
(1.137)

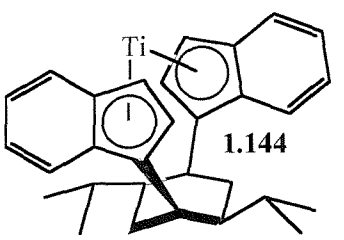
Table 1.5

1.3.3 Reduction of Ketones.

The reduction of ketones catalysed by titanocene dichloride, in the presence of alkyl magnesium bromides containing a β-hydride, was published over 20 years ago. Attempts to produce a chiral version of this reaction using chiral titanocene catalysts have so far failed with only racemic alcohols being formed.

Halterman and Chen have had limited success adapting a mild titanocene dichloride catalysed hydrosilation first reported by Buchwald. Chiral *ansa*-bis(indenyl) titanium complex **1.144** activated according to the method of Buchwald is used to reduce a number of prochiral ketone substrates in the presence of triethoxysilane, with e.e.'s ranging from 1-20%.

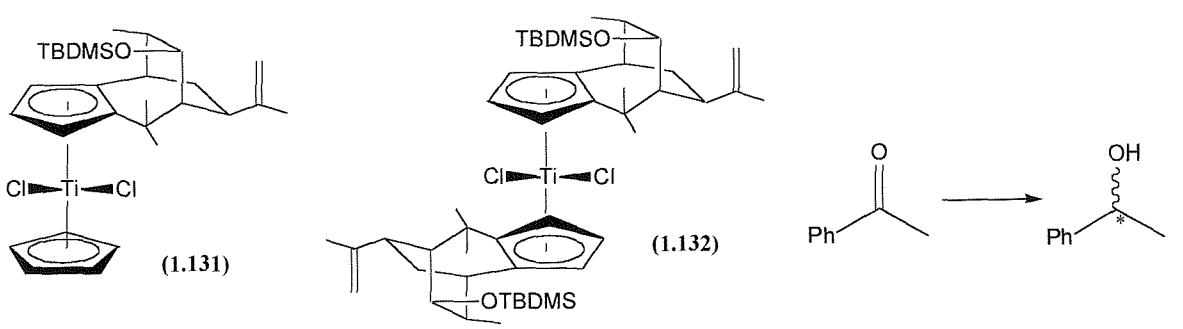




results: 2-octanone: 1% e.e.
acetophenone: 7% e.e.
2-acetonapthone: 20% e.e.

Scheme 1.51

Green and Whitby also attempted the reduction of ketones via hydrosilation using complexes **1.131** and **1.132** however no e.e.'s were recorded.[24]



Scheme 1.50

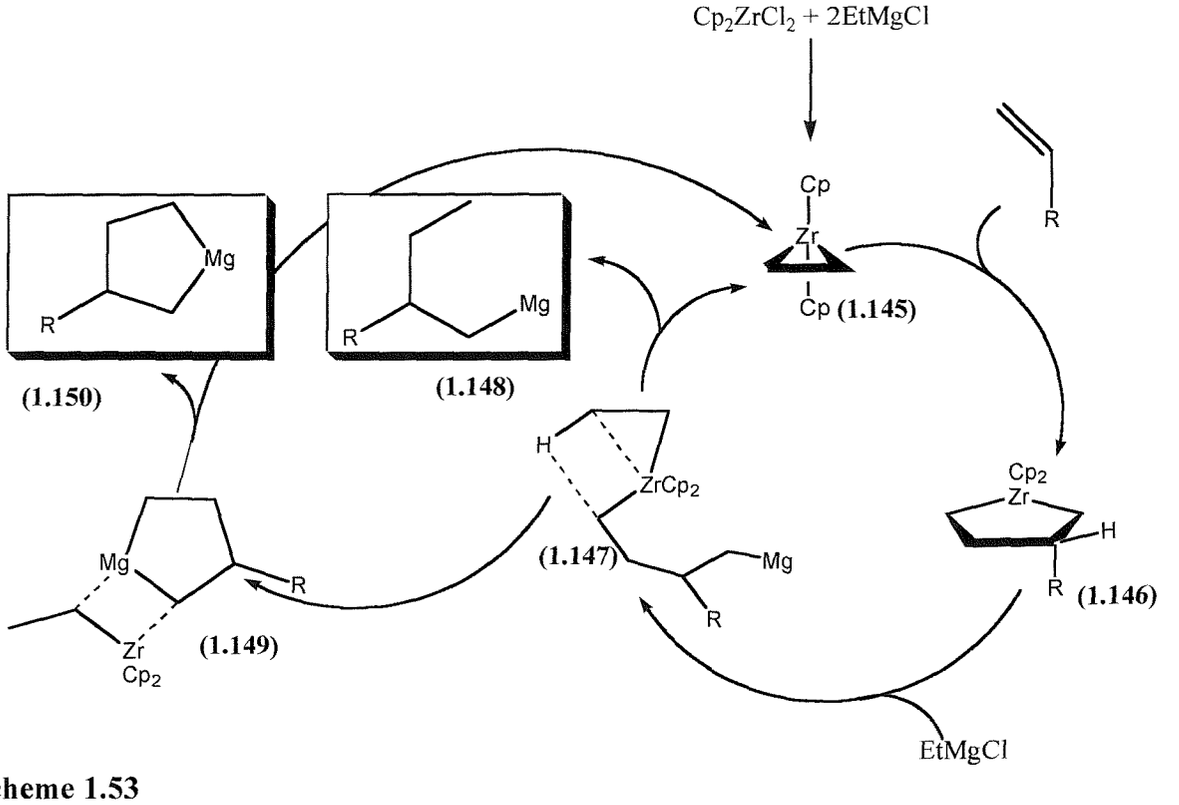
Buchwald has again applied titanocene **1.137** to this reaction, reducing ketones by titanium-catalysed hydrosilation to give alcohols with very high enantiomeric purities. However as with the above examples high e.e.'s were usually only obtained for ketones with two

substituents of very different sizes i.e. acetophenone. The origin of stereocontrol for ketones was postulated to be the same as that for the hydrosilation of imines.

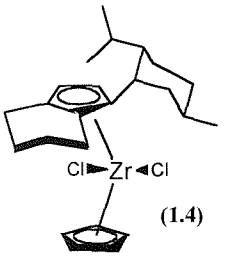
1.3.4 Catalytic Ethlymagnesiation of Alkenes.

1.3.4.1 The Catalytic Cycle.

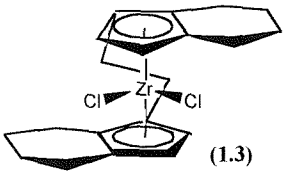
In 1985 Dzhemilev first reported the Zirconium catalysed ethylmagnesiation of unactivated alkenes, which has become a useful means of carbon-carbon bond formation.[56] It is a well-understood process as a result of extensive investigation by a number of groups and the following catalytic cycle is widely accepted as the mechanism:[57,58,59] Treatment of Cp_2ZrCl_2 with EtMgCl results in the formation of the zirconocene ethylene complex **1.145**. Insertion of the alkene to form the zirconocyclopentane intermediate **1.146** occurs regiospecifically with the least sterically hindered end of the alkene orientated closest to the zirconium centroid. The substrate approaches from the side of the complex, as this is where the empty zirconium d-orbital is located. Addition of EtMgCl leads to intemediate **1.147** from where β-hydride elimination can occur affording the ethylmagnesiated product **1.148** and regenerated catalytic complex **1.145**.



Scheme 1.53



(1.4)



(1.3)

In 1991 Whitby and co-workers discovered a second pathway. Quenching the reaction with D_2O showed that metallocycle **1.150** was also formed, and that the ratio of this hitherto unknown product to ethylmagnesiated product **1.148** was dependant on solvent.[59] In Et_2O and using Et_2Mg used instead of the Grignard reagent, a ratio of 40:60 in favour of metallocycle **1.150** was observed, but if THF was used as the solvent the ratio dropped to 5:95, with ethylmagnesiated product favoured almost entirely. Further to this discovery it was found that when sterically bulky zirconocenes such as **1.3** and **1.4** were used, ethylmagnesiated product **1.148** was the only outcome irrespective of the reaction conditions employed.

1.3.4.2 Complexes for use in Enantioselective Ethlymagnesiation.

In sections 1.3.1, 1.3.2 and 1.3.3 it was seen that Buchwald's application of Brintzinger's chiral titanium complex **1.3** to enantioselective hydrogenation and hydrosilation has been highly successful. Similarly, Hoveyda and co-workers have employed chiral zirconium complex **1.4** in an attempt to develop an enantioselective ethylmagensiation, and their efforts have met with great success when applied to heterocyclic olefin substrates where Et addition is accompanied by elimination.[8,38]

This reaction proceeds by the same catalytic cycle as already described in above. After the final step, the β-hydride abstraction, an intramolecular magnesium-alkoxide elimination provides the observed unsaturated product, which avoids further reaction of the terminal alkene due to the much slower rate of ethlymagnesiation for terminal alkenes compared to cyclic substrates.

It should be noted that for hetrocyclic alkenes six-membered or bigger, insertion of the substrate is regiospecific such that the Zr-C is formed α to the heterocyclic C-X bond, although the explanation for this has not yet been fully determined.

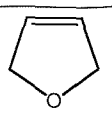
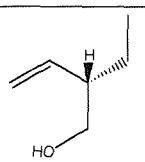
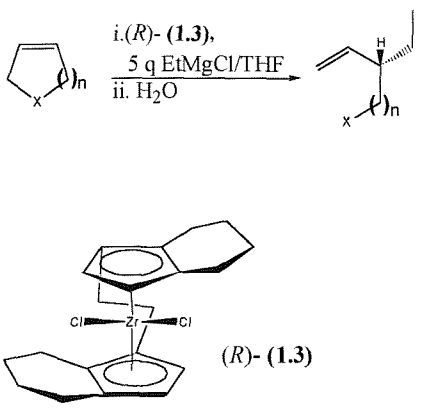
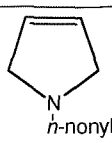
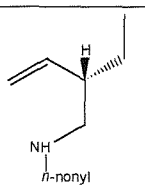
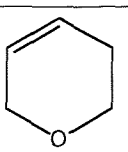
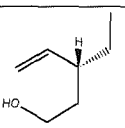
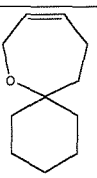
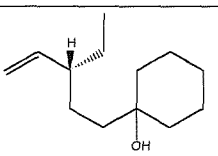
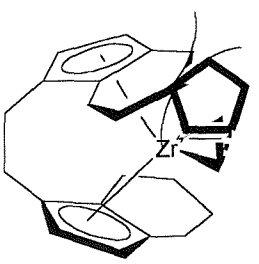
Substrate	Product	e.e.	catalyst
		99%	
		95%	
		95%	
		92%	

Table 1.6

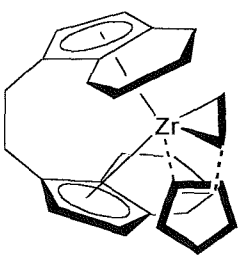
Products of this reaction of synthetically useful as both ends of these enantiomerically pure compounds can be further elaborated.

1.3.4.3 Origin of Enantioselectivity.

The following transition state model has been used as an explanation of the origins of enantioselctivity in the ethlymagnesiation reaction catalysed.by zirconocene **1.3.**



Unfavoured TS: considerable steric interactions between substrate and indenyl ring of ligand



Favoured TS: reduced steric interactions

Scheme 1.54

It has also been as an explanation of why. although this complex achieves excellent results for cyclic heterocyclic substrates, the e.e.'s are considerably lower for terminal linear alkenes e.g. 26% for N-allylaniline. Hoveyda argues that the smaller bulk of terminal alkenes reduces the steric interactions that occur between the ligand architecture and the substrate resulting in less selective ligand binding from both enantiofaces. Whitby and co-workers have developed the menthyltetrahydroindenyl zirconocene **1.4** and applied it to the ethlymagnesiation of terminal alkenes with some success.[12] Compared to the yields and e.e's observed for other known chiral metallocenes, the results were high, with a 75% e.e. achieved for the ethlymagnesiation of N-allylaniline. In addition results comparable to those achieved by Hoveyda were achieved when **1.4** was applied to the ethlymagnesiation of heterocyclic substrates. Thus the success of zirconocene **1.4** is significant. Not only are observed e.e.'s high for both terminal and heterocyclic alkenes, but **1.4** is also non C_2-symmetric, cheaper and easier to prepare than ebthi complex **1.136**.[12]

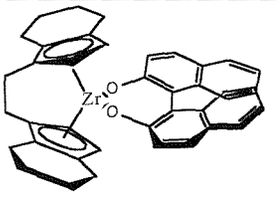
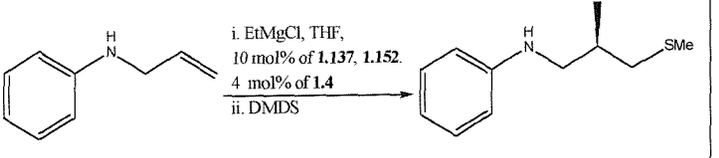
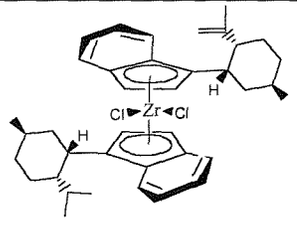
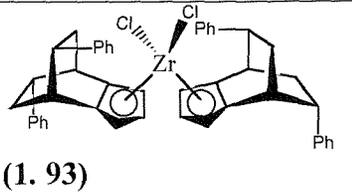
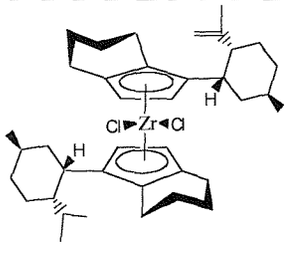
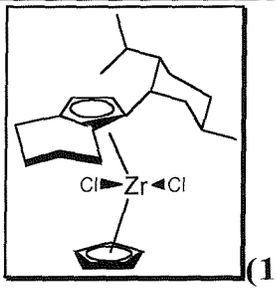
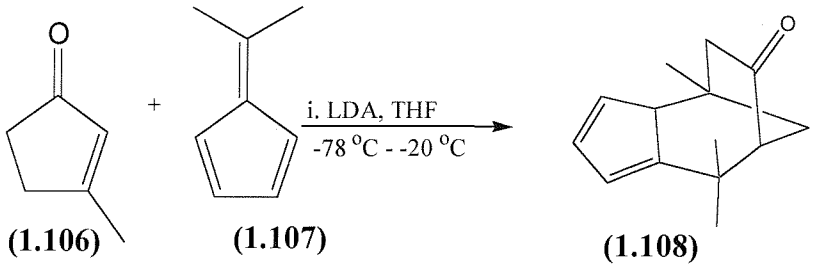
Catalyst	**Yield**	**e.e.**	**Reaction**		
 **(1.136)**	39%	26%			
 **(1.151)**	18%	26%	 **(1. 93)**	**Yield** Inactive	**e.e.** N/A
 **(1.152)**	Inactive	N/A	 **(1.4)**	**95%**	**75%**

Table 1.7

2. Diastereocontrol in the Double Michael Addition Reaction, Leading to Novel Chiral Cyclopentadienyl Ligands.

2.1 Introduction.

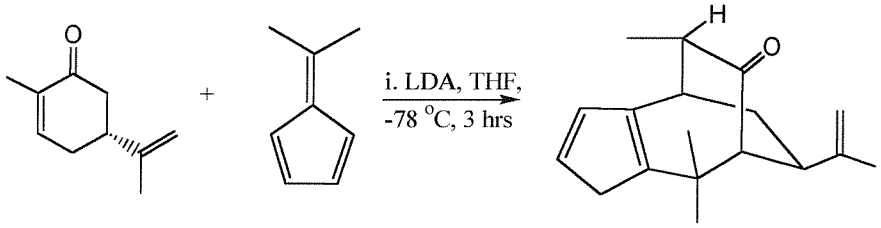
In chapter one the formation of a new tricycloalkane based ligand system formed via the double Michael reaction was discussed.[24,34] The highly efficient one pot stereoselective synthesis of these ligands (Scheme **2.1**) had identified this series as worthy of further investigation.



(1.106) **(1.107)** **(1.108)**

Scheme 2.1

The main disadvantage of the reaction as shown in scheme **2.1** was that although diastereocontrol was good, enantiocontrol was, by the very nature of the starting materials non-existent. Previous work within the group had attempted to overcome this by replacing flat enone **1.106** with homochiral naturally occurring carvone **1.124**, and this was initially successful as reaction with fulvene **1.107** gave rise to novel, enantiopure cyclopentadiene ligand **1.126**.[24]



(1.124) **(1.107)** **(1.126)**

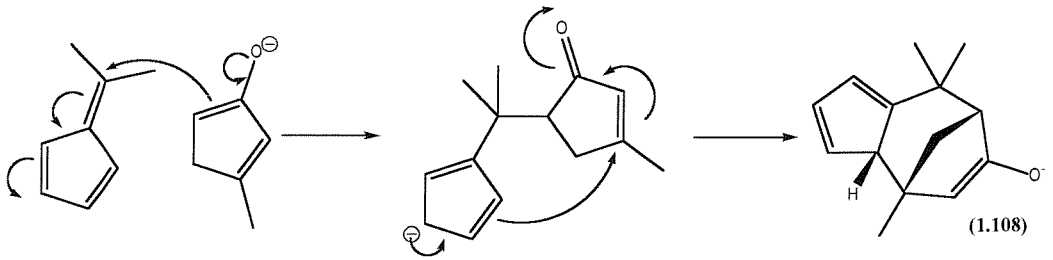
Scheme 2.2

However this system seemed to be less reactive than its enantiomer-producing counterpart, so that attempts to vary the fulvene as shown in Chapter **1** scheme **1.34** were unsuccessful.

Furthermore when reduced to alcohol **1.127**, the product had a tendency to ring close, forming furan **1.128,** although this was problem was addressed. (Chapter **1**, Scheme **1.40**).

2.1.1 Mechanism of Double Michael Reaction.

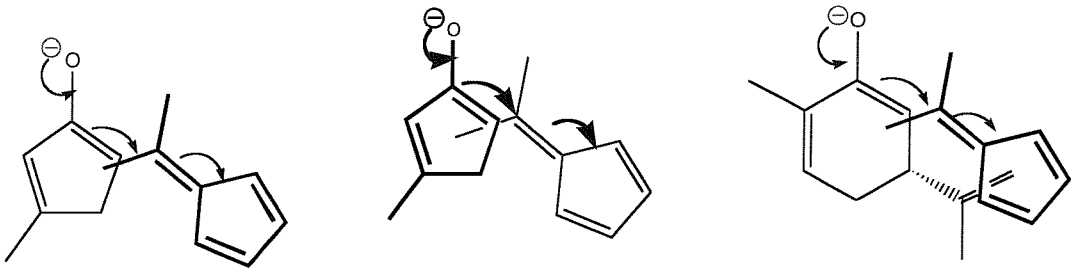
The mechanism of the double Michael reaction as first described by Hong and Hong results from the reaction of lithium dienolates with 6,6-dimethylfulvene, which is known to act as an electron deficient olefin, displaying some of the properties of α,β-unsaturated carbonyl compounds. The initial movement of electrons is attack by the enolate onto the six position of the fulvene.



(1.108)

Scheme 2.3

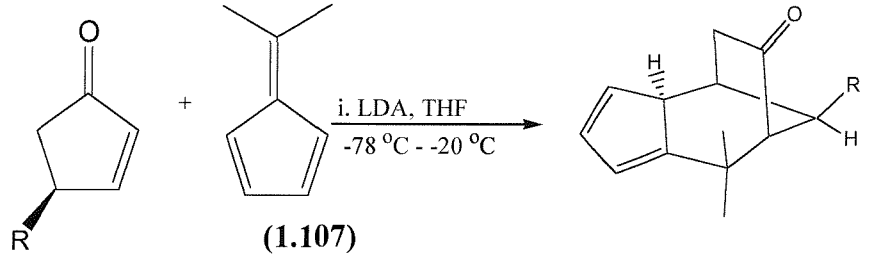
This same mechanism can be used to show the origins of diastereoselectivity in the carvone derivative. When the first Michael attack occurs as in scheme **2.4**, the chiral isopropenyl group in (*R*)-carvone prevents the enolate orientating itself above the fulvene and therefore attack can only occur from below, and once the first bond is formed the chirality is "fixed" in the molecule.



(2.1) (2.2) (2.3)

Scheme 2.4

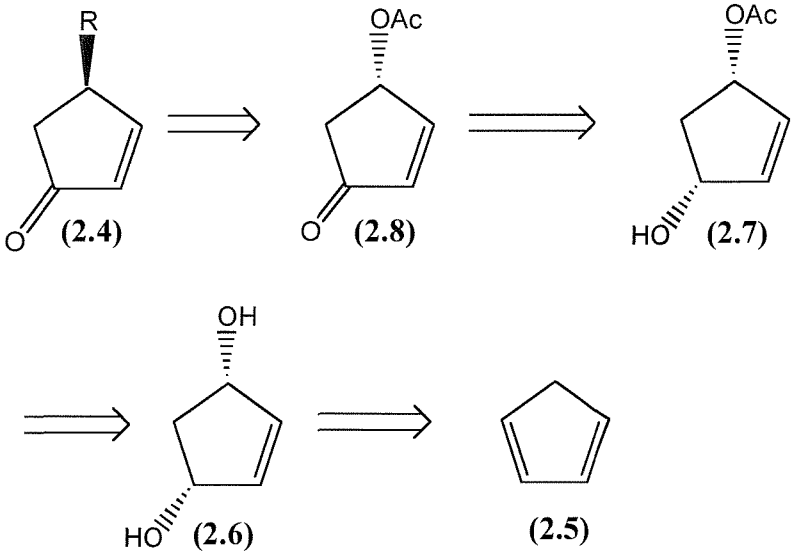
It was therefore decided to investigate whether a similar approach but using chiral five-membered cyclopentenones would be similarly successful in terms of chiral induction, and avoid the stability/reactivity problems associated with the (*R*)-carvone series.



Scheme 2.5

2.2 Synthesis of Homochiral Five-membered Cyclopentenones.

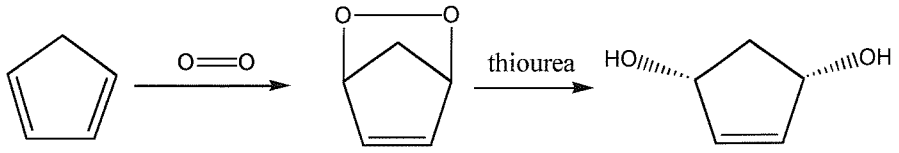
The most obvious chiral cyclopentenones to try and synthesise were 4-substituted cyclopentenones such as **2.4**. Such compounds contain the chiral information in the same place as (*R*)-carvone i.e. next to the site of enolisation, and in addition lent themselves to an attractive disconnection.



Scheme 2.6

2.2.1 Preparation of (1*R*,3*S*)-4-cyclopentene-1,3-diol 2.6.

Several routes have been published for the preparation of cis diol **2.6**. The most oft used is that of Tanaka and co-workers, the singlet oxygenation of cyclopentadiene.[60] This presented the best opportunity to gain access to large quanitities of diol **2.6**, but scaling up the reaction presented quite a technical challenge. The procedure involves the generation of singlet oxygen by irradiating a steady stream of oxygen bubbling through solution of cyclopentadiene and thiourea in methanol, with Rose Bengal as the sensitiser. The thiourea serves to reduce the initial endo- peroxide product to the diol.

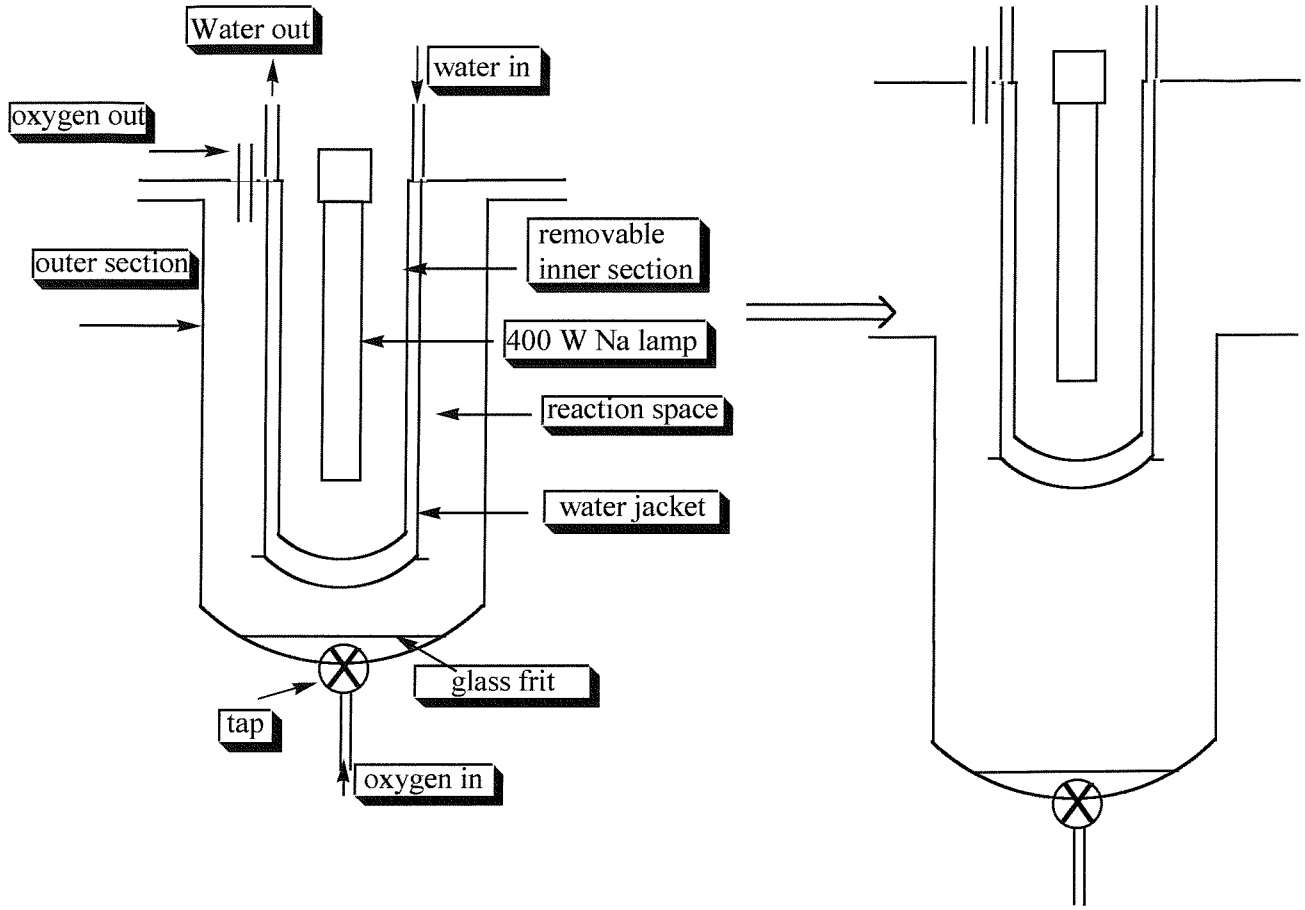


(2.5) **(2.9)** **(2.6)**

Scheme 2.7

Initially it was possible to synthesise up to 1-gram quantities with the use of a desk lamp and a round-bottomed flask, but this reaction took 6 hours and therefore was not conducive to the synthesis of large quantities. Therefore it was necessary to design a piece of apparatus in order to scale up the reaction. The reaction scale was initially limited by the output of the irradiation source. Normal light bulbs by their nature produce only a fraction of their energy at the correct wavelength for absorption by Rose Bengal, and additionally are relatively weak. By changing to a 400 W sodium bulb, which emits in the sodium d-line, all of the visible energy can be harnessed, this though requires a change in sensitiser as Rose Bengal does not absorb at this wavelength, so tetraphenylporphyrin (TPP), which does, was employed instead. This though also had a knock-on effect as TPP is insoluble in methanol, and replacing the methanol with a non-protic solvent stops the reaction as well as rendering the thiourea insoluble. However by using a 40:60 mix of DCM and methanol it was possible to dissolve sufficient quantities of both reagents. As well as producing a lot of light, 400 W sodium lamps generate a huge quantity heat. So an internal water jacket around the cavity for the light source was required, to keep the reaction temperature a low as possible. This is important for two reasons, firstly endo-peroxides are rather unstable and so heating them is potentially dangerous, secondly cyclopentadiene, DCM and methanol are volatile solvents and so evaporation must be controlled. The water temperature entering the water jacket was maintained at 4 °C with a recirculating pump.

This system enabled a dramatic increase in the quantities of diol **2.6** could be produced, with a mole of freshly cracked Cp being converted to diol **2.6** in a 70% yield in 2 hours, this enabled the quick production of tens of grams of **2.6** quickly and efficiently.

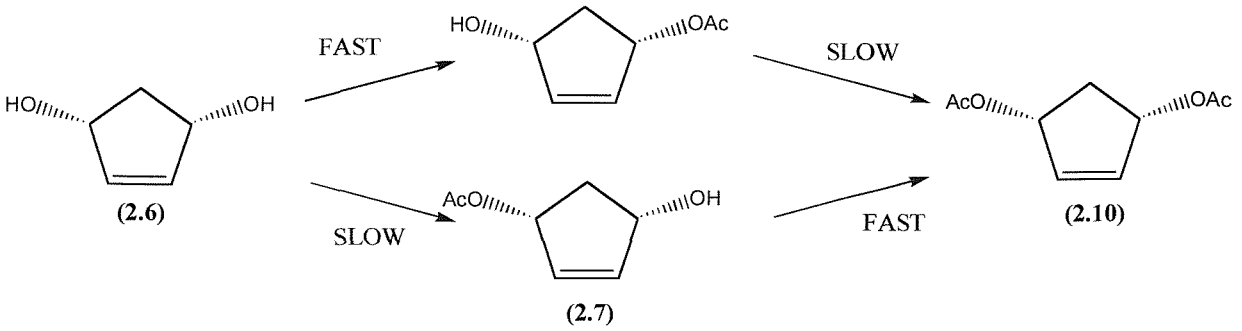


Scheme 2.8

2.2.2 Synthesis of (1*S*)-4-oxo-2-cyclopentenyl acetate.

Pancreatin catalysed asymmetric acylation was employed to afford (-)-monoacetate **2.7** in a 50% yield of the desired compound, and a 27% yield of the bis-acetate **2.10** as a by-product.[61] The e.e. of the product following recrystallisation was > 95% as measured by chiral GC. Using pancreatin creates a difference in reactivity between the (*S*) and (*R*)-hydroxyl groups of **2.6.** The enzyme will quickly catalyse the acylation of the (*S*)-hydroxyl but will only slowly acylate the (*R*)- hydroxyl. Therefore over the course of the reaction far more (*S*)-acylated product will be produced, and any (*R*)-acylated product will quickly have

its (*S*)-hydroxyl acylated as well generating bis-compound **(2.10)** thus ensuring a high e.e. and the separation of the two products by column chromatography.

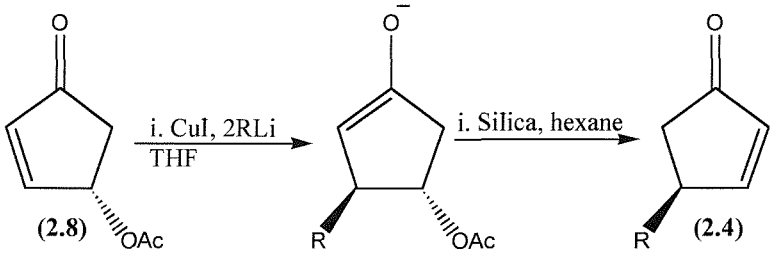


Scheme 2.9

(-)-Acyl compound **2.7** was then oxidised to corresponding enone **2.8** in a disappointing yield of only 38% using PCC as the oxidant.

2.2.3 Synthesis of (1*R*)-4-alkyl-2-cyclopenten-1-ones.

A copper catalysed elimination/addition reaction was envisaged and has been thoroughly investigated. Precedent for such a displacement was found in the literature with a similar procedure employed by Saito and co-workers with some success, using CuI with two equivalents of an organolithium as an organocopper catalyst. Copper reagents were chosen as they meet our demands in respect of stereochemistry: Organic transformations carried out using copper reagents have long been shown to exhibit strong stereoselectivity. i.e. if a compound has a (*R*) or (*S*)-chiral substituent α to the site of addition, then addition will occur exclusively from the opposite face.



Scheme 2.10

Butylcyclopentenone **2.13** was chosen as our immediate target, as our route to synthesising these chiral 4 substituted cyclopentenones via the copper mediated conjugate addition

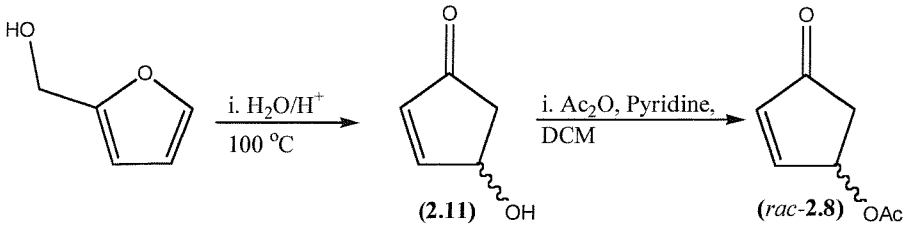
elimination reaction using alkyllithiums as the nucleophile, made very readily available butyllithium the obvious choice for optimisation of this procedure

When applied to acetoxy enone **2.8** using CuI/BuLi to form the organocopper species, the resulting yields were very disappointing with less than 5% conversion observed, therefore it was decided to use an alternative copper reagent.

When copper cyanide is mixed with two equivalents of alkyl metal, a higher order cuprate is formed rather than the organocopper, and these reagents are particularly useful for conjugate addition reactions such as that being investigated. Higher order cuprates differ from organocopper reagents in that the initial anion, i.e. the CN^-, remains "attached" to the copper throughout the process, whereas the alkyl or "R" group as used in cuprates and organo coppers, displaces the I^-.

In order to make the reaction more quantifiable TMSCl was used in the reaction as a means of trapping the enolate following attack by the higher order cuprate species. This effectively turns the reaction into two distinct components, each of which can be analysed using GC.

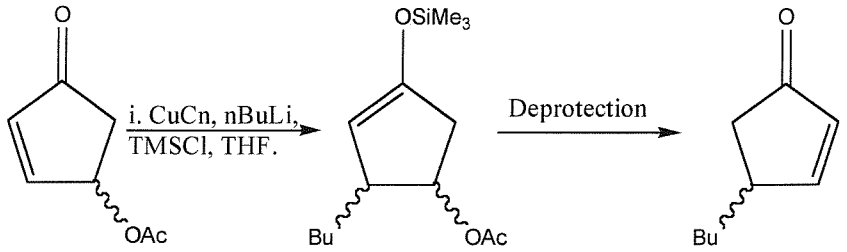
In order to preserve high value homochiral acetoxy enone **2.8,** a less expensive, easier to prepare racemic **2.8** was investigated. Whilst looking for routes to synthesise cis-diol **2.6**, one route, which was discarded due to the large number of steps and high costs of some of these steps, did provide a potential solution for the synthesis of racemic **2.8**. The first step of this route was an acid catalysed rearrangement of furfuryl alcohol to give hydroxyenone **2.11** in a 45% yield.[64]



Scheme 2.11

This procedure was amenable to scale up and afforded large quantities of **2.11** as an extremely hydrophilic oil. The lack of solubility in organic solvents required that a rather dilute solution was required for the acylation reaction, which gave racemic acetoxy enone **2.8** in a 70% isolated yield.

2.2.3.1 Conjugate Addition/elimination with TMSCl Trap.



rac-(2.8) (2.12) (2.13)

Scheme 2.12

With quantities of *rac*-**2.8** in hand the conjugate addition/elimination reaction as shown in scheme **2.12** was explored, using nBuLi and CuCN to form the higher order cuprate. This was successful employed using TMSCl to form butyl silyl ether **2.12** in quantitive GC yield. However the deprotection/ elimination step has proved to be a more challenging problem:

With the formation of TMS ether **2.12** as a stable intermediate, it was now necessary to formulate a deprotection strategy, as elimination could not occur without reforming the enolate. Conditions capable of removing the protecting group and initiating elimination simultaneously, without decomposing the product were explored. Normally TMS groups would be removed with a dilute acid such as HCl, but when these conditions were used the yield of the target enone was reduced considerably and occurs in an uncontrollable fashion. In order to solve this problem, trial reactions using a variety of conditions on a small scale were performed, with reaction monitoring by GC. **Table 2.1** shows the conditions used and the outcome of the experiments. (It should be noted that the product butylenone **2.13** has shown evidence of instability whilst on the GC column and so GC results cannot be considered entirely accurate).

Conditions	Area of Starting Material	Area of Product * **A**	Area of Internal Standard** **B**	**A/ B** ratio
START	21.03	0	36.44	0
KOH,MeOH 1 min		24.22	40.14	0.60
KF 1 min		21.21	42.32	0.50
HCl 1 min		20.23	59.65	0.33
TBAF 10 min		24.23	40.14	0.61

Table 2.1

As **Table 2.1** shows TBAF and KOH/MeOH would appear to be the most suitable reagents. It was initially decided to investigate the latter, as it offered a several advantages over TBAF both in terms of cost and ease of use as. However as with many of the other conditions, KOH achieved both elimination and deprotection instantaneously in a rather uncontrollable fashion and immediately started decomposing enone **2.13**. It was therefore decided to investigate some other conditions based upon the use of milder dilute bases in the hope that a suitable reagent could be found. The ideal scenario would entail shaking the reaction mixture with a solution of either K_2CO_3 or KOH in water in a separating funnel, so 10% K_2CO_3/H_2O and 10% KOH/H_2O were tested alongside homogenous mixtures of KOH and MeOH in Methanol. The results of this are shown in **Table 2.2**

Conditions	Area of Product* **A**	Area of Internal Standard** **B**	**A/ B** ratio
KOH/H_2O 10 min	0	177.25	0
KOH/MeOH 10 min	63.54	191.93	0.33
K_2CO_3/H_2O 10 min	74.56	395.84	0.18
K_2CO_3/ MeOH 10 min	121.34	342.61	0.35

Table 2.2

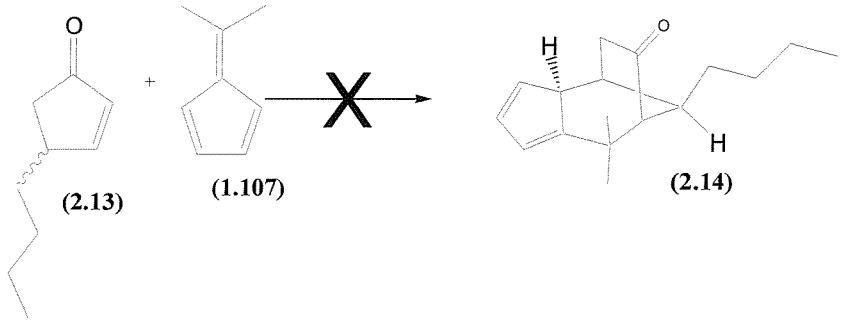
The main conclusion drawn from these results in small-scale reactions was that a homogenous mixture of K_2CO_3 in MeOH gave the best results for deprotection/elimination. Unfortunately this was not mirrored when applied to larger scale reactions: Although the use of either KOH/ MeOH or K_2CO_3/MeOH on 1 mmol and 20 mmol scale reactions was shown to deprotect and eliminate the silyl ether **2.12**, the increase in reaction time resulted in considerable loss of enone **2.13** according to GC, and indeed the recovered mass of this reaction is very poor, with yields of 0 – 10%. When TBAF was applied to the larger scale reactions, GC results indicated that although the deprotection/elimination is instantaneous, the enone is stable for the 10 seconds or so that it is exposed to the F^- and so therefore recovery should be considerably more efficient. The conclusion to be drawn from this was that TBAF was the most suitable reagent to use in the deprotection/elimination reaction, as it affords much higher GC yields in large-scale reactions. However although we had improved the reaction conditions, mass recovery was still poor. It was found that this was due to the high volatility of butyl enone **2.13** which made it very difficult to handle. Two solutions to this were explored: Replace the butyl group with one of larger mass to reduce the volatility or distillation in order to remove the solvents but not the product. Due to the restrictive choice of commercially available alkyllithiums and the difficulties in synthesising them, only phenyllithium was investigated. Neither method was successful. Distillation conditions just exacerbated the volatility problems and attempts to synthesise the phenyl enone **2.14** were unsuccessful with the phenyl lithium dimerising.

Therefore it was decided to continue to produce as large amounts of *rac*-butyl enone **2.13** as possible in order to attempt the double Michael addition reaction using chiral 5-membered enones, to see whether the strategy designed to introduce diastereocontrol to the double Michael reaction would be a success.

2.4 Double Michael Reaction Between Dimethylfulvene and Chiral Cyclopentenones.

Initial attempts to form novel Cp ligands were disappointing with mixtures of products being formed in the reaction between dimethylfulvene **1.107** and *rac*-butylcyclopentenone **2.13** all with similar R_f values for column chromatography, and as a result not enough pure material isolated for proper characterisation. This suggested that the reaction was likely to require thorough investigation, more so than could be achieved with the current route to

racemic chiral 4-substituted cyclopentenones. It was therefore decided to explore other means of providing sufficient quantities of enones to meet these aims.

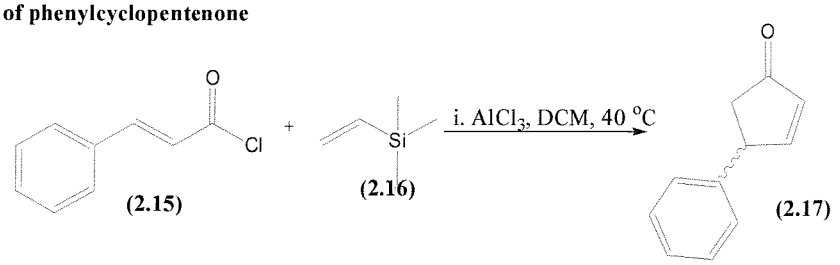


Scheme 2.13

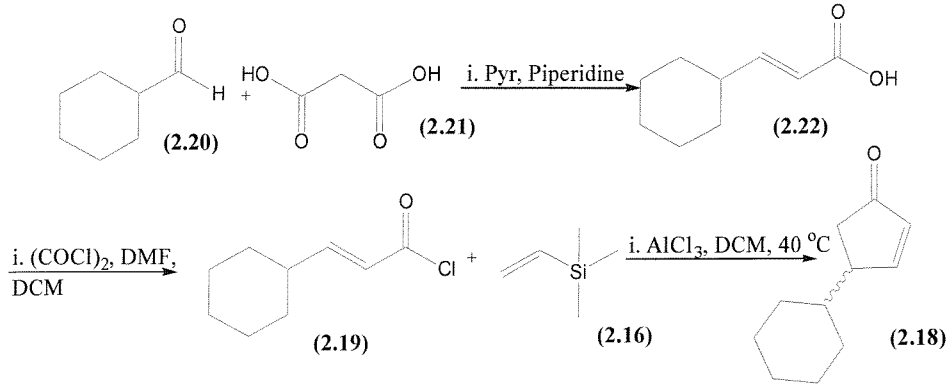
2.4.1 Alternative Routes to Racemic Chiral Cyclopentenones.

The most promising route was the Nazarov cyclisation between cinnamoyl chloride **2.15** and vinyltrimethysilane **2.16**, both commercially available, in the presence of aluminium chloride to give 4-phenylcyclopentenone **2.17** in 50-80% yields, a reaction repeatable on a large scale.[65] In addition novel cyclohexyl enone **2.18** was also prepared by the same reaction, although acid chloride **2.19** was not commercially available and had to be synthesised as shown in scheme **2.14** from the carboxylic acid product of the Knoevenagel condensation between cyclohexanecarboxaldehyde **2.20** and malonic acid **2.21**.[65,66] The overall yield in synthesising enone **2.18** was 40-50 %. The cyclohexylenone was also prepared for fear that the increased acidity of the proton α to the phenyl group in **2.17** compared to the acidity of an enone with an alkyl group present at the four position, might unfavourably alter the kinetics of the double Michael reaction; a fear that was to prove unfounded. So now armed with large quantities of both phenyl and cyclohexyl cyclopentenones the synthesis of tricyclic annulated ligands via the double Michael addition reaction was investigated.

Synthesis of phenylcyclopentenone



Synthesis of cyclohexylcyclopentenone

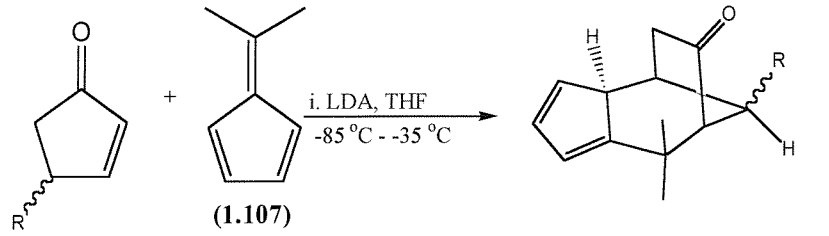


Scheme 2.14

2.4.2 The Double Michael Reaction Between 6,6-Dimethylfulvene and Cyclohexyl and Phenyl Cyclopentenones.

Initial attempts to synthesise the double Michael addition products using the enolates of **2.17** and **2.18** and 6,6-dimethylfulvene **1.107** applying the Hong's conditions ended in failure with only self-condensation products of the two enones observed. However by ensuring that the temperature of the reaction mixture during enolate formation did not rise above -85° C this side reaction was avoided. Further problems have arisen with this reaction as it seems that the position of substitution on the cyclopentenone ring makes a crucial difference to the kinetic and thermodynamic nature of the reaction and this may well have been the problem with the carvone system. This was seen in that the temperatures at which reaction occurred was dependant on where the enone was substituted. For 3-substituted cyclopentenones, such as 3-methylcyclopentenone **1.106**, the reaction with 6,6-dimethylfulvene occurs in 1-2 hours at -20°, but by switching to a 4-substituted cyclopentenones such as **2.17** and **2.18** it would appear that reaction time was considerably increased, with comparable mass recovery poor. However the sheer number of variations in reaction conditions that can be applied meant that it was not possible to determine exactly the cause of failure in this reaction. In the phenyl case **2.17**, the reaction reached its

maximum product formation point after 8 hours stirring at - 30° with a 10% isolated yield of ketone **2.23** the most favourable outcome. Increasing the temp to either –25 or –20 °C did not appear to hasten the reaction time and resulted in a lower isolated yield. For the cyclohexyl derivative **2.24** 6 hours is the time taken for the reaction to reach the maximum level of conversion with an isolated yield of 12% the best recorded. In both cases the starting enone was not completely consumed.



R = Ph **(2.17)**
R = cC_6H_{11} **(2.18)**

(1.107)

R =Ph **(2.23)**
R = cC_6H_{11}**(2.24)**

Scheme 2.15

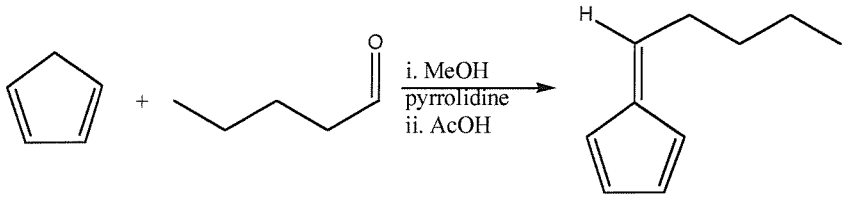
In an attempt to increase the rate of reaction without increasing the temperature, the phenyl reaction was attempted using potassium diisopropylamide instead of the more standard LDA. The use of the larger potassium cation has been shown to increase the rate of enolate nucleophilic addition, and indeed this was found to be the case with maximum product output obtained at a slightly accelerated rate. However the outcome of the reaction was the same with low (<10 %) isolated yields.

Again it was not possible to isolate enough material for full characterisation, as once again the products were formed as complex mixtures of compounds with very similar R_f values in a variety of organic solvents.

2.4.3 The Double Michael Reaction with a Different Fulvene.

As has been described above the double Michael addition reactions occurred very slowly when compared with similar reactions with cyclopentenones substituted only at the 3-position. This is possibly due to increased steric bulk around the enolate anion derived from a 4-substituted cyclopentenone, which hinders the initial nucleophilic attack on dimethylfulvene **1.107**. It was therefore decided to try the reaction using a less hindered mono-substituted fulvene, 5-pentylidene-1,3-cyclopentadiene **2.26,** the synthesis of which

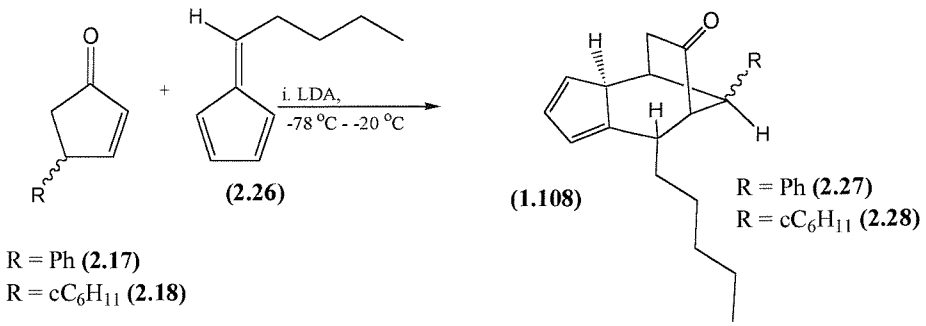
is shown below. This fulvene was chosen as a supply of valeraldehyde **2.25** was readily available and was synthesised according to the method of Stone and Little in an 80% yield.[35]



(2.25) **(2.26)**

Scheme 2.16

The subsequent double Michael addition reactions with both 4-cyclohexylcyclopentenone **2.18** and 4-phenylcyclopentenone **2.17** proceeded with reasonable product formation, 60% and 40% respectively, in a reaction time of 6 hours, but only for small (<2 mmol) scale reactions. Any attempt to increase the scale of the reaction led to ever diminishing returns. However ketones **2.27** and **2.28** were formed as single diastereoisomers, suggesting that the strategy for introducing diastereocontrol in the double Michael reaction was a success, even though the enones used were racemic. If diastereocontrol was not observed, then the product ketones would have been formed as mixtures of diastereoisomers. It should also be noted that unlike the dimethylfulvene cases, the starting cyclopentenones were entirely consumed during the reaction, however the temperature again had to be very carefully controlled and remain between –30 °C and –40 °C to maximise product formation.



R = Ph **(2.17)**
R = cC_6H_{11} **(2.18)**

(2.26) **(1.108)**

R = Ph **(2.27)**
R = cC_6H_{11} **(2.28)**

Scheme 2.17.

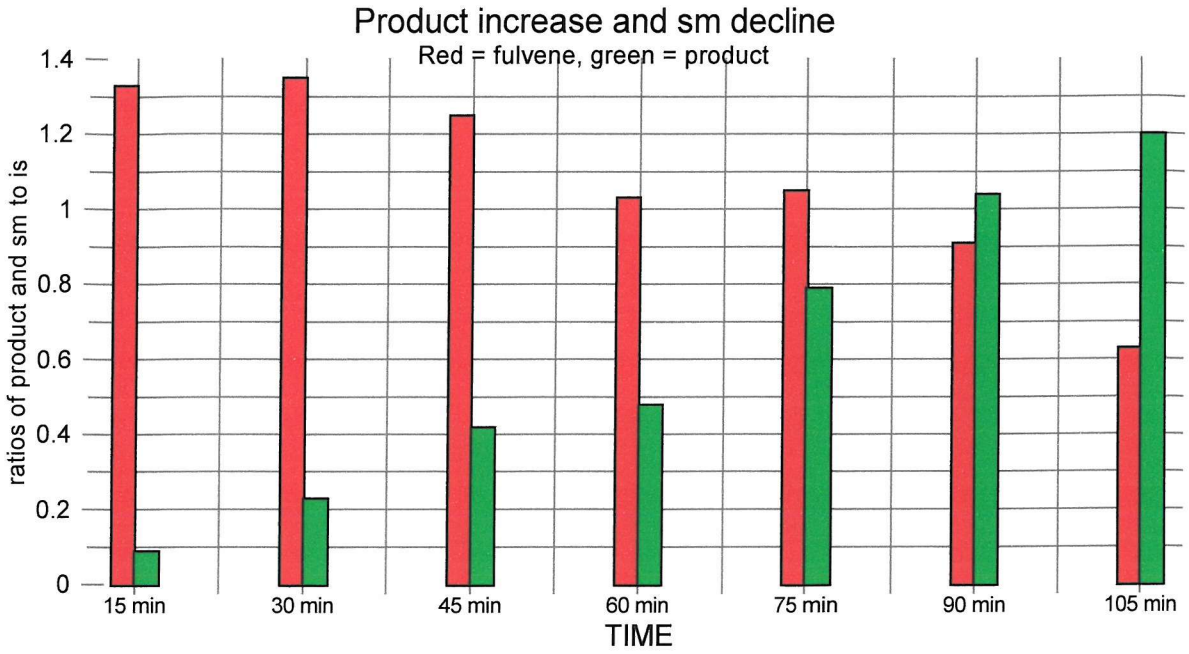
2.5 Investigation into the Rate Determining Step of the Double Michael Reaction.

One of the tenets of catalyst design in chapter 1 states that the synthesis must be cost efficient and a double Michael reaction yielding only 40% in small scale reactions, struggles to fulfil this criteria. So the rate-determining step of the double Michael addition reaction between the fulvenes and cyclopentenones was investigated. This was to shed light on as to why reactions between 3-methyl cyclopentenone and a fulvene proceeded much more smoothly than those reactions between a fulvene and 4-substituted cyclopentenones. The mechanistic understanding of the reaction is that initial addition of the lithium salt of the cyclopentenone to the fulvene is followed by intra-molecular Michael attack to the back on the enone. If the first step was rate limiting, fulvene would gradually be used up over time and product would slowly be produced. This meant that the enolate of the cyclopentenone would exist in the reaction mixture for a long time and only slowly be used up. If the second step were rate limiting then the fulvene and cyclopentenone would all be used quickly and there would have been gradual appearance of product, and the intermediate enolate would exist for long periods in the reaction mixture. These processes were observed using GC using tridecane as an internal standard in the reaction mixture. The table below shows the results observed when GC was used to monitor the reaction between 3-methylcyclopentenone **1.106** and 6,6-dimethylfulvene **1.107**.

Reaction time	Area of fulvene **A**	Area of product **B**	Area of internal standard **C**	**A/C**	**B/C**
15 min	62.77	4.26	46.91	1.33	0.09
30 min	183.76	31.03	136.07	1.35	0.23
45 min	235.41	77.74	187.19	1.25	0.42
60 min	144.56	91.32	140.99	1.03	0.48
75 min	219.40	165.13	208.37	1.05	0.79
90 min	155.16	179.40	171.21	0.91	1.04
105 min	111.77	174.93	145.52	0.63	1.20

Table 2.3

This is visualised in the graph below, which plots the ratios of fulvene **1.107** to internal standard and product to internal standard against time.



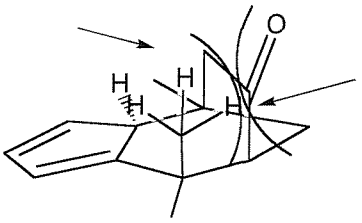
Graph 2.1

These results appear to show that the 1st step was the rate-limiting step, as the ratio of dimethyl fulvene **1.107** to tridecane gradually diminishes with time. It should be noted that the reaction does not go to completion if only one equivalent of fulvene was used, probably due to polymerisation of the fulvene. In addition 3-methlcyclopentenone **1.106** does not appear by GC.

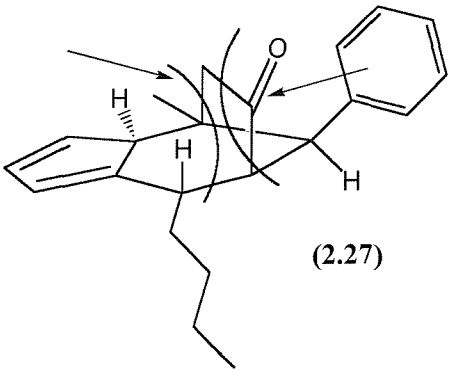
The main conclusion to be drawn from this experiment is that the cyclopentenone enolate is forced to loiter during the reaction. This does not seem to effect the enolate of 3-methylcyclopentenone **1.106** adversely but as it reacts with fulvenes considerably more quickly than the 4-substituted enones, it could be that this does not have time to arise as a problem. However with the increased reaction times associated with enolates of 4-substituted enones, combined with experimental evidence from Ikeda and co-workers that such enolates are unstable at temperatures above –65 °C suggest that this a problem requiring a considerable degree of further investigation.

2.6 Formation of TBDMS Ethers of Novel Tricyclic Annulated Ligands.

As in the systems developed by Green and Whitby, it was decided to reduce the ketone to the alcohol and then protect the hydroxyl groups as TBDMS ethers, a necessary step for complexation to Ti and Zr, as well as to see if the excellent diasteroselectivity observed for reduction with Dibal-H by Green and Whitby would be reproduced with ketones **2.27** and **2.28**.[24] Ketone **1.108** contains a methyl group on one side of ketone, ensuring attack by bulky Dibal-H from one side only. In **2.27** and **2.28** the methyl-group is replaced by a proton, and it was not clear whether this would be a sufficiently sized blocking group and whether the extra R group such as the phenyl group would provide further complication.



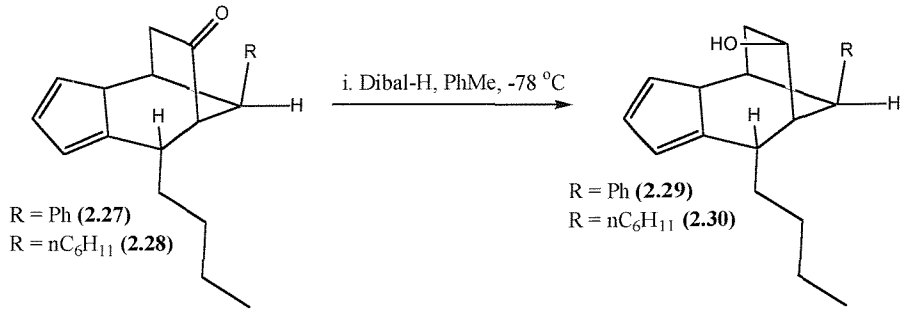
(1.108)



(2.27)

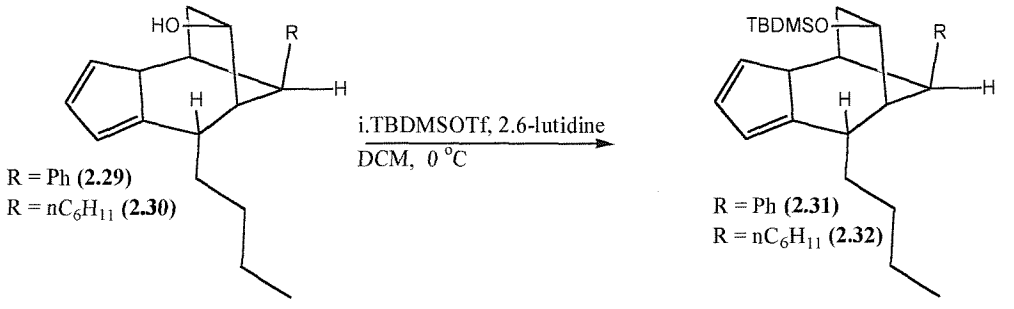
Scheme 2.18

When the reduction was performed however, the fears that stereoselectivity would be compromised were unfounded, with high diastereoselectivity observed for the reduction, leading to alcohols **2.29** and **2.30**. The yield of the reductions was 50% and 40% respectively.



Scheme 2.19

Both alcohols were then protected as TBDMS-ethers to provide novel tricylic annulated ligands **2.31** and **2.32** 70% and 69% yields respectively.



Scheme 2.20

2.7 Application of Homochiral Enones to the Double Michael Reaction.

Unfortunately time constraints mean that it was not possible to apply the methodology for the formation of enantiopure cyclopentenones to the double Michael addition reaction.

2.8 Attempt Syntheses of Novel Complexes.

Unfortunately all attempts to complex ligands **2.31** and **2.32** have been unsuccessful despite many attempts using a variety of different metal sources and methods. The reasons for this are unclear and due to time constraints, further investigation was not possible.

2.9 Conclusions.

The results in this chapter have provided some important insight into the development of the double Michael addition reaction as a means of producing new chiral Cp ligand systems for use as chiral catalysts. Although some new ligands were prepared there were major limitations in several steps of the synthesis.

- The conjugate addition elimination reaction using alkyl lithiums is limited to those that are commercially available. The ideal choices, isopropyl lithium and cyclohexyl lithium are both problematic. The former due to the troubles of volatility with the nine carbon butylcyclopentenone **2.13** let alone an eight carbon enone, and the latter due to the impracticalities of cyclohexyl lithium which is very

difficult to make and almost completely insoluble. Furthermore, attempts to try the displacement with Grignard reagents were unsuccessful.

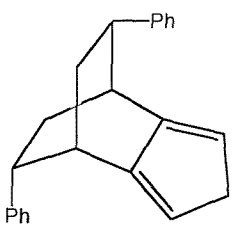
- The double Michael addition reactions between 6,6-dimethyfulvene **1.107** and enone **2.13,** and between cyclohexyl and phenyl enones **2.17** and **2.18** and fulvene **1.104** were very low yielding, probably due to the increased steric hindrance encountered in enolates substituted at the 3-position rather than the 4-position. This improved when mono-substituted fulvene **2.26** was used, although the reactions were only relatively efficient on a small scale. This is probably due to the instability of the enolates of four substituted enones.

However there was some significant progress, not least in overcoming the chemical engineering challenge of performing the singlet oxidation reaction on a massive scale. Furthermore four new Cp Ligands were produced, two suitable for complexation with rhodium, and two suitable for complexation with zirconium and titanium although more investigation into the complexation reactions is required.

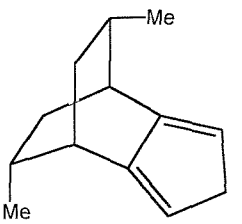
3. Synthesis of Ligands Based on a Novel C_2-symmetric Ligand System.

3.1 Introduction.

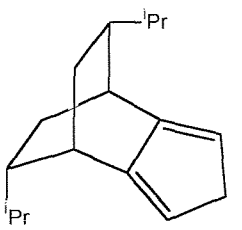
As reported in chapter **1** Halterman has developed a range of C_2- symmetric ligands based on bicyclo[2.2.2]octane, **1.79**, **1.07** and **1.90**.[11,28,29]



(1.79)



(1.7)



(1.90)

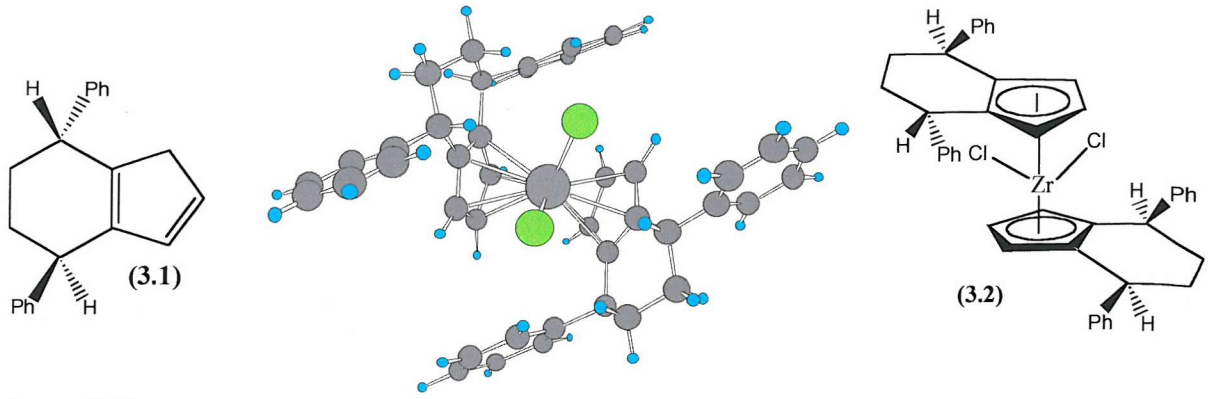
Scheme 3.1

Although these complexes have provided some excellent results, particularly in the hydrogenation of 2-phenyl-1-butene, they are quite difficult to make and their preparation requires expensive reagents.[28,31] This limits their application as catalysts, as preparing them in commercially viable quantities is unlikely.

However the C_2-symmetric design concept does have very real advantages. Chapter one describes how such structures have homotopic Cp faces, that is faces, which upon complexation lead to stereochemically identical materials irrespective of which face is complexed. That is of course dependant on the optical purity introduced earlier in the synthesis being maintained after its introduction into the synthesis.

3.2 A New C_2-symmetric Design.

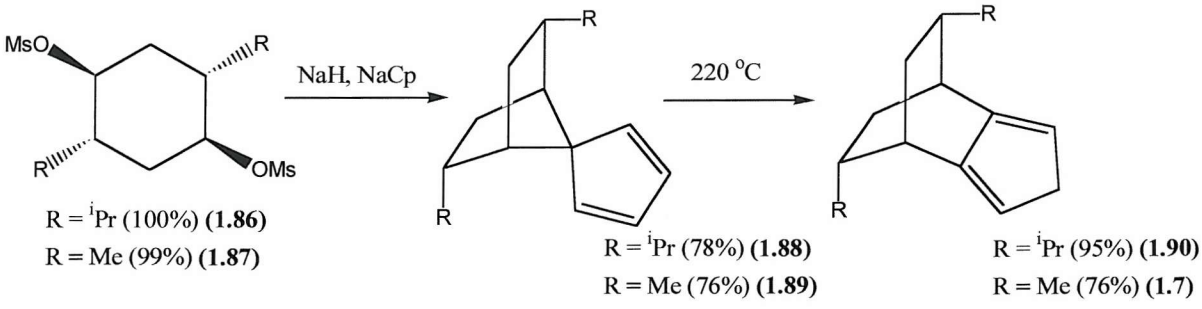
Molecular modelling showed that a new simpler C_2 symmetric design **3.1** had potential for usage as a chiral catalyst. The predicted structure of the zirconocene complex in particular showed a similar level of blocking at the active site to that seen in the same projection of Brintzingers catalyst **1.2**, and this made the synthesis of **3.1** a worthwhile target.



Scheme 3.2

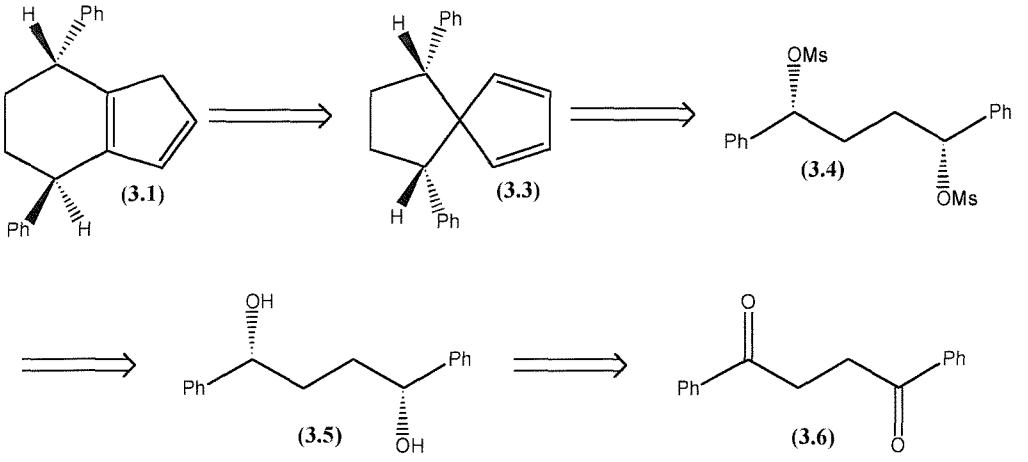
3.2.1 Disconnection of Novel Ligand 3.1.

Having identified ligand **3.1** as the target, a viable disconnection of the molecule back to available starting materials was required. The most obvious way was to try and devise a route similar to that of the most analogous series of ligands, the bicyclooctane structures of Halterman shown in **Scheme 3.1**. The synthesis of these structures involved the displacement of 1,4-bis mesylate groups by a single molecule of Cp to give a spirocycle, which then rearranged during thermolysis to the give the desired cyclopentadiene.[31]



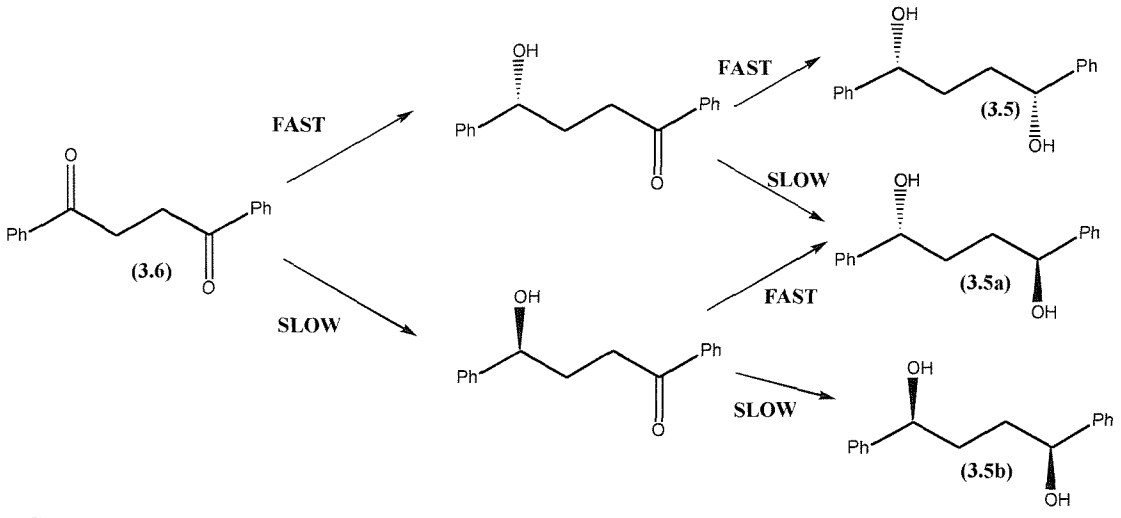
Scheme 3.3

A similar route was envisaged for ligand **3.1**. Disconnection back to the spirocycle yields compound **3.3** and subsequent removal of the Cp group from this compound yields bis mesylate **3.4,** which is a protected form of chiral diol **3.5,** which would be generated via the asymmetric reduction of bisketone **3.6**.



Scheme 3.4

This asymmetric reduction was likely to be the key step, and the fact that the molecule of interest would be a bis-ketone further increased the likelihood that this step could be achieved with a high degree of enantiocontrol. This is because the "*meso* trick" seen in chapter 2 would again apply (assuming the reduction of each ketone is independent). The reduction of each ketone moiety in a bisketone to give the "correct" chiral alcohol should be a much quicker process than the formation of the "wrong" enantiomer, but even if any of the wrong enantiomer should form it is almost certain that the other ketone moiety in the molecule will be have been reduced to the correct enantiomer i.e. the reduction to give the incorrect stereochemistry is so slow that the chances of it happening twice in the same molecule are negligible, and even if the first ketone functional group in any molecule was to display the incorrect stereochemistry, the compound would be highly likely to form the *meso* compound, which has been shown to be separable by recrystallisation from the desired optically active compound.

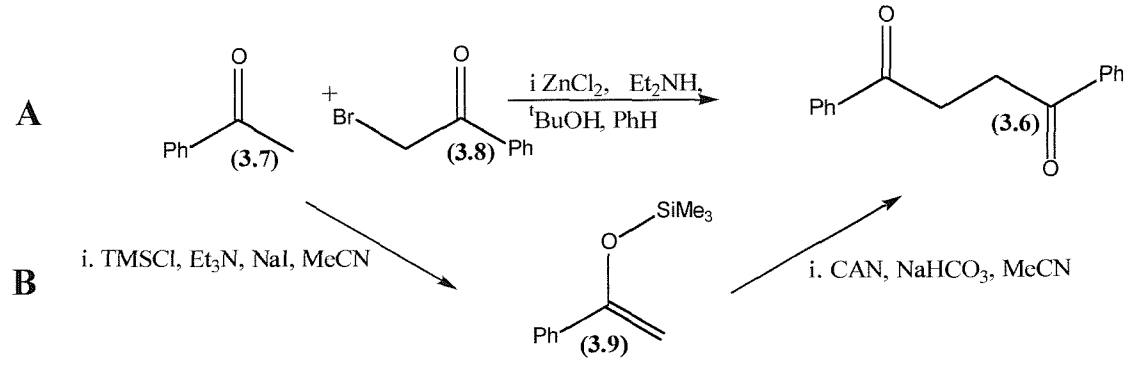


Scheme 3.5

Initially therefore the production of large quantities of bisketone **3.6** was investigated.

3.3 Synthesis of bisKetone 3.6.

A search of the literature revealed two likely routes for the synthesis of ketone **3.6**. The first was a CAN mediated radical self-coupling of the silyl ether of acetophenone, and the second was a zinc mediated coupling of acetophenone and phenacyl bromide.



Scheme 3.6

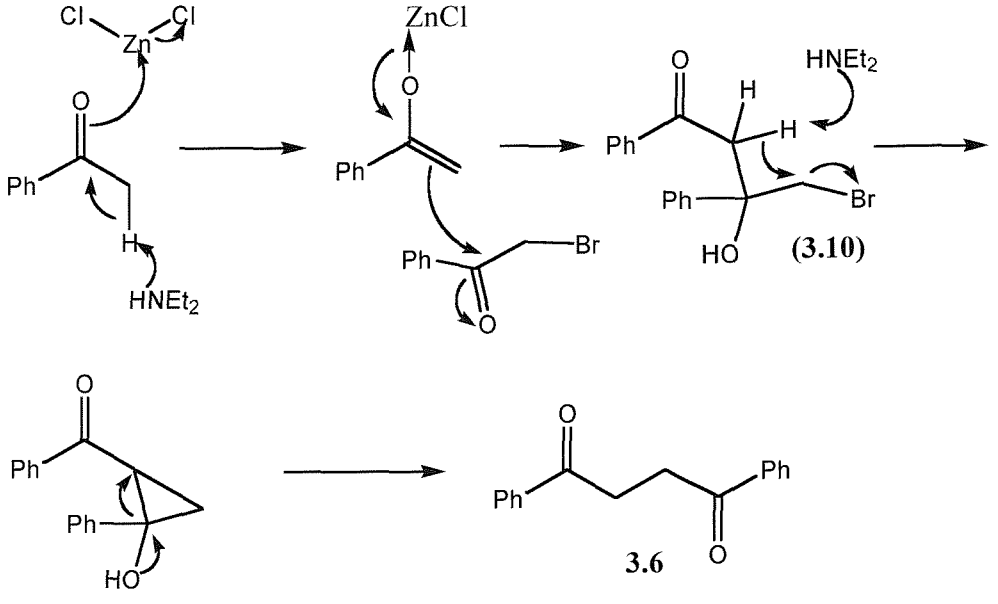
It was initially decided upon the silyl ether route **B** to bisketone **3.6,** as this was potentially a faster and in practical terms more facile approach to generating the desired compound. The initial paper demonstrates how this approach can be used to generate 1,4-bisketones with different terminal substituents by a radical coupling reaction between the silyl ethers of two participating ketones, with a large excess of one silyl ether required in order to

ensure heterocoupling occurs.[68] However as the intention in this case was to couple acetophenone to itself this was not an issue.

In order to generate the silyl ether **3.9** the method of Dunogues and co-workers was followed. This uses sodium iodide to facilitate the enolisation of acetophenone **3.7**, a less experimentally demanding alternative to more current enolisation methods (i.e. LDA, –78 °C).[69] However neither the enolisation reaction nor the subsequent coupling reaction worked well with a maximum overall yield of only 8% for the formation of ketone **3.6**.

Route **A**, Kulinkovich's coupling of acetophenone **3.7** and phenacyl bromide **3.8** was therefore investigated in the hope that this would provide the desired compound in higher yield.[70] This method employs dry zinc chloride as a Lewis acid in order to drive the coupling reaction in the presence of diethylamine and tertiary butanol. The zinc chloride is heated at very high temperatures under vacuum, then solubulised in benzene by the addition of the diethylamine and tertiary butanol. The two reactants are then added in any order and the reaction left to stand for 7 days without stirring, during which time large crystals of product are produced which are collected by filtration. This reaction proved very successful in providing large quantities of the desired diketone **3.6** as a white crystalline solid in a reasonable yield of 65-70%. The reaction was repeatable and the scale limited only by the size of the reaction vessel.

The mechanism of this reaction is somewhat unusual: After the enolisation of acetophenone the first displacement is not of the bromide of **3.8** as one would expect but attack onto the ketone moiety in the same molecule. This is followed by a base catalysed cyclopropanation that displaces the bromide. Reforming the ketone then opens the cyclopropane.



Scheme 3.7

The evidence presented by the authors for this mechansism is that independent synthesis of alcohol **3.10** followed by exposure to base leads also to the production of diketone **3.6.** [70]

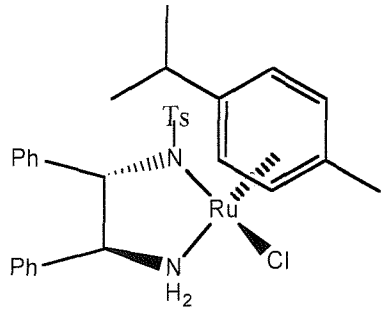
3.4 Asymmetric Reduction of Ketones.

3.4.1 Introduction.

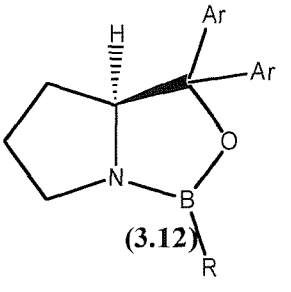
The next step was to introduce chirality into the synthesis via the asymmetric reduction of ketone **3.6**. Several methods were available for this and a brief review of these methods follows.

3.4.2 Current Methods for the Asymmetric Reduction of Ketones.

The main methods for the asymmetric reduction of ketones up until 1992 have been reviewed elsewhere.[71] Of the methods contained in that review and other developed since then two have emerged that have become favoured above the others. These are Noyori's (*S*,*S*)-N-tosyldiphenylethylenediamine *p*-cymene ruthenium complex **3.11**, and Corey's oxazaborolidine catalysts **3.12**. It was necessary to evaluate both of these compounds in terms of efficacy and cost in order to plan a way ahead for the reduction of ketone **3.6**.



3.11

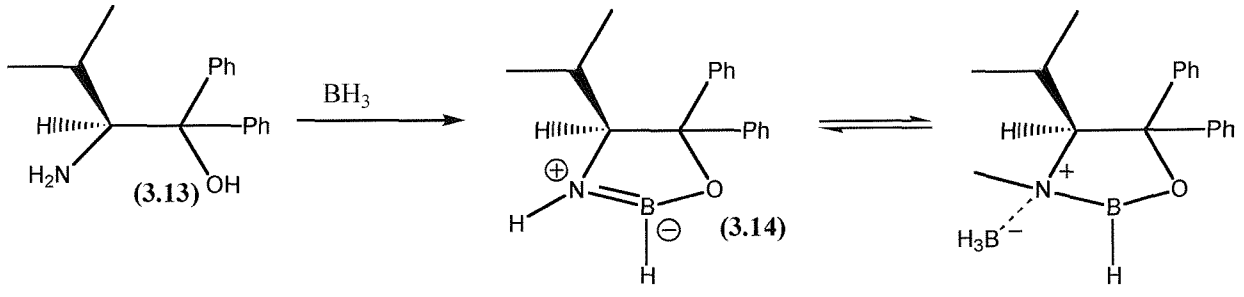


(3.12)

Scheme 3.8

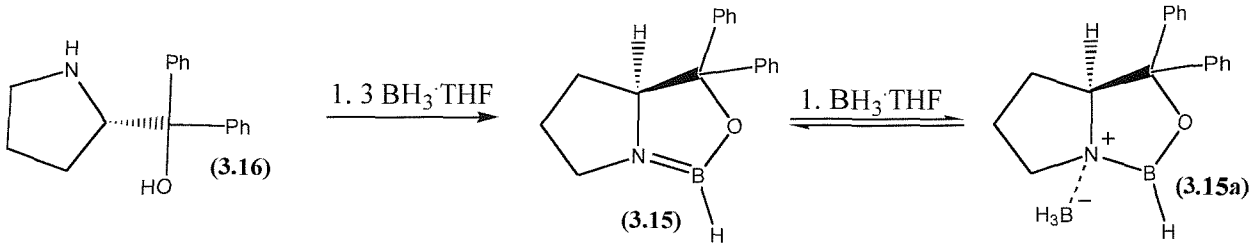
3.4.2.1 Corey's Oxazaborolidine Catalyst for the Reduction of Aryl-substituted Ketones.

In 1983 Itsuno and co-workers demonstrated that a mixture of 2.5 equivalents of borane in THF and a chiral vicinal alcohol such as (*S*)-2-amino-3-methyl-1,1-diphenybutan-1-ol **3.13**, would produce an effective reducing mixture when stirred for 2.5 hours.[72] This reducing mixture would then, when used in stoichiometric quantities, reduce acetophenone to (*R*)-1-phenylethanol with an e.e. of 95%. Corey and co-workers found that if amino alcohol **3.13** was stirred with 2 equivalents of borane in THF at 35 °C, the product oxazaborolidine **3.14** could be isolated as a crystalline solid.[73] However on its own, compound **3.14** was incapable of reducing acetophenone, but when stirred with anywhere from 0.6 –2.0 molar equivalents of BH_3·THF, the complete reduction of acetophenone was effected in under one minute.[76] Using 1 equivalent of **3.14** and 1.2 equivalents of BH_3·THF at room temperature provided (*R*)-phenylethanol in a quantitive yield and 94.7% e.e. Identical results were achieved when the mixture was applied catalytically with 0.1 or even 0.025 equivalents of **3.14**.[76]



Scheme 3.9

Developing this further, Corey also developed oxazaborolidine **3.15** as an even more effective catalyst by heating (*S*)-diphenylprolinol **3.16** at reflux with 3 equivalents of BH_3·THF in THF in a closed atmosphere of Ar-BH_3, and although oxazaborolidine **3.15** took longer to form than **3.14**, the results for a range of substrates was impressive. The reaction was generally under a minute at room temperature.[74]

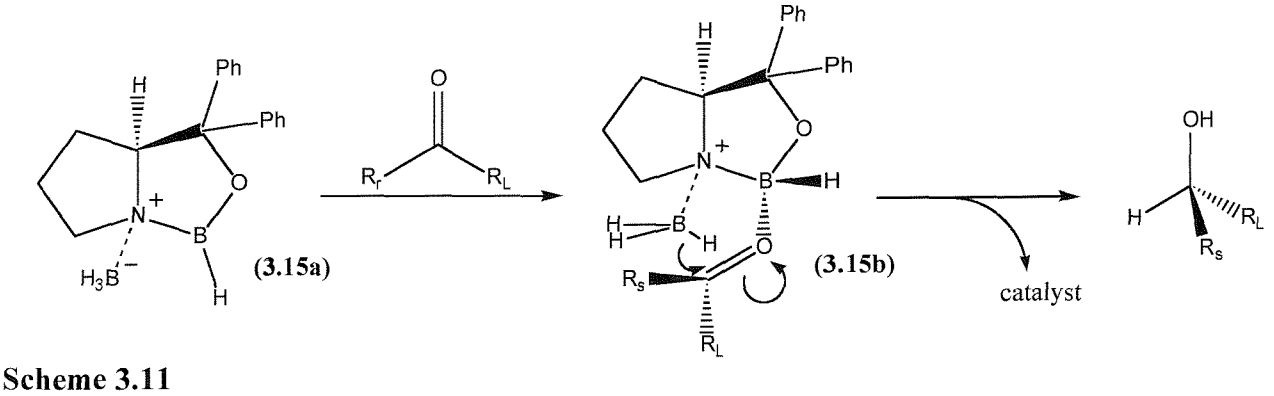


Scheme 3.10

Ketone	Equiv BH_3	Equiv **3.15**	e.e. (%)
PhCOMe	1	0.1	97
PhCOEt	0.6	0.05	90
t-BuCOMe	0.6	0.1	92
α-tetralone	0.6	0.05	89
$PhCOCH_2Cl$	0.6	0.05	97

Table 3.1

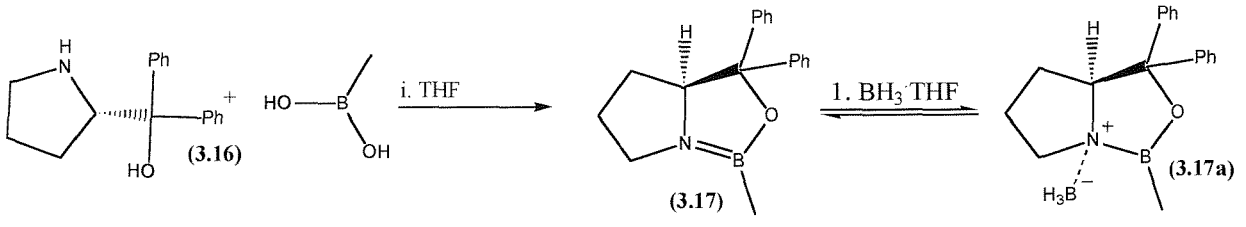
Corey has proposed that the equilibrium transition states of the active catalysts as shown in schemes **3.7** and **3.8**, feature in the mechanism for the reduction of ketones. The addition of another unit of BH_3 to **3.15** leads rise to **3.15a**, and the Lewis acid nature of the cyclic boron holds the ketone in place underneath the plane of the chiral centre with the smaller substituent nearest to the exocyclic borane due to steric issues, ensuring enantiocontrol during the hydrogen transfer.[74,75]



Scheme 3.11

3.4.2.2 An Air and Moisture Stable Oxazaborolidine.

Although oxazaborolidine **3.15** was an effective catalyst for the reduction of ketones, it was a moisture and oxygen sensitive solid, and so not as easy to use as it might be, so shortly after the publication of oxazaborolidine **3.15,** Corey published the synthesis of an air and moisture sensitive derivative **3.17**, capable of storage long term in lidded containers and transfer for weighing under normal atmospheric conditions.[76] This was achieved rather simply, by the preparation of a β-methylated analogue of existing oxazaborolidine **3.15**, with the added benefit of also being simpler to prepare, by reacting (*S*)-diphenylprolinol **3.16** for three hours at reflux with a solution of boronic acid in THF with a Dean-Stark apparatus to collect excess water. **3.17** was then isolated as a colourless solid by evaporation.



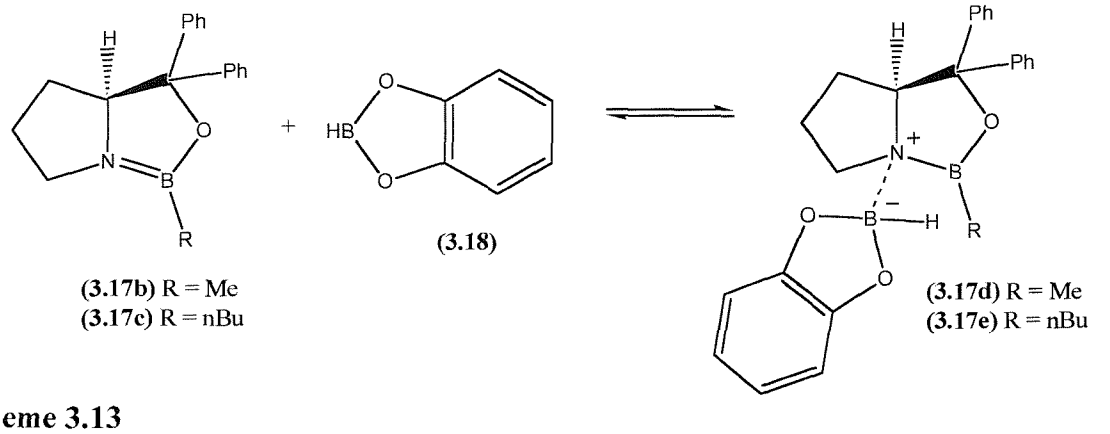
Scheme 3.12

The results for catalyst **3.17** were even more impressive than for oxazaborolidine **3.15** with e.e.'s for a similar range of substrates as shown in table **3.1** around 96-98 %, although the results for α-tetralone were less impressive using **3.17**. Corey reports that the overall yields of the reactions were generally around 86 %.[76]

3.4.2.3 Increasing the Functional Group Compatibility of Oxazaborolidine Catalysts.

Although a useful tool for the reduction of more simple less functionalised ketones, the catalysts were not suitable for functional groups such as amides and olefins, which are themselves susceptible to reduction by borane, the reducing agent employed by Corey and co-workers during their initial investigations. Furthermore at low (i.e. –78 °C) temperatures, the observed e.e.'s tended to drop, eliminating the possibility of reducing thermally unstable ketones.

However, by switching to catecholborane **3.18** as the reducing agent in conjunction with methyl or butyl-substituted oxazaborolidine **3.17,** these concerns were largely eradicated.[80]



Scheme 3.13

3.4.2.4 Improvements to the Synthesis of Oxazaborolidine Catalysts.

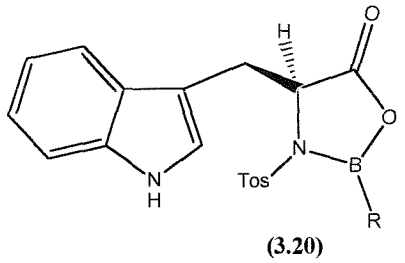
Although oxazaborolidines **3.17b** and **3.17c** had proved to be effective catalysts, the reaction times for the formation of the catalysts were often up to 3 hours, whereas the reaction time for the catalytic reaction was measured in minutes. In order to reduce the preparation time therefore, Corey and Link published the synthesis of oxazaborolidines such as **3.17c** from bis(trifluoroethyl) alkylboronates and (*S*)-diphenylprolinol **3.16**.[77] By mixing together **3.16** with bis(trifluoroethyl) *n*-butylboronate **3.19** in toluene, then removing the solvent and excess **3.19** under vacuum, then heating the remainder at 110 °C for 30 minutes at low pressure, the synthesis of **3.17c** was accomplished. In addition this also allowed for the *in situ* use of the catalyst. After the above procedure is carried out the isolated catalyst can be stored as a stock solution and the remaining components, i.e. the substrate and catecholborane can then be added to the stock solution at the correct temperature to afford the desired chiral alcohol in good yield and with e.e.'s comparable to the results observed with oxazaborolidine **3.17c** synthesised the origin way.[77]

substrate	catalyst	Reducing agent	T, °C	Time (min)	e.e.%
PhCOMe	3.17b	BH_3·THF	**23**	**0.1**	**96**
$PhC_2H_5COCCl_3$	3.17b	Catecholborane	**-60**	**12**	**96**
PHCOMe	3.17c	BH_3·THF	**23**	**0.1**	**96**
$PhC_2H_5COCCl_3$	3.17c	Catecholborane	**-78**	**12**	**94**

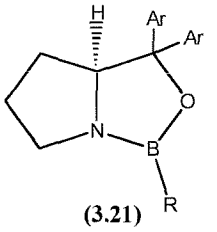
Table 3.2

3.4.2.5 Other Oxazaborolidines for Ketone Reduction, and Other Applications.

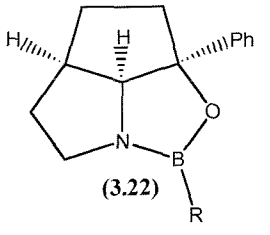
Corey has also published a number of other oxazaborolidines compounds that are suitable for the reduction of ketones and other applications and these are shown below. Compound **3.20** has been shown to be useful for enantioselective Diels-Alder reactions, and **3.21** and **3.22** are variants of oxazaborolidine **3.17** that have been applied to ketone reduction.[77]



(3.20)



(3.21)



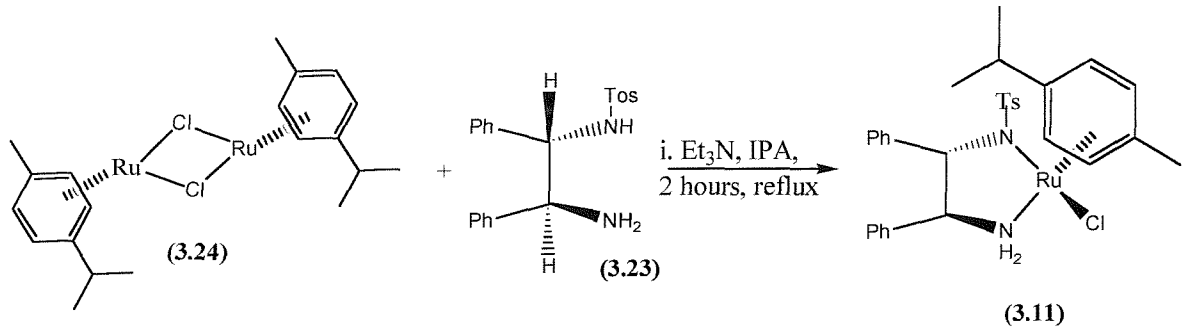
(3.22)

R = H, alkyl, phenyl. Ar = phenyl or ß-napthyl

Scheme 3.14

3.4.2.6 Noyori's Ruthenium/Cymene TsDPhEN Hydrogen Transfer, Hydrogenation Catalyst.

Noyori has also investigated the asymmetric reduction of aryl-substituted ketones, but using ruthenium based catalysts.[78] These are made from ruthenium chloride complexed to either *p*-cymene or mesylitene and then complexed to a chiral ligand, in this case (*S*,S)-N-tosyldiphenylethylenediamine (TsDPhEN) **3.23** to give the desired chiral complexes i.e. compound **3.11**. In practical terms the ruthenium cymene complex **3.24** exists as a dimer, and so in order to synthesise **3.11**, a mixture of the dimer was heated with a two-fold excess of chiral ligand **3.23** in IPA with triethylamine as the base.[78]



Scheme 3.15

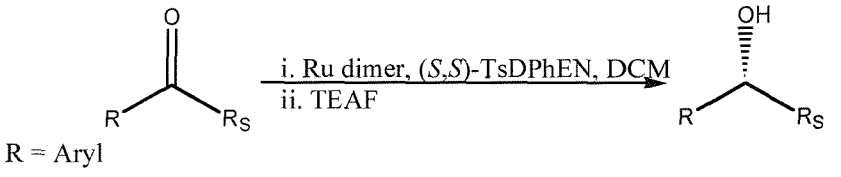
The catalyst was originally used as a hydrogenation catalyst with startling results. Amongst these was the reduction of mole of acetophenone under 1000psi of hydrogen, with catalyst loading of 0.01%, giving a 99% isolated yield and an e.e. of 86%, an impressive performance for such a large quantity of substrate. Increasing the catalyst loading to 0.1% improved the e.e. to greater than 95%.[79]

However the catalyst has found its main role in chemistry as a hydrogen transfer catalyst, leading to the award of the 2000 Nobel Prize for chemistry to Noyori. At first the hydrogen transfer agent used in conjunction with the catalyst was IPA. This functions by reaching equilibrium with the substrate and acetone, the by-product of the reaction. The great advantage of using IPA is that it could also function as the solvent of the reaction, meaning that the concentration of the hydrogen transfer agent is always high, helping drive the reaction forward. If the substrate is not very soluble in IPA, then the addition of a small quantity of DMF is usually enough to achieve complete dissolution However the IPA reaction has one significant drawback, in that for more hindered or kinetically slow substrates, the fact that the reaction is in equilibrium means that excessively long reaction times result in a loss of e.e., This occurs as the desired chiral alcohol product can, if in the reaction mixture for long enough set up its own equilibrium with the acetone formed as a by product of the catalytic reaction, eventually resulting in racemised alcohol as a significant product.[79]

3.4.2.7 A new hydrogen transfer agent for Noyori's Asymmetric reduction catalyst.

The difficulty of racemisation caused by the IPA/product equilibrium for more hindered/kinetically slow substrates was addressed by the publication by Noyori and co-workers of the use of a 5:2 triethylamine/formic acid azeotrope (TEAF), which does not function within an equilibrium as one of the by-products is carbon dioxide which bubbles

off.[80] TEAF is formed by carefully adding freshly distilled formic acid to freshly distilled triethylamine at 0 °C. The azeotrope is long term stable and does not need re-purification before use. In addition the azeotrope enables Noyori's catalyst to be employed as an *in situ* catalyst, as the azeotrope retains enough basic character to encourage formation of the active catalyst. In practical terms this makes Noyori's catalyst simple to use. The ruthenium cymene/dimer **3.24** is mixed with two equivalents of (*S,S*-TsDPhEN) in DCM under a nitrogen atmosphere for 10 minutes. Then the substrate is added, followed by the TEAF.

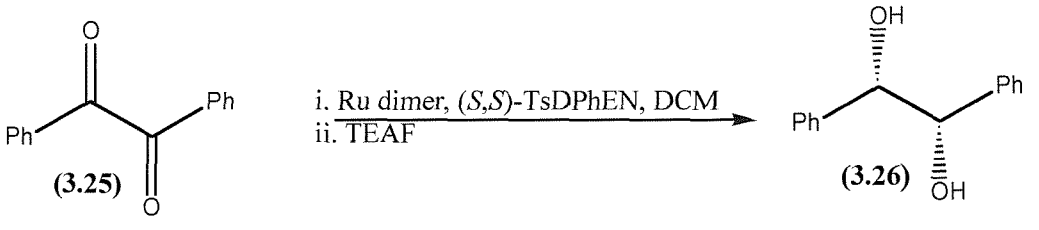


Scheme 3.16

The reaction times are generally longer than those observed by Corey for the oxazaborolidine catalysts, but the reaction can be heated, or cooled depending on the substrate. The reaction times are usually in the range of 30 minutes hour to 4 hours but can be much longer. Substrates with really short reaction times are often reduced at lower temperatures as overly rapid reduction often results in a lower e.e.

3.4.2.8 The Origins of Enantioselectivity in Noyori's Asymmetric Reduction Catalyst.

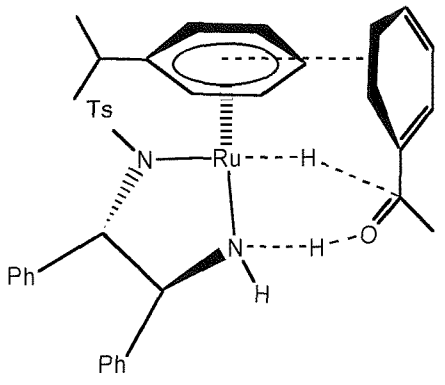
The results for Noyori's asymmetric reduction catalyst are rather impressive with e.e.'s of 95% and over recorded for a variety of substrates, including 98% e.e. for the reduction of benzil, a 1,2 bis ketone.[81]



Scheme 3.17

This high degree of enantiocontrol is attributable to two main structural features of the catalyst. Firstly the presence of the chiral ligand, which regulates the approach of the substrate to the metal centre, and secondly the presence of the cymene group which holds the substrate in place by pi stacking with the phenyl group of the substrate.[82]

Scheme 3.18



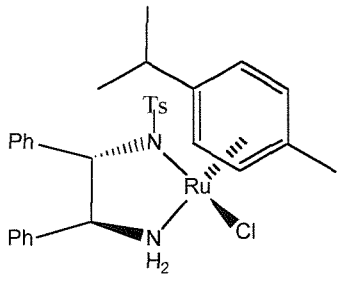
3.4.2.9 Conclusions.

Both catalysts are highly capable asymmetric ketone reduction tools, each with pros and cons. For Corey's oxazaborolidine catalyst the high activity and quick reaction times are obvious benefits, but the cost of the reagents, not so much in the catalytic part but the stoichiometric reagents, either catecholborane or even BH_3·THF would have become expensive especially as large quantities of the reducing agents were required. For example the typical cost of borane/THF solution is £80 per litre of a 1M solution, and the cost of 100g of catecholborane is £267.74.[83] When this is compared to the cost of the TEAF reducing agent in the Noyori system then the significance becomes apparent. Triethylamine is approx. £20 per litre and formic acid is £14 per litre.[83]

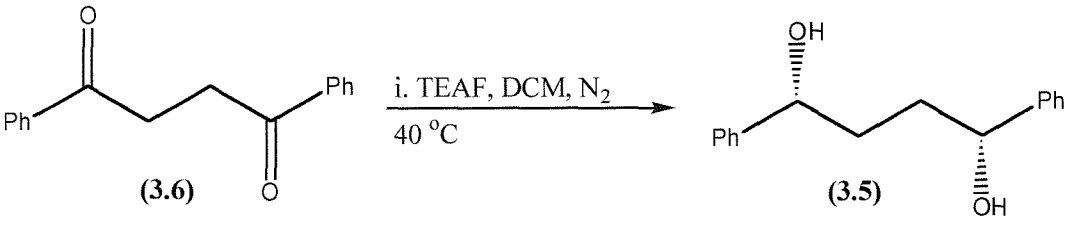
So the resulting cost benefits combined with the fact that the difference in results for the two systems was negligible for the type of substrate that was going to be used, was enough to ensure that the Noyori system was initially employed for this project.

3.4.3 Synthesis of (*R*,*R*)-1,4-diphenyl-2-butan-1,4-diol 3.5.

As stated above, it was initially decided to investigate the reduction of asymmetric ketones using Noyori's asymmetric hydrogen transfer catalyst **3.5**. As stated in the review, the catalyst can be either preformed or generated *in situ* and the former was initially investigated to simplify any potential optimisation and indeed the reaction did require a fair degree of optimisation. Initial attempts to perform the reduction were hampered by the reluctance of the reaction to reach total conversion to diol **3.5**. The reaction would proceed slowly and although heating the reaction at reflux, not normally necessary with these catalysts helped the rate of reaction, the process appeared to stop after 48 hours. This required further investigation.



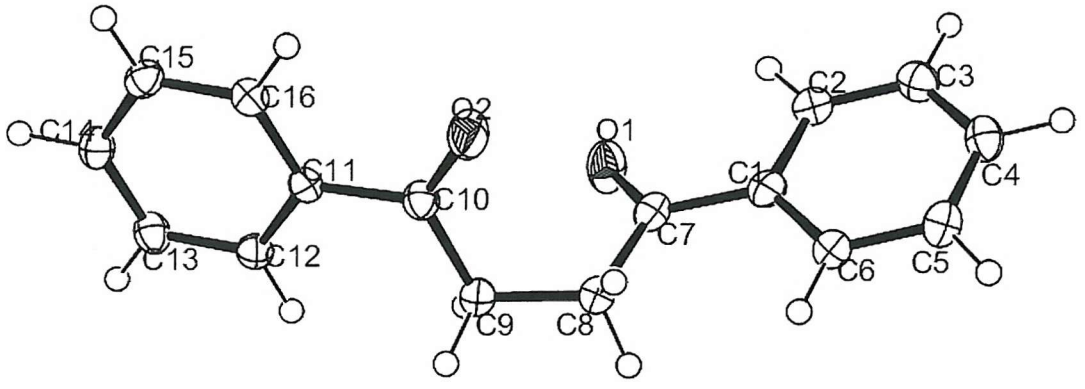
3.11



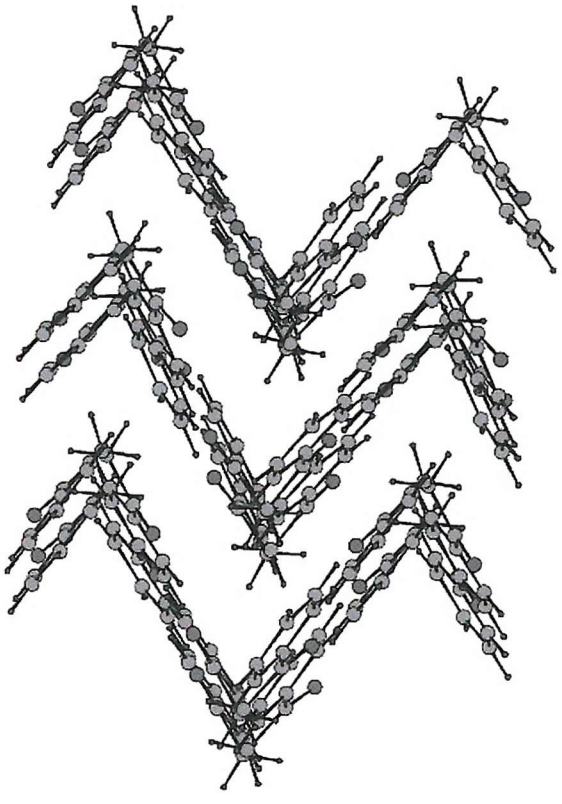
Scheme 3.19

There were a number of variables to investigate in order to achieve the desired outcome: Catalyst loading, order of addition of reagents, solvent, substrate concentration, substrate and product solubility, product effects on the catalyst and hydrogen transfer agent can all effect the reaction. Using GC we were able to investigate these variables. First the most appropriate hydrogen transfer system had to be selected. As stated previously two are available, IPA and a triethylamine/formic acid azeotrope (TEAF). IPA reactions are generally performed with much lower catalyst loading as IPA also acts as the solvent; therefore the system is more concentrated, hopefully leading to a much higher turnover rate than the TEAF system. However the IPA system has drawbacks of its own. The reaction with IPA is an equilibrium between IPA and acetone, and as time progresses this results in a lower degree of stereoselectivity in the hydrogen transfer reaction. The main drawback to this method in this example was the lack of solubility of bisketone **3.6** in IPA, even using DMF as co-solvent, resulting in lowered reaction concentration and vastly increased

reaction times, further lowering the selectivity of an already slow reacting substrate. In fact bisketone **3.6** is very insoluble in IPA, even with heating and ultrasound to aid the process, and perhaps more surprisingly, it is also insoluble in a wide range of organic solvents from pentane to ethanol and from benzene to ethyl acetate. This is probably attributable to the close packing of the compound in the crystalline form, which prevents molecules of solvent gaining access to the compound and disrupting the highly ordered nature of the crystalline form. Xray structures 1 and 2 below show the unit cell and a view of the close packed structure.



X-ray 1: unit cell of compound 3.6



X-ray 2 close packaged structure of compound 3.6

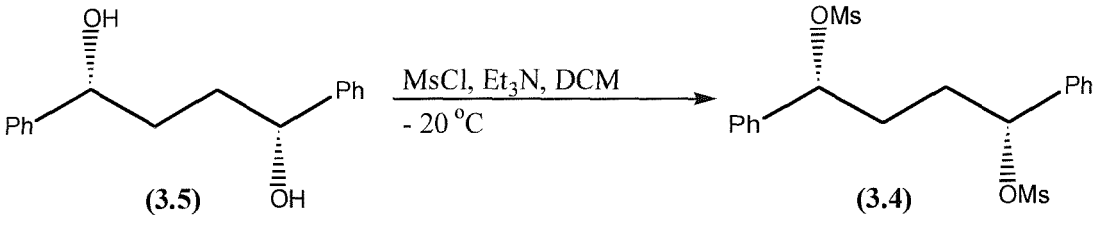
The only solvent in which a high degree of solubility was observed was dichloromethane, which meant that although the reaction using the TEAF system was giving poor results (22%) the chances of recording a high degree of enantiocontrol were better than the IPA method, which was giving terrible results (4-5%). Therefore TEAF was the transfer agent of choice and DCM the solvent.

In order to see if the fault was with the catalyst, the conditions or the substrate, the TEAF/DCM system was tried on acetophenone, a literature example. Upon treatment with pre-formed catalyst and TEAF, acetophenone was quantitatively reduced to the corresponding alcohol with high e.e. The reaction was then repeated, but this time the desired diol **3.5** was added to the acetophenone reaction mixture to see if it was poisoning the catalyst, providing an explanation for the poor results. Again the reaction was successful with acetophenone reduced quickly and with good enantiocontrol. Unfortunately though diketone **3.6** was still giving poor results. Other components of the reaction were then varied to see if the 22% yield could be improved upon. Varying the order of addition of reagents from one reaction to another and increasing the catalyst loading to 10% had no effect. With increasing frustration a fresh batch of catalyst was added to the reaction after 24 hours to see if this would extend the catalytic reaction. When this was not successful adding the catalyst batch-wise every 8 hours was tried. Again the reaction was still not reaching completion. This did however reduce the number of things that could be responsible: If the catalyst was not the problem, the solvent was not the problem and the substrate was not the problem there was only the hydrogen transfer agent left. So the batch-wise approach was tried again, but this time adding the TEAF portion wise and this proved to be highly successful the reaction reaching total conversion after 48 hours. The isolated yield was 90 %, and this reaction has proved repeatable upon scale up. Unfortunately the e.e. was immeasurable by chiral HPLC and GC due to non-separation on the available chiral columns, however the optical rotation of the compound was identical to that found in the literature for compound of >98% e.e. In addition, the *rac* to *meso* ratio was favourable, as determined by melting point analysis, and recrystallisation from DCM/hexane provided pure compound.

3.5 Preparation of a Novel Cp Ligand.

3.5.1 Synthesis of Bis mesylate 3.4.

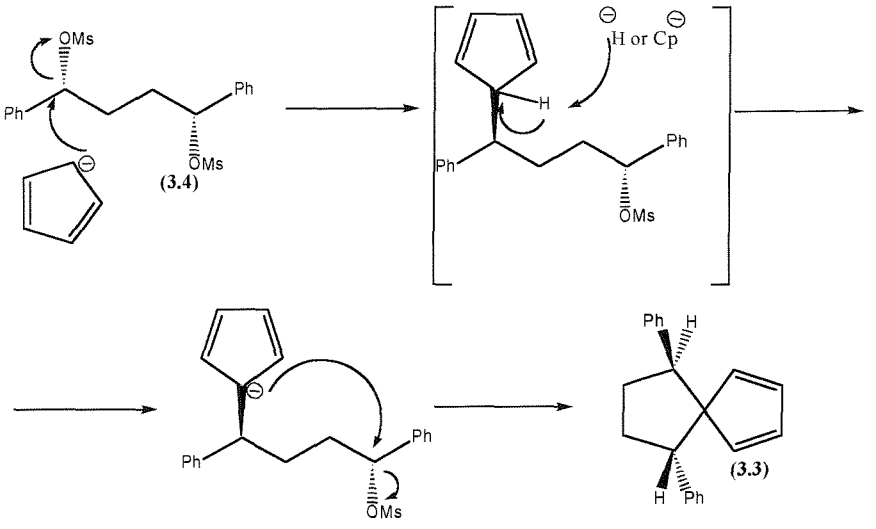
With large quantities of chiral diol **3.5** in hand, the synthesis of the desired Cp ligand was investigated. In order for the addition of a Cp ring to the molecule to be successful, it was necessary to turn the hydroxyl moieties into suitable leaving groups, and the synthesis of the bis mesylate compound was explored. Benzylic mesylates are always liable to be unstable, and this compound was no exception, and once formed was used immediately as storage, even in dry ice, was impossible. However by carefully following the preparation of Taylor and co-workers it was possible to prepare multi-gram quantities of the bis-mesylate, as long as certain procedures were followed to the letter, the most important regarding the removal of solvents at reduced pressure.[84] If all of the final solvent, ethyl acetate, was removed on a rotary evaporator then the compound would immediately decompose, but if the 98% of the ethyl acetate was removed, then the compound could be successfully precipitated via the addition of hexane. Final isolation was then performed by suction filtration at water pump pressure, with excess ethyl acetate removed by extensive washing with hexane. This renders the desired mesylate of sufficient purity for further usage.



Scheme 3.20

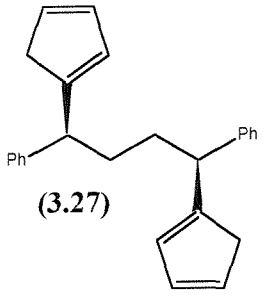
3.5.2 Displacement of Mesylate Groups with Sodium Cyclopentadienide.

The displacement of both mesylate groups by a single equivalent of Cp to give spirocycle **3.3** was envisaged. Two methods were available for the displacement of the mesylate groups: 1 equivalent of cyclopentadiene and an excess of sodium hydride, or an equal excess of Cp and sodium hydride.[29,30]



Scheme 3.21

It was decided to use an excess of sodium cyclopentadienide to effect the substitution of the mesylate groups. Although on the face of it this seems a little strange, as it would appear to encourage the formation of the bis Cp compound **3.27** via displacement of each of the mesylate groups with a molecule of Cp, the vastly increased rate of an intermolecular second substitution renders this insignificant. Furthermore, by using high concentration of the nucleophile it was hoped that the reaction would proceed more rapidly than for Halterman's analogous systems, i.e. ligand **1.79,** which required refluxing overnight.



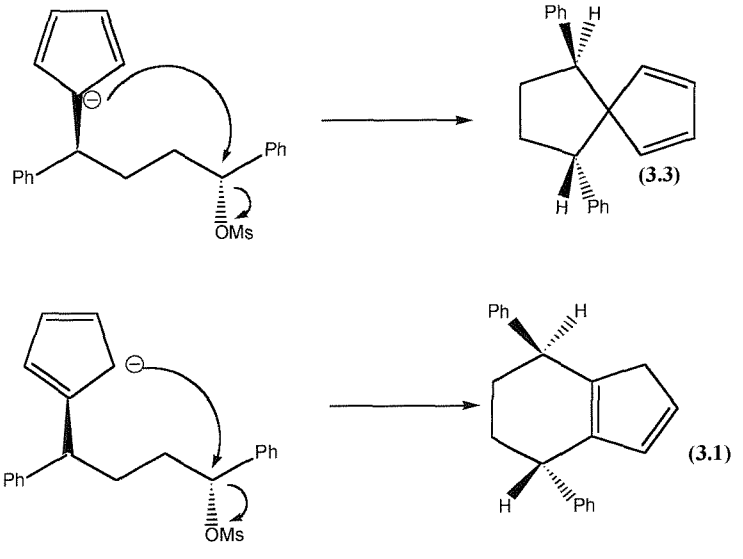
(3.27)

Treatment of mesylate **3.4** with an 8-fold excess of sodium cyclopentadienide in THF at -78°C, which was then allowed to warm to room temperature overnight, led to the formation of at least three compounds all with very similar Rf values for TLC in 100% petrol. Crude NMR showed unexpected results. Instead of the simple alkene doublets expected for spirocycle **3.3** a far more complex spectrum was produced, the main components of which had overlapping alkenyl proton signals and a very complex region between 1 and 4 ppm, which made assignment very difficult. The ^{13}C NMR was more conclusive in that quaternary alkyl centre expected at ~60 ppm was notable only by its absence. However GC CI mass spec was far less ambiguous and gave m/z 273 as the major component, which was the correct M+H for spirocycle **3.3**. (Not unexpectedly trace amounts of m/z 339, the M+H for bis Cp **3.27** were also shown to be present by mass spec.)

Following crude purification of the reaction mixture, achieved by swift flushing through silica, NMR and mass spec gave the same results as the previous analysis, and in terms of GCMS, as the exact concentration of the sample was known, this suggested that there was no other component that could have given the NMR data but not have flown by GCMS due to mass or volatility and that the as yet unidentified compound was the major constituent of the recovered mass. The isolated yield of the reaction was 52%. The reaction was repeated twice with identical results and the unknown compound was still not pure enough in the NMR spectrum for unambiguous assignment.

3.5.3 Synthesis of Novel Cp Ligand 3.1.

As is so often the case the answer was very simple, the problem was being so sure of the reaction outcome due to relying on all known precedent, that the obvious answer was temporarily ignored. Instead of forming spirocycle **3.3,** the reaction was proceeding directly to Cp **3.1,** which was formed as a mixture of mainly two double bond isomers as well as small quantities of the bis Cp compound. This was occurring as the second deprotonation was not occurring from the carbon centre in the Cp ring attached to alkyl skeleton, but from the site adjacent to it



Scheme 3.22

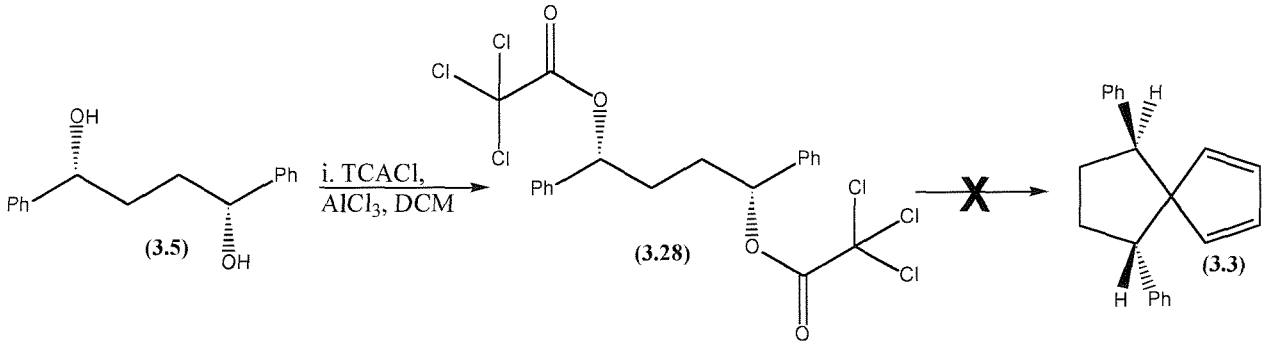
The existence of Cp **3.1** as a mixture of double bond isomers as well as the presence of small amounts of Cp, which had re-dimerised during workup, meant that the NMR spectra of this reaction were unclear. Isolation of the double bond isomers and other by-products

was difficult due to the extreme non-polarity of the all components of the crude product and the purification conditions used at that time. Cp's are often unstable species, particularly when exposed to the acidic conditions of column chromatography on silica, and so the reaction mixture was either pushed quickly through silica pads or purified on neutral alumina. Unfortunately alumina did not show any of the separation seen on silica TLC plates of the components of the crude reaction mixture, even when run in pure petrol.

3.5.4 Varying the Reaction Conditions to Encourage Spirocycle Formation.

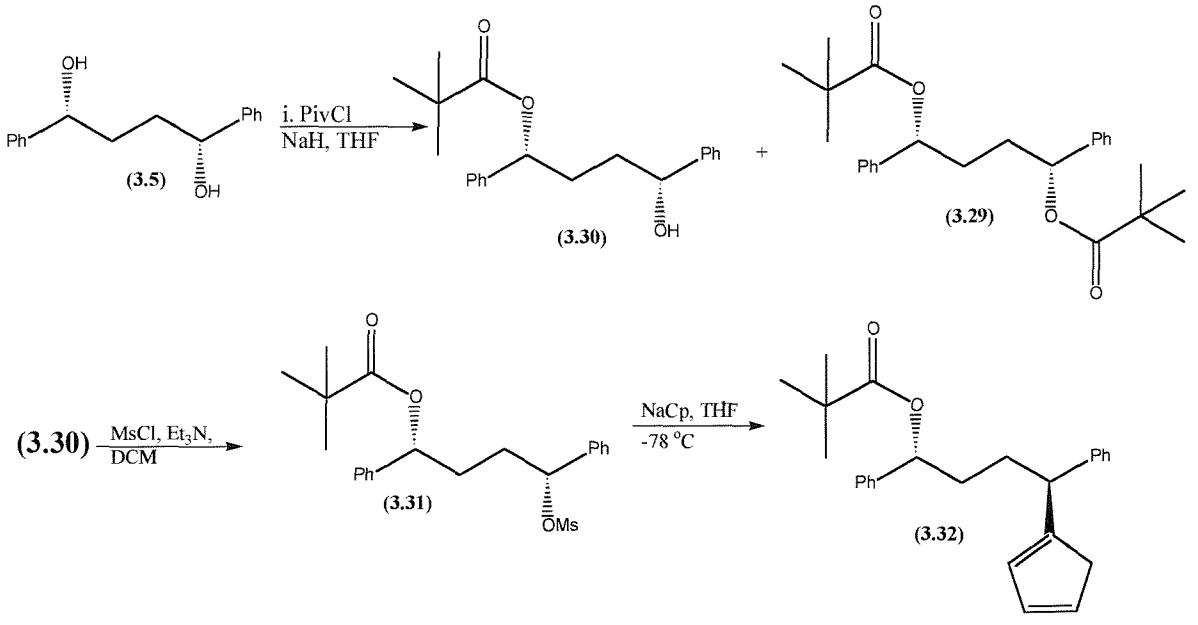
The most effective way of solving this problem was to encourage the reaction to form spirocycle **3.3** instead of the Cp. The advantages of this were threefold. Firstly it would be formed as a single compound, secondly it would most likely be a crystalline solid and finally it would be probably be stable in the long term. The combined effects of all this would have been a significantly easier isolation procedure and an increased potential for long term storage. Amongst the variations in the reaction conditions that were tried in order to accomplish this were: Using a single equivalent of Cp with an excess of NaH, changing the counter iron from Na to Li and Potassium, using different bases including potassium tert-butoxide and LiHMDS, changing the temperature at which mesylate **3.4** was added to the Cp and using ether and DME as the solvent instead of THF. Finally different leaving groups were investigated. Trichloroacetyl chloride and pivaloyl chloride were to hand and so the syntheses of bis TCA ester **3.28** and bis pivaloyate ester **3.29** were attempted.

Bis-TCA ester **3.28** was synthesised in an 86% yield, but all attempts to displace the TCA esters with Cp were unsuccessful.



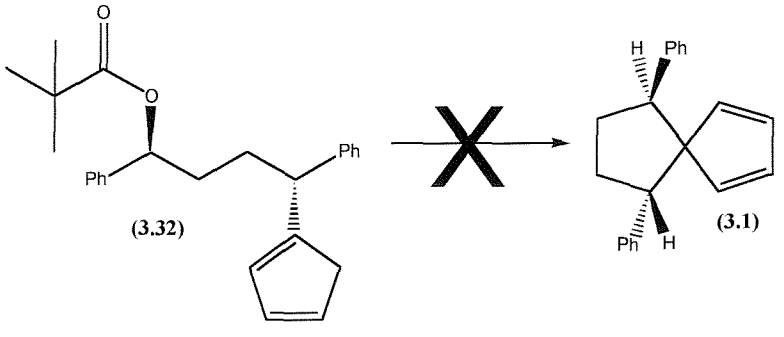
Scheme 3.23

Bis pivaloyl ester **3.29** however, offered an intriguing alternative route to ligand **3.1** because irrespective of how forcing the reaction conditions used were, the main product of the esterification reaction was monoester **3.30** with only a small amount of bis- pivaloyl ester **3.29** produced. This was probably due to an increase in steric hindrance once the first pivaloate group had been introduced. This allowed therefore an opportunity to investigate the formation of Cp **3.1** on a step-by-step basis, as with one hydroxyl group protected, mesylate **3.31** could be prepared and then substituted by sodium cyclopentadienide. This was completed with an overall yield of 47% through to Cp **3.32**.



Scheme 3.24

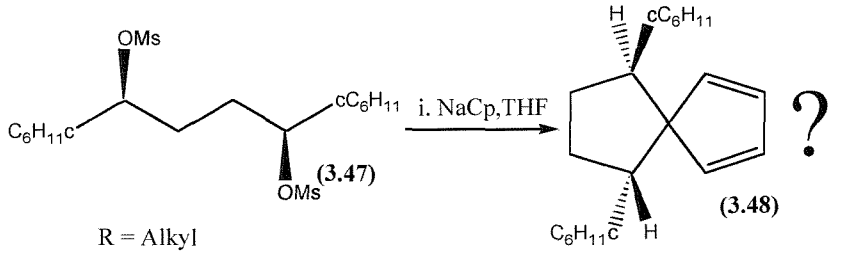
However all attempts to displace the pivaloyate group by reforming the Cp anion were unsuccessful and so this was not a viable route of for the synthesis of spirocycle.



Scheme 3.25

So in spite of these numerous attempts to produce spirocycle **3.3**, the only variation was in the yield of the reaction. Absolutely no trace of spirocycle **3.3** was seen by carbon NMR or any other spectroscopic analysis and the only products were the mixed double bond isomers of Cp **3.1**.

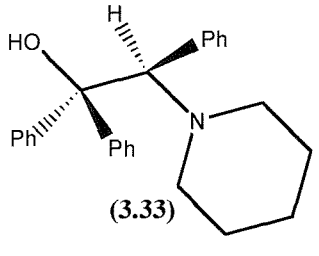
This would have been satisfactory if the ratio of desired product to undesired by-product or the ratio of double bond isomers was showing any sign of an improvement but this was not the case and so it was decided to investigate the possibility of synthesising an analogous system with alkyl substitution rather than the phenyl side chains found in **3.1.** The rationale behind this was that the presence of the electron donating phenyl groups was somehow directing the second mesylate displacement from α to the site of the bond already formed between the Cp and the alkyl chain. By changing the electronic character of the transition state mono mesylate/Cp molecule there was the hope that a more favourable outcome would be achieved. In addition the introduction of the cyclohexyl group was the desired aim, as molecular modelling showed that although not as ideal as the phenyl group as a means of providing a blocking group on one side of the metal centre, it was closer in size than other widely used alkyl groups such as isopropyl or butyl.



Scheme 3.26

3.6 An Alkyl Alternative to Cyclopentadiene 3.1.

Initially it was decided to look at the addition of chiral zinc reagents to succinaldehyde. The enantioselective addition of alkyl zincs to carbonyls using chiral ligands well known, and number of ligands able to mediate such transformations is extensive. One of the best in terms of e.e. is amino alcohol **3.33**, first published by Pericas and co-workers, which is shown to mediate the addition of alkyl zincs to simple aldehydes such as heptanal with e.e.'s of 98% and above.[85] In addition it avoids the use of stoichiometric quantities of $TiCl_4$, the Lewis acid long associated with such reactions, making the process more user friendly both in practical terms and in economic terms.



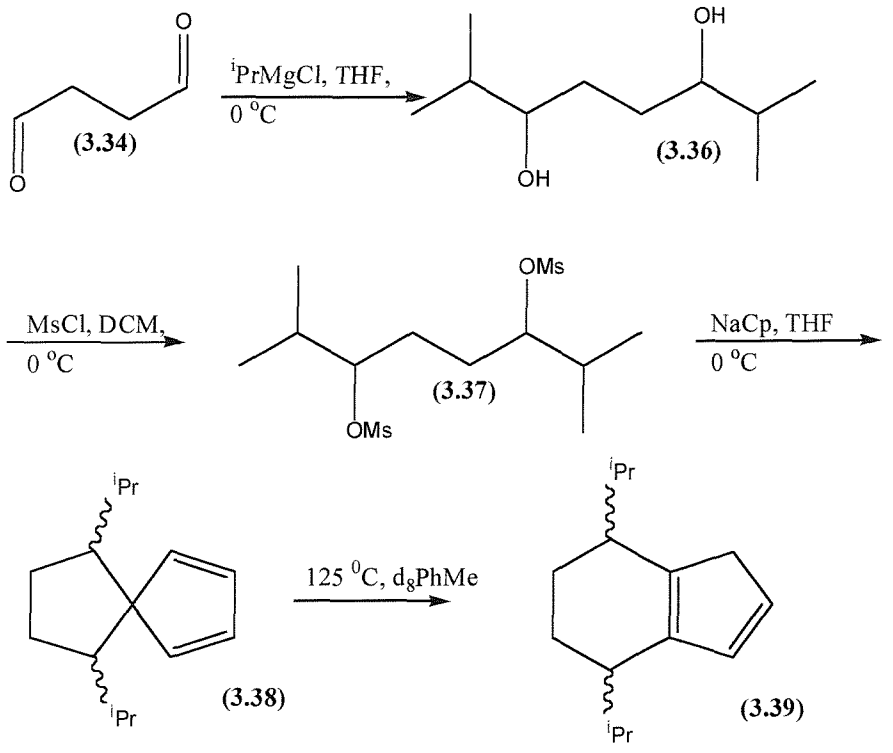
(3.33)

Before the reaction was attempted using pyrophoric dialkylzincs and the catalyst, the idea was examined using much less expensive although non-chiral Grignard reagents.

3.6.1 Synthesis of Racemic Dialkyl Bis Ketones.

Succinaldehyde, **3.34,** was prepared according to the method of House and Cronin from dimethoxytetrahydrofuran **3.35** but in low yield and poor purity.[86] This was then added to a large excess of diisopropyl magnesium chloride at –78 °C. This gave the desired diastereomeric diisopropyl diol **3.36** in a 10% overall yield from succinaldehyde. (By later adapting the procedure of House and co-workers it was possible to increase the yield of succinaldehyde to 70%)

The following dimesylation reaction gave diastereomeric diisopropyl dimesylate **3.37** in a 50% yield. The bismesylate was then added to a solution of sodium cyclopentadienide in THF at low temperature. Unlike the phenyl example however the reaction was successful although low yielding and went through to a mixture of compounds including desired spirocycle **3.38** as a mixture of diastereoisomers (33%). The NMR was complicated by the presence of diastereoisomers but the quaternary carbon at 76.97 ppm was clearly present, and MS confirmed that the correct molecule was present. A small scale thermal re-arrangement of the spirocycle was attempted in D_8-toluene and after 12 hours at 120 °C the quaternary signal was lost from the NMR spectra of the reaction mixture. As this was only a guide neither spirocycle **3.38** or Cp **3.39** were properly characterised. The presence of diasteriosmers in these compounds made NMR assignments impossible.

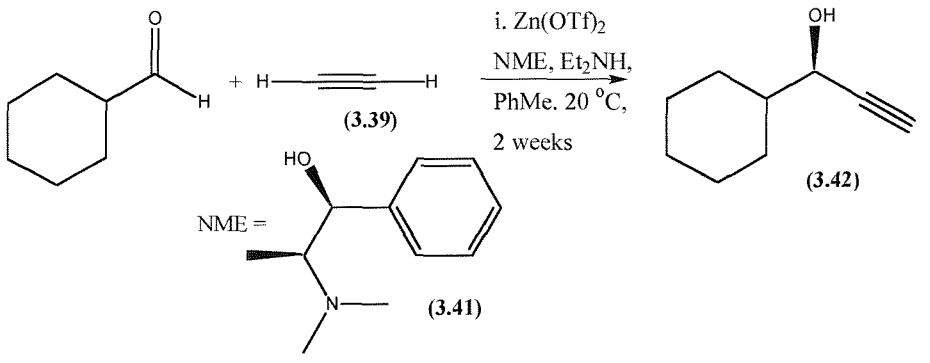


Scheme 3.27

Although the procedure was successful as a means of forming the isopropyl compound, when the reaction was repeated with cyclohexyl and ^{t}butyl magnesium chlorides there was a much lower degree of success. The major products were very insoluble white powders, which were believed to be cyclised by-products, and only small amounts of the desired 1,4-diols were formed.

3.6.2 Chiral Addition of Zinc Acetynides to Cyclohexane Carboxaldehyde.

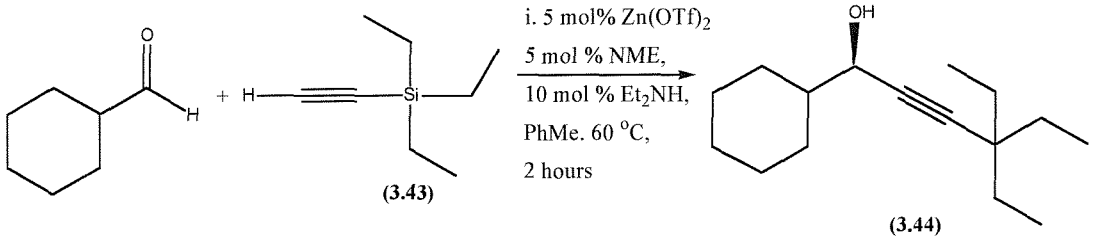
As obtaining and storing large quantities of pure succinaldehyde was likely to prove impossible, combined with the practical difficulties of preparing dialkyl zinc reagents (only diethyl zinc is commercially available) other routes were investigated. The most promising of these was the chiral addition of zinc acetynides to cyclohexane carboxaldehyde first published by Carreira and co-workers.[87] In this reaction the acetylide is generated either from acetylene gas **3.39** or triethylsilylacetylene **3.40** and zinc triflate in the presence of diethylamine and chiral ligand N-methylephedrine **3.41**. It has several advantages over the dialkyl zinc routes: Firstly it affords propargyl alcohols with very high e.e's, secondly it is a much more mild procedure as it does not involving strong acids or bases and finally the reaction can be either stoichiometric or catalytic in zinc triflate and ligand depending on the aims of the reaction and the conditions used.



Scheme 3.28

Scheme **3.28** above shows how Carreira initially used the reaction to create chiral propargyl alcohols from acetylene gas with stoichiometric quantities of zinc triflate and NME. However the reaction times were extremely long (11 days) and although acetylene gas is very cheap, the other reagents are not.

Obviously one of the best ways of increasing the rate of a reaction is to heat it, however heating acetylene gas in a sealed system on a large scale is fraught with problems and so unsurprisingly Carreira used triethylsilyl acetylene **3.43** as a replacement in order to investigate the heated reaction. He discovered that not only did the reaction show the same degree of enantiocontrol, but also that the extra energy in the system was enough to make the reaction catalytic in terms of NME and zinc triflate. Presumably this is because the energy barrier, which allows the chiral zinc species that forms to dissociate from the transition state and be reused, is overcome upon heating.



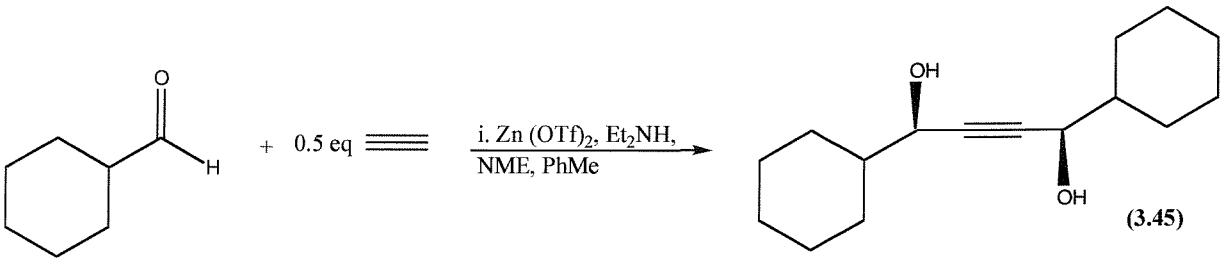
Scheme 3.29

The reaction is heated at 60 °C instead of reflux, as the boiling point of toluene is much higher than the boiling point of triethylsilylacetylene **3.43**. Furthermore aside from the initial stages of the reaction where the zinc triflate is heated at 120 °C using Schlenk techniques, the rest of the reaction is reasonably robust to the presence of both water and air. Solvents purchased as anhydrous (not usually suitable for moisture or air sensitive reactions without distillation from Na/benzephenone) are sufficiently dry and oxygen free

for usage straight from the bottle. The reaction is not without drawbacks however, the main being the currently high cost of triethylsilyl acetylene (approximately £7 per gram).

3.6.3 Synthesis of 1,4-Dicyclohexyl-butyne-1,4-diol 3.45 using Zinc Acetylide Chemistry with Acetylene Gas.

Both of these methods were potentially useful as a means of synthesising desired chiral diol **3.46** and so a reaction using the first method was initiated, and a thorough investigation of the second method was performed. For the acetylene gas reaction Carreira used a large excess of acetylene in order to push the reaction to completion and to ensure that no double addition product could be formed i.e. the addition of a molecule of cyclohexane carboxaldehyde to each end of the acetylene molecule. However this double addition reaction was the desired outcome in this case, as it would avoid the need for two reactions using expensive zinc triflate and NME. The first reaction was performed on a 1 mmol scale using 12 cm^3 of acetylene gas taken from a balloon using a gas tight syringe. The reaction was sealed and left to stir for 2 weeks, after which time the desired product was shown to have formed by TLC and was isolated in a 60% yield with an e.e. of 95%.

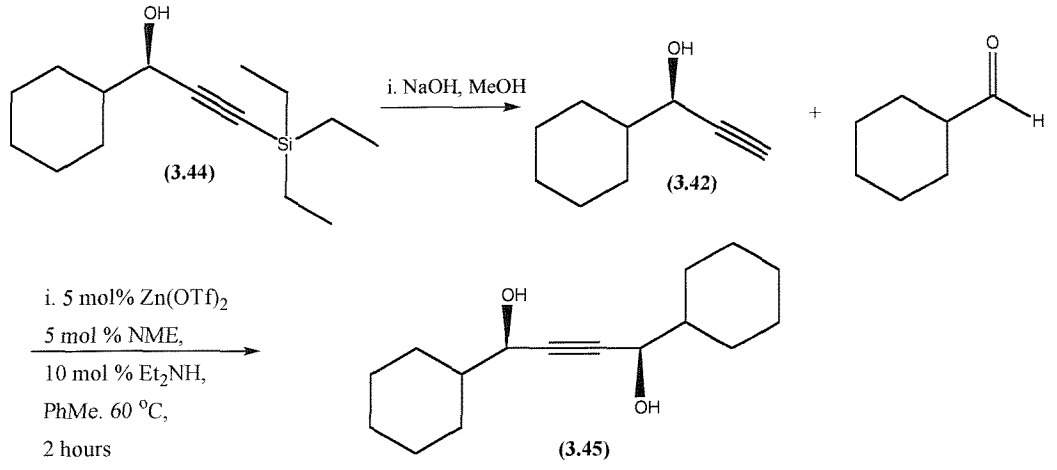


Scheme 3.30

3.6.4 Synthesis of 1,4-Dicyclohexyl-butane-1,4-diol 3.46 using Zinc Acetynide Chemistry and Triethylsilylacetylene.

The initial product of the catalytic method, silicon protected propargyl alcohol **3.44,** was synthesised in a good yield (73%) and was ideal for further elaboration. Following the method of Katsuhira, Harada and Oku, NaOH/MeOH, removed the silicon-protecting group in 90% yield, leaving propargyl alcohol **3.42**.[88] This was then used as the acetylene unit in a repeat of the coupling reaction, subsequently giving rise to propargyl diol **3.45**. This was

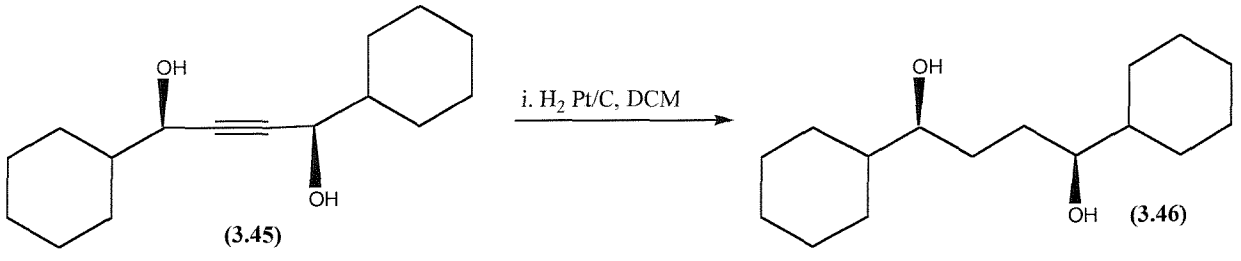
possible without having to protect the alcohol group due to the mild nature of the reaction conditions.



Scheme 3.31

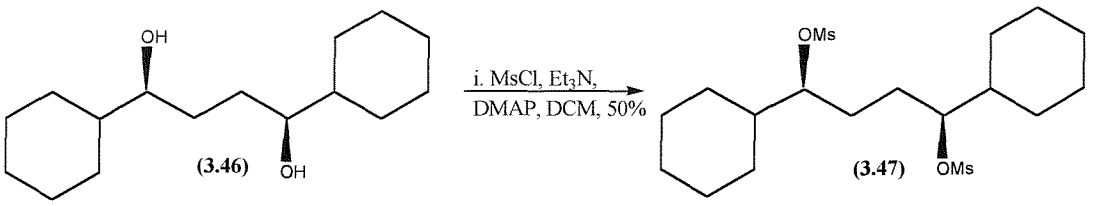
With propargyl alcohol **3.45** in hand it was possible to investigate the synthesis of spirocycle **3.48**.

Propargyl diol **3.45** was quantitively reduced over Pt/C according to the method of Bach and co-workers to give diol **3.46** as a white crystalline solid.[89]



Scheme 3.32

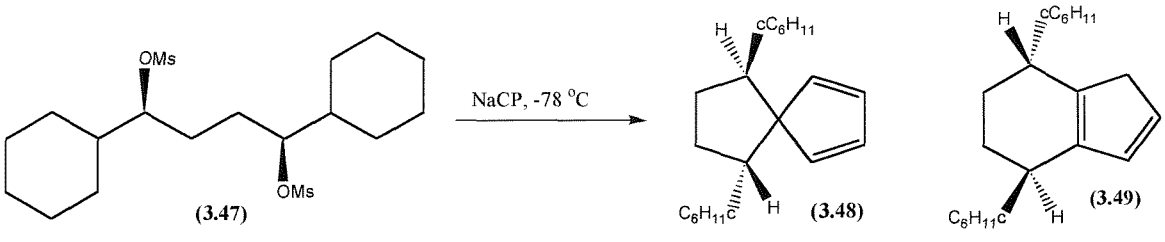
The next step, the mesylation of the hydroxyl groups, proved to be somewhat problematic as diol **3.46** proved to be incredibly insoluble in organic solvents. In order to produce a solution in DCM for the mesylation reaction a ratio of 50 mL per mmol of diol was required, resulting in a reaction mixture of very low concentration and consequently low reaction rate, although this was subsequently improved with the use of DMAP and several equivalents of MsCl.



Scheme 3.33

3.6.5 Synthesis of Spirocycle and Cp Ligand from Bis-mesylate 3.46.

Using the same procedure as for the phenyl substituted ligand; bis-mesylate **3.47** was treated with an excess of sodium cyclopentadienide in THF at −78 °C to give a mixture of Cp **3.49** and spirocycle **3.48** by NMR analysis. Unfortunately the two compounds were completely inseparable by TLC with both spots running at the solvent front in pure hexane, pentane and heptane. Attempts to separate them by selective crystallisation in a variety of solvent systems were also unsuccessful. The ratio of compounds **3.48** and **3.49** in the NMR was approximately 1:1 and so a solvent change was investigated as a possible means of affecting the outcome of the reaction. The reaction was repeated using both DME and ether as solvents. The DME reaction gave a similar outcome to the THF reaction, but when the reaction was performed in ether, the outcome had been effectively reversed with approximately 75% of the product according to analysis of the product by NMR spectroscopy spirocycle **3.48**. Unfortunately it was still proving impossible to separate the two components, and further investigation of the reaction conditions did not proffer an improvement in the respective ratios of the two compounds.



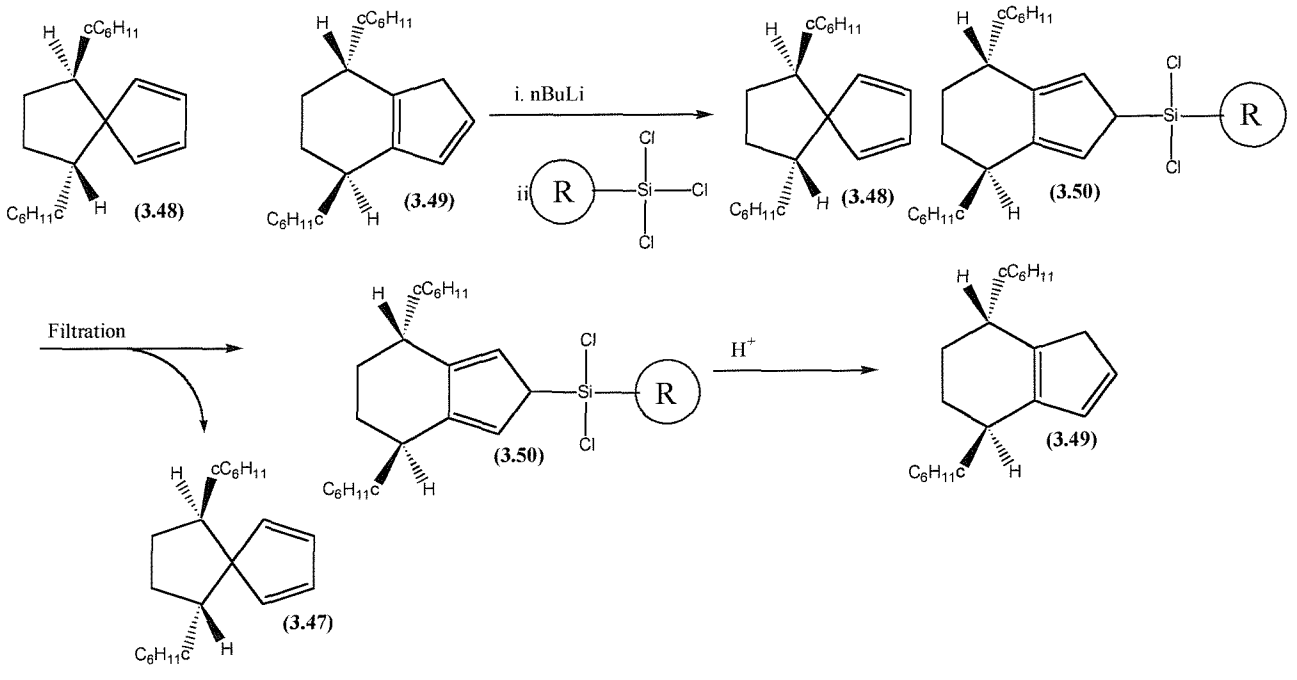
THF	50%	50%
DME	50%	50%
Ether	90%	10%

Scheme 3.34

As a means of avoiding the separation problem, the thermal 1,5 sigmatropic rearrangement of the spirocycle was attempted whilst in the mixture with Cp **3.49**. If successful then all of the compound would be converted to the Cp, without any loss of the Cp already present. Unfortunately monitoring of the reaction by NMR showed reduction of Cp both **3.48** and spirocycle **3.49** levels in comparison to the internal standard. The reaction was run at 130 °C in xylene.

3.6.6 A Potential Solution to the Separation of Spirocycle 3.48 and Cyclopentadiene 3.49.

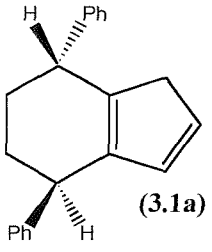
Unfortunately time constraints meant that further investigation into the isolation and purification of spirocycle **3.48** and Cp **3.49** was not possible, however potential solutions have been identified, the most promising of which would see the use of a silicon scavenger resin as a means of isolating the Cp, enabling the spirocycle to be washed away via filtration and then isolated by evaporation. The remaining silylated Cp component could then be cleaved from the resin in mildly acidic conditions i.e. stirring with silica gel, and then isolated.



Scheme 3.35

3.7 Re-examining the Isolation of Bis-Phenyl Ligand 3.1.

Although the investigation into the synthesis of alkyl substituted variants of ligand **3.1** was ultimately unproductive, the attempts to purify and isolate the Cp and the spirocycle suggested that Cp's of this design might well be more robust to the presence of silica than was originally thought. This lead to re-examination of the purification of phenyl substituted ligand **3.1**. By carefully subjecting small amounts of the reaction mixture to column chromatography on long columns of silica with 100% HPLC grade hexanes, which required the collection of an enormous number of fractions, it was possible to isolate the various components of the reaction mixture. The major component following chromatography was the double bond isomer **3.1a** as assigned by NMR spectroscopy, and could be isolated in a yield of approx 40 % from the treatment of the bis mesylate with NaCp. Following concentration and storage at –20 °C, compound **3.1a** solidified to form a white amorphous solid, stable for weeks if stored at –20 °. The reaction was repeatable and was performed on a scale of up to 10 mmol.



(3.1a)

The isolation of compound **3.1a** was an important step as it now allowed for the investigation into the synthesis of organometallic compounds derived from compound **3.1a**.

3.8 Conclusions.

The results in this chapter have demonstrated that a new chiral ligand system derived from inexpensive achiral starting materials was possible, although the synthesis is still in need a great deal of optimisation, with particular regard to scale and purification. However there are still some problems particularly with the system especially in regard to the displacement of the mesylate groups by NaCp.

The means by which the site at which the anion is formed is chosen is still unclear. It would appear to be both substituent and solvent related, but only in the case of phenyl substitution is it unambiguous in that there is no sign at all of the spirocycle. Why this system should display such differing characteristics to Halterman's system as well as to the closely related systems of Whitby and Gathergood is a mystery that has not yet been unravelled.

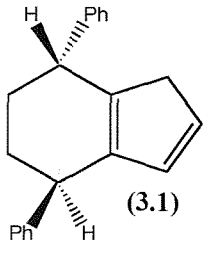
As a result this means that further development of the ligand system has been limited only to the phenyl variant **3.1a.** More investigation is clearly needed in order to bring through the alkyl substituted ligands, with the biggest potential breakthrough into them the possibility of using silicon scavenger resins to isolated the two components.

Nevertheless some excellent results were achieved for both the extension of Noyori's hydrogen transfer to the reduction of 1,4 diketones and the extension of Carreira's zinc acetynide chemistry to the synthesis of chiral propargyl diols. In addition there were some interesting experimental observations including the extremely insoluble nature of cyclohexyl diol **3.45** and phenyl ketone **3.6**.

4. The Synthesis of an η-5-cyclopentadienyl Chiral Transition Metal Complex Based on a Novel C_2-Symmetric Ligand.

4.1 Introduction.

Having been able to synthesise ligand **3.1** in relatively large quantities it was imperative to try and accomplish the synthesis of complexes based on this design. In chapter one the three criteria for the synthesis of novel chiral complexes were stated. Three of them, the cost of production, variability in structure and the induction of planar chirality have been met in that none of the reagents used during synthesis of **3.1** are expensive, with the exception of the ruthenium catalyst and ligand. (However the efficacy of these reagents at very low catalyst loadings means that in fact the reduction of bis-ketone **3.6** is economically viable.) With regard to structural adaptability, chapter three demonstrates that it is possible to synthesise a number of variations of **3.1** by replacement of the phenyl groups with cyclohexyl and other alkyl moieties. In addition the structure of Cp ligand **3.1** makes it suitable for complexation to a variety of transition metals either by the addition of a single molecule of ligand to $CpZrCl_3$ or $CpTiCl_3$ or the addition of two molecules of ligand to $TiCl_3$, $ZrCl_4$ or $RhCl_3$. As highlighted in chapter one different transition metals are suitable for different catalytic applications. Finally the induction of planar chirality: This does not really apply to ligand **3.1,** as the Cp faces are homotopic rather than diastereotopic, yet the results are the same if not better, because as mentioned previously homotopic Cp faces are stereochemically identical and so complexation results in an enantiopure complex, and in this ligand, the presence and size of the phenyl substituents should allow asymmetric induction in catalytic reactions.



(3.1)

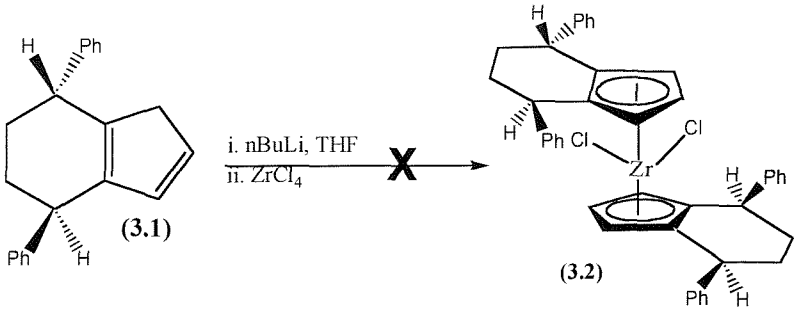
With regard to the fourth criterion, that a complex must be highly active, this was as yet unknown as no complexes had yet been synthesised.

Our first choice of targets was the C_2-symmetric zirconene **3.2** for the reasons stated in chapter **3.**

A review of the methods pertaining to the complexation of transition metals to form η-5-cyclopentadienyl complexes is available elsewhere and only those that do not form part of that review are discussed in here in detail.[3]

4.2 Attempted synthesis of [(4*S*,7*S*)-4,7-diphenyl-5,6,7,7a-tetrahydro-4*H*-indenyl][(4*S*,7*S*)-4,7-diphenyl-5,6,7,7a-tetrahydro-4*H*-indenyl zirconene dichloride 3.2.

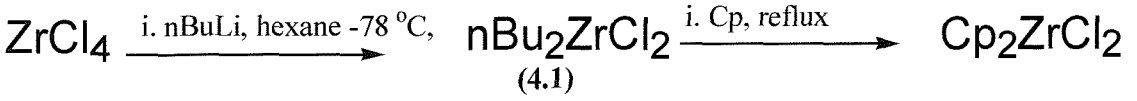
Based on previous experience within the group, the method initially used in an attempt to synthesise complex **3.2** was the deprotonation of ligand **3.1** at room temperature with nBuLi, followed by the addition of resulting the lithium salt to a solution of $ZrCl_4 \cdot 2THF$ at -78° C. The reaction mixture was then allowed to warm up overnight to room temperature at which time crude ^1H NMR analysis showed that no reaction had in fact occurred. The reaction was repeated several times using different temperatures for the lithium salt formation (–78 °C - -20 °C) and the reaction mixture was allowed to warm to room temperature and then heated in order to encourage complex formation, but with no encouraging results. The crude NMR still showed no signs of reaction had occurred. It was therefore decided to explore some other methods for the complexation of Cp ligands to $ZrCl_4$.



Scheme 4.1

One of the more recent methods for the synthesis of zirconocenes, first published by Eisch in 2001, involves the preparation of the dialkyl metal dichloride by treatment of a suspension of $ZrCl_4$ in hexane or toluene at –78 °C with nBuLi.[90] The subsequent mixture of Bu_2ZrCl_2 **(4.1)** and LiCl is then allowed to warm slowly to room temperature over an 8 hour period resulting in the reductive elimination of the alkyl groups leaving $ZrCl_2$, which can then be utilised in the metallation of a variety of Brønsted acids including alkynes, alkoxy and aryloxy compounds, disubstituted amines and pertinently in this case substituted cyclopentadienes. After the addition of 2.5 equivalents of the Cp, the reaction is stirred at –78 °C for 1 hour and then heated at a gentle reflux for four hours to afford the sandwich Cp complex.

In order to test this method, simple freshly distilled Cp was used as the Brønsted acid and was used in accordance with the above preparation on a 5 mmol scale. After the final four hours at reflux, the reaction mixture was allowed to cool and filtered to remove the LiCl. The LiCl was extracted extensively with a 3:1 mixture of hexane and DCM, and the extracted portions were combined with the filtrate and all solvents removed. NMR analysis revealed that that the desired compound, zirconocene dichloride, was the only product of the reaction and was isolated in a 60 % yield.

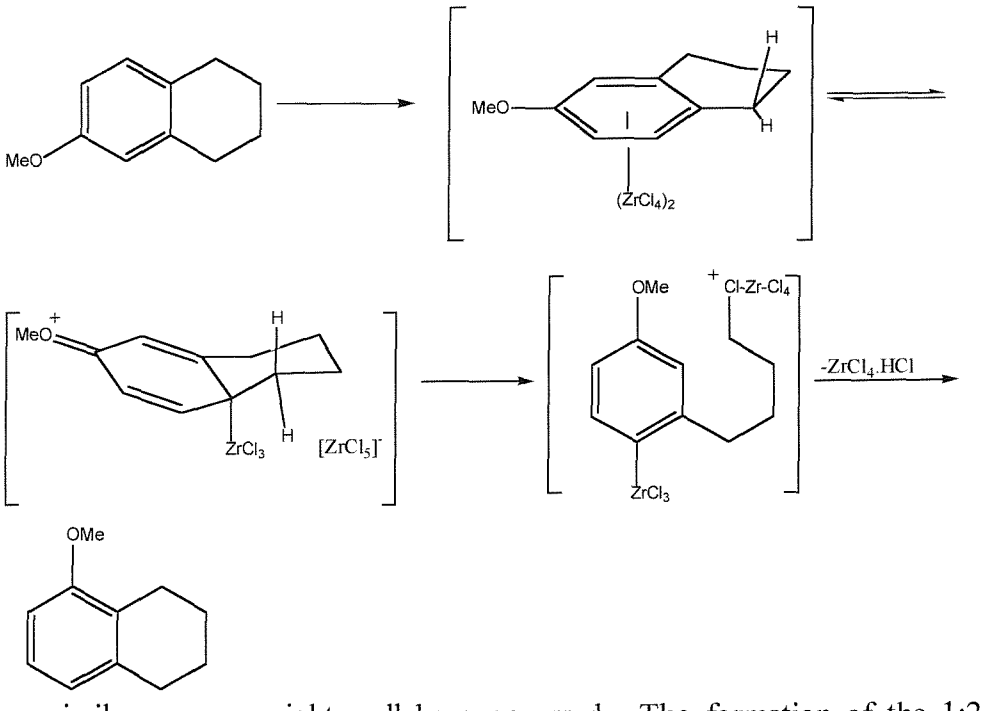


Scheme 4.2

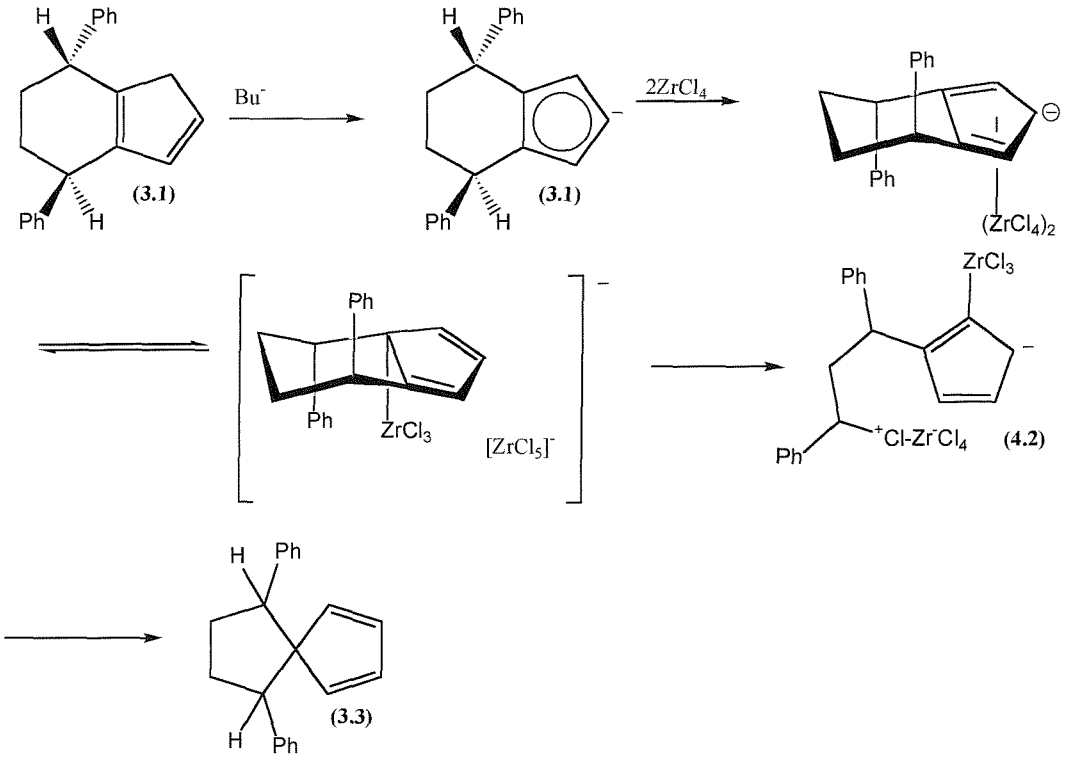
The reaction was then tried with Cp ligand **3.1**. Unfortunately the initial reaction was unsuccessful with no sign of the desired metallocene product. The reaction was repeated, but after the formation of the dialkyl species, the reaction mixture was split between to two Schlenk vessels. Into one vessel was added, at – 78 °C, 2.5 equivalents of freshly distilled Cp and to the other, also at –78 °C was added 2.5 equivalents of Cp ligand **3.1.** Both were stirred in accordance with the literature preparation at – 78 °C for 1 hour before being allowed to warm to room temperature and the heated at gentle reflux for 4 hours. At this time crude NMR of the first reaction mixture, that containing only cyclopentadiene showed that the reaction had proceeded according to literature precedent. The second vessel, that containing ligand **3.1** again showed that no reaction had taken place. However this time the crude ^{13} C NMR showed the appearance of a quaternary carbon peak at 70 ppm; the place at which the quaternary carbon should appear in spirocycle compound **3.3**. Unfortunately the NMR was a complex mixture of a number of compounds that ran at solvent front on silica TLC in pure hexane, and so purification via column chromatography was not possible. Although there was not enough experimental data or evidence to support the idea that the reaction conditions forced the formation of the spirocycle from the Cp, effectively reversing the 1,5 sigmatropic shift that was expected to be the main route to ligand **3.1**, the presence of such a peak in the ^{13}C was difficult to explain in the context of the compounds present in the reaction mixture, without entertaining the possibility that this is what had happened. If this is the case the answer is most likely to be a Lewis acid catalysed rearrangement similar perhaps to the $ZrCl_4$ driven sliding cyclohexane rearrangement first

published by Harrowven and Dainty, whereby 6-methoxytetralin is converted to 8-methoxytetralin by the action of Lewis acids.[91] The authors argue that in that case the mechanism relies on the equilibrium between extreme tautomeric forms of the 1:2 η-6 half-sandwich zirconium complex of 6-methoxytetralin which leads to the shift of the cyclohexyl ring from one position to another in relation to the methoxy group substituent.

Scheme 4.3



In this case a similar process might well have occurred. The formation of the 1:2 η-5 complex occurs following aromatisation of the acidic Cp ring by removal of a proton, and is followed by scission of the saturated ring, which then undergoes a retro Friedel-Crafts alkylation to give compound **4.2**. An aromatic Friedel Crafts reaction then leads to spirocycle **3.3,** with the reaction conditions i.e. gentle heating ensuring that the thermodynamic product, the 5- membered ring is formed. The driving force for this reaction must be sufficient to overcome the loss of aromaticity. Once the reaction is opened to the air for filtration hydroysis of the zirconium carbon bond occurs. A possible mechanism is given below.



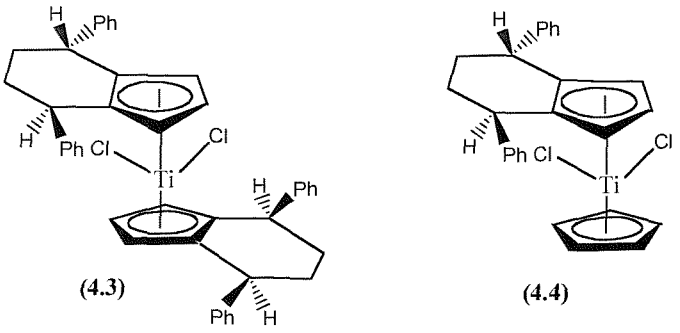
Scheme 4.4

4.2.1 Other Methods Attempted for the Synthesis of a C_2-symmetric Zirconocene.

As neither of these methods was being particularly effective with regards the aim of synthesising a novel C_2 symmetric zirconocene several other methods were used. Including isolation of the lithium salt of Cp ligand **3.1** by precipiation in hexane, preparation of the TMS derivative of the ligand and finally, reversing the order of addition, i.e. adding the $ZrCl_4$ complex to the ligand solution. However none of these was successful and it was not possible to synthesise the desired complex.

4.3 Synthesis of Novel Chiral η-5-Cyclopentadienyl Titanium Complex 4.3.

As it was looking increasing unlikely that the synthesis of the desired zirconcene was possible, potential alternatives were considered. The most suitable option was the synthesis of a titanocene compound, either the C_2-symmetric titanonocene **4.3** from $TiCl_3$ or the compound with only one substituted Cp, complex **4.4**, synthesised from $CpTiCl_3$.

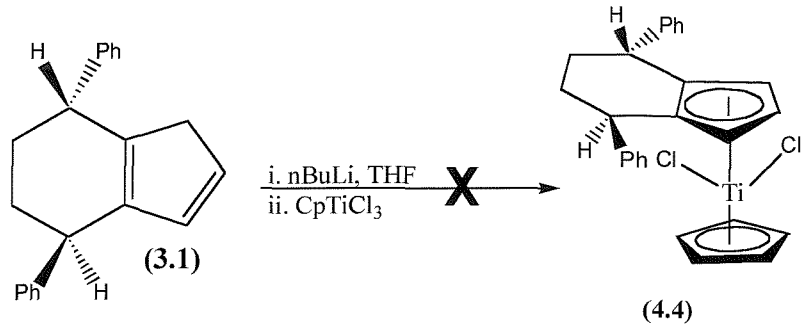


Scheme 4.5

The easiest option was to attempt the synthesis of complex **4.4.** Unlike the difficult preparation of $CpZrCl_3$, the synthesis of $CpTiCl_3$ is a vastly simpler process, being a simple disproportionation between $TiCl_4$ and Cp_2TiCl_2, accomplished by heating the two compounds in xylene, isolating the product and then recrystallising it from hot benzene. This also makes it easier to prepare and use than $TiCl_3$, which used to be a commercially available compound but now requires synthesis.

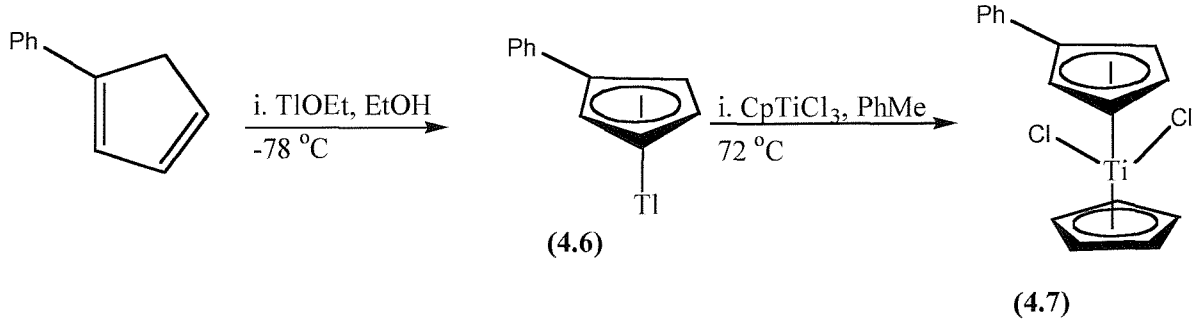
4.3.1 Synthesis of (4R,7R)-(4,5,6,7-tetrahydro-4,7-bisphenylindenyl) (cyclopentadienyl) titaniumdichloride.

Initially the method used by other researchers within the group for the synthesis of such compounds was followed.[24,30] The lithium salt of the ligand was prepared by treatment of the ligand as a solution in THF with n-BuLi at room temperature. The lithium salt solution was then cooled to - 78°C and added to a solution of $CpTiCl_3$ in THF at -78 °C. The reaction mixture was then allowed to stir for 24 hours at which time analysis by ^1H NMR revealed that no reaction had occurred. This was repeated and there was still no sign of reaction. The reaction was carried out using simple Cp to see if the conditions used were amenable to the synthesis of Cp_2TiCl_2 and this was found to be the case.



Scheme 4.6

So an alternative method was sought for the synthesis of the titanocenes. Bitterwolf, Rausch and Sing have shown that the thallium compounds of benzyl and phenyl cyclopentadiene are useful intermediates in the preparation of a wide range of metallocenes, including titanocenes.[92] The addition of thallium ethoxide to a solution of the relevant Cp in ethanol at room temperature leads to the synthesis of thallium compound **4.5,** as a yellow precipitate. Filtering the reaction mixture, and washing the residue with ethanol, ether and hexane removes all unwanted material. The thallium compound is then dried under vacuum and then added along with $CpTiCl_3$ to dry air free toluene in a Schlenk flask equipped with a reflux condenser. The suspension is then heated at 72 °C for four hours or longer depending on the reactivity of the thallium Cp. When the reaction is completed the reaction mixture is filtered through celite and then concentrated at reduced pressure. The desired product is then usually purified by recrystallisation.

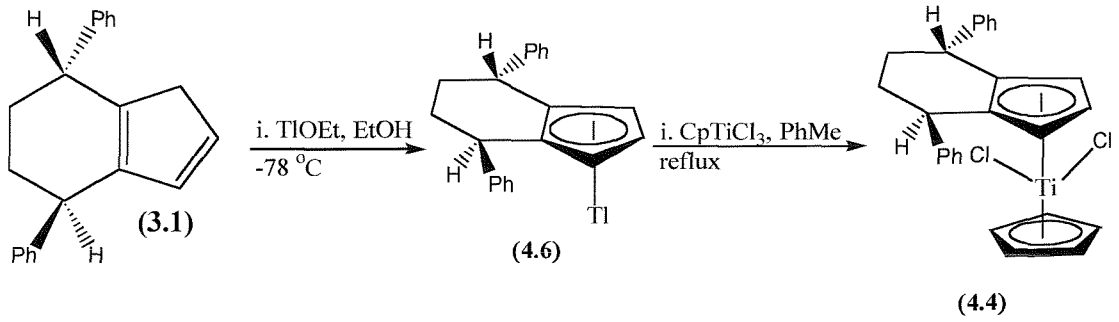


Scheme 4.7

This procedure was used for the attempted complexation of ligand **3.1** and proved to be a successful method for the isolation of the η-5- Cyclopentadienyl titanium complex **4.4**. The thallium Cp compound was formed as a silver/white precipitate, which was added to a

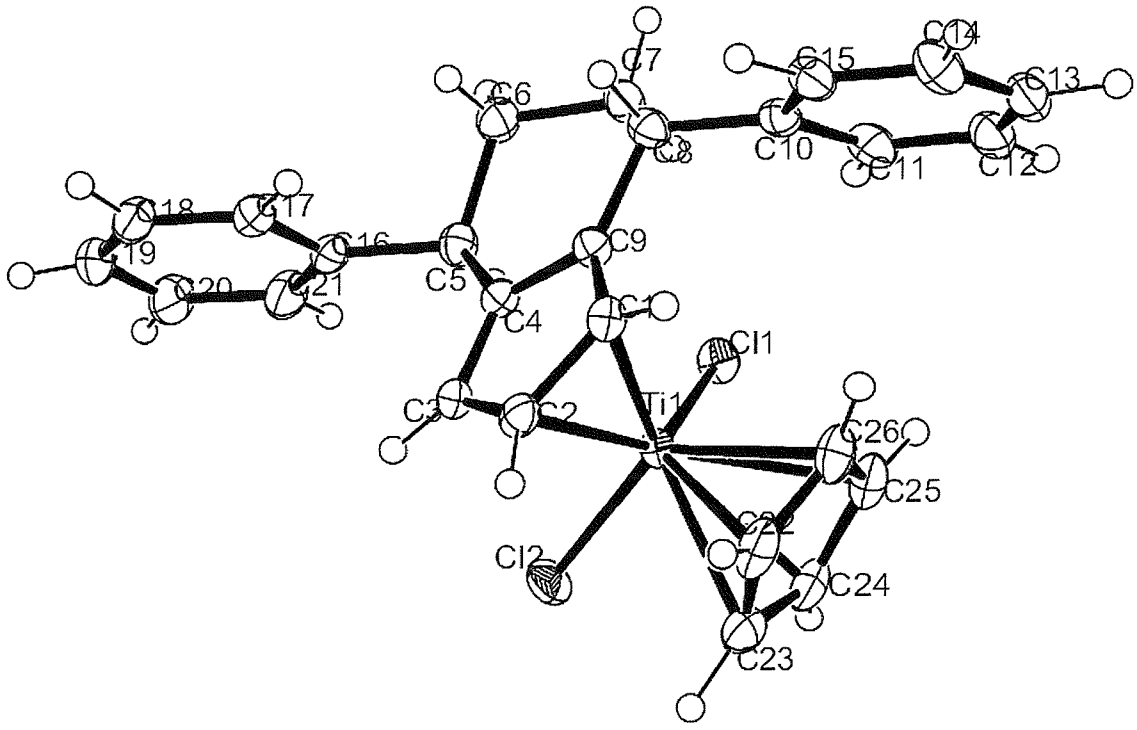
solution of $CpTiCl_3$ in toluene. During the reaction the toluene phase turned a deep red colour.

The reaction was allowed to cool to room temperature, and filtered. The filtrate was then concentrated and the dark red solid was recrystallised from DCM/hexane to provide the desired compound as red X-ray quality crystals, which were shown by X-ray analysis to be the desired complex **4.4**, formed as expected as a single compound in a 20% overall yield from the starting ligand.



Scheme 4.8

The x-ray structure is shown below and in the tables of data in appendix **2**. The structure is pseudo-tetrahedral about titanium and the Cl-Ti-Cl bond angle is 90.5°. Bond distances from titanium to the unsubstituted Cp ring span a range of 0.028 Å, from 2.365 to 2.393 Å. However the bond distances for the substituted Cp span a range of 0.193 Å from 2.304, 2.358 and 2.406 for C(1), C(2) and C(3) respectively to 2.479 and 2.499 Å for C(4) and C(9) respectively. Thus an asymmetric Cp-Ti ring interaction is apparent with shorter Ti-C distances for the unsubstituted carbons, C(1), C(2) and C(3), whilst the sterically encumbered quaternary carbons C(4) and C(9) show much greater Ti-C distances.



X-ray structure of titanocene 4.4.

4.4 Conclusions.

The results in chapter **4** have provided some insight into the preparation of complexes derived from ligand **3.1** and although the failure to synthesise the desired zirconocene species is disappointing, the synthesis of complex **4.4** has demonstrated that there is potential in this system. Unfortunately time constraints meant that the amount of time that could be spent searching for solutions to the current problems in synthesising the complexes was limited and so future work needed on this system includes:

- Overcoming the difficulties in getting ligand **3.1** to bond to zirconium.
- Testing of any complexes for catalytic activity and enantiocontrol.
- Improvement in the yield of the titanium complexation reactions.

5. Experimental Section.

5.1 General.

All reactions involving air or moisture sensitive compounds were carried out under an argon atmosphere using standard Schlenk and syringe techniques. Solvents were routinely removed under reduced pressure using a Büchi rotary evaporator. All apparatus was either flame dried and cooled under vacuum (0.1 mm Hg) immediately before use, or dried for 24 hours in a hot oven (140° C) before cooling in a sealed dessicator over silica gel.

^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on Bruker AM300, AC300 and DPX400 spectrometers. The chemical shifts, δ, in 1H spectra are reported as values in parts per million (ppm) referenced to the residual solvent signals at 7.27 ppm in deuterated chloroform ($CDCl_3$). Coupling constants J are measured in hertz (Hz). ^{13}C spectra were proton decoupled and referenced to the deuterated $CDCl_3$ triplet at 77.2 ppm. The numbering system used to assign the atoms in the spectra is not necessarily the IUPAC numbering system used when naming the molecules.

Infrared spectra were recorded Nicolet Impact 400 machine equipped with a Spectra Tech Thunderdome impact single beam laser emission detection device. Peaks are given in wavenumbers (cm^{-1}) with the following terms used to describe peak strength strong, medium and weak. All can be broad (b).

Melting points were performed on an Electrothermal melting point apparatus and are uncorrected.

Optical rotations were measured on an Optical Activity Ltd Polaar 2001 machine at 293-298 K and at 598 nm.

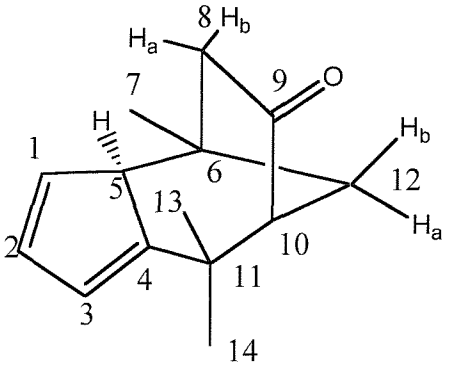
Mass spectrometry was carried out by the University of Southampton Mass Spectrometry Service.

Unless otherwise stated, materials are obtained from commercial sources and are used without further purification. Diethyl ether, THF, toluene, DME and hexane were freshly distilled from sodium/benzephenone. Methanol was dried over anhydrous calcium chloride ($CaCl_2$) and distilled prior to use. DCM, benzene and pentane were distilled from and stored over CaH_2. Petrol refers to the petroleum fraction that boils between 40 and 60 °C and was either distilled through a Vigreux column before use or if of suitable grade, used fresh from the bottle.

Thin layer chromatography (TLC) was performed using 0.25 Kieselgel 60G/ UV_{254} precoated aluminium and plastic plates and compounds were visualised with a 254 nm UV lamp (for compounds containing a chromophore), followed by either phosphomolybdic acid (12 g in 150 mL ethanol) or iodine. Unless otherwise stated, flash column chromatography was performed on Merck Matrex Silica (230 – 400 mesh) and was run under a slight positive pressure. Solvent volumes are described as volumes before mixing. Chiral HPLC was carried out on a Hewlett Packard 1050 series instrument using 250 nm x 4.6 mm i.d. Chiralcel OD-H column. Peak size analysis was performed using Hewlett Packard HPLC Chemstation software. GC was performed on a Hewlett Packard 6900 series machine via autosampler injection onto a Hewlett Packard HP-5 crosslinked 5% PhMe siloxane column with helium as the carrier gas and a flame ionisation detector. Chiral GC was carried out on a Hewlett Packard 6890 series machine, with helium as the carrier gas and a flame ionisation detector via manual injection onto a Chiracel FS-hydrodex-β column with 30 m x 25 μm dimensions. In both cases peak size analysis was performed using Hewlett Packard GC Chemstation software.

5.2 Preparation of *rac*-6,11,11-trimethyltricyclo[6.2.1.$0^{2,6}$] undeca-3,5-dien-9-ol 1.117.

5.21 Synthesis of *rac*-1,7,7-trimethyltricyclo[6.2.1.$0^{2,6}$] undeca-3,5-dieneone 1.108.



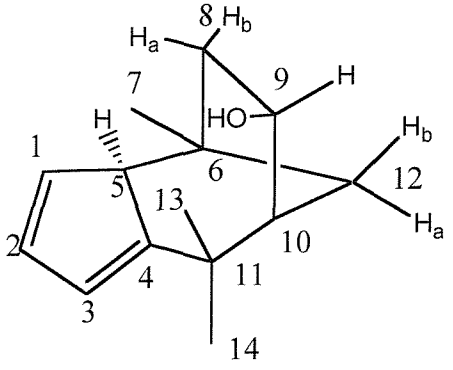
To a solution of diisopropylamine (1.8 mL, 13 mmol) in dry THF (50 mL) at –78 °C was added *n*-butyllithium (nBuLi) (5 mL, 2.5 M in hexanes, 12 mmol) and the solution was stirred for 30 minutes. A solution of 3-methyl-2-cyclopentenone **1.106** (1.2 mL, 12 mmol) in dry THF (10 mL) was added drop wise so that the temperature did not exceed –65 °C and stirred at –78 °C for 1 hour. A solution of dimethylfulvene **1.107** (CARE- STENCH) (1.2 mL, 10 mmol) (prepared according to literature methods) in dry THF (10 mL) was added and the mixture warmed to –20 °C and stirred for 90 minutes. The reaction was quenched with distilled water and diluted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulphate and concentrated to provide 1.79 g of crude product as a yellow oil. Purification was achieved by flash column chromatography (5% ethyl acetate in petrol, R_f = 0.5) providing the title compound as a clear oil (1.19 g, 5.9 mmol, 59 %), which crystallised upon refrigeration at 4 °C. The product was formed as single diastereoisomer with ^{1}H and ^{13}C data in accordance with literature values.[34]

^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm = 6.40 (1H, ddd, *J* = 5.5, 1.8, 1.8 Hz, *1*), 6.25 (1H, ddd, *J* = 5.5,1.5,1.5 Hz, *2*), 5.95 (1H, ddd, *J* = 1.9, 1.5, 1.5 Hz, *3*), 2.90 (1H, br. s, *5*), 2.27 (1H, dd, *J* = 12.9, 3.5 Hz, *12a*), 2.06 (1H, d, *J* = 4.9 Hz, *10*), 1.71 (1H, dd, *J* = 12.9, 5.0 Hz, *12b*), 1.39 (3H, s, *7*), 1.35 (1H, m, *8a* or *b*), 1.26 (3H, s, *13* or *14*), 1.23 (3H, s, *13* or *14*), 1.22 (1H, m, *8a* or *b*).

^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm = 219.1 (C=O, *9*), 154.7 (C, *4*), 134.1 (CH, *1*), 132.8 (CH, *2*), 124.1 (CH, *3*), 60.1 (CH, *5*), 59.7 (CH, *10*), 44.0 (CH_2, *8*), 42.2 (C, *6* or *11*), 40.0 (CH_2, *12*), 37.8 (C, *6* or *11*), 29.1 (CH_3, *7*), 26.2 (CH_3, *13* or *14*), 24.9 (CH_3, *13* or *14*).

IR (neat film): ν = 2959 (w), 1736 (s), 1459 (w), 1399 (w), 1308 (w), 1261 (w), 1171 (w), 877 (w) cm^{-1}.

5.22 Synthesis of *rac*-6,11,11-trimethyltricyclo[6.2.1.0^{2,6}] undeca-3,5-dien-9-ol 1.117.



To a stirred solution of ketone **1.108** (1.02 g, 5 mmol) in dry toluene at – 78 °C was added DIBAL-H (lithium diisobutylaluminium hydride) (4 mL, 1.5 M in toluene, 6 mmol). After two hours the reaction was allowed to warm to room temperature and sodium bicarbonate (15 mL) was added and the reaction stirred for 45 minutes. The reaction was then diluted with ether (15 mL) and water (15 mL), and the organic phase extracted with ether (2 x 15 mL). The combined organic fractions were dried over anhydrous magnesium sulphate and the solvents removed to afford the product as a colourless oil and as a single diastereoisomer (1.02 g, 99 %). Upon slow evaporation of a solution of **17** in ether, crystallisation occurred. Melting point and NMR spectral data are in accordance with published values.[24]

M. Pt. (44-46 °C) lit M. Pt. (45-47).

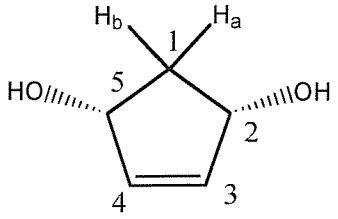
^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm = 6.52 (1H, ddd, *J* = 5.5, 1.9, 1.9 Hz, *1*), 6.26 (1H, ddd, *J* = 5.5,1.1, 1.1 Hz, m, *2*), 6.11 (1H, ddd, *J* = 1.8, 1.1, 1.1 Hz, *3*), 4.24 (1H, ddd, *J* = 10.7, 6.2, 6.2 Hz, *9*), 2.82 (1H, br, s, *5*), 1.96 (1H, dd, *J* = 13.0, 2.9 Hz, *12a*), 1.94 (1H, m, *10*), 1.49 (3H, s, *7*), 1.48 (1H, m, *8b*), 1.43 (1H, s, *OH*), 1.30 (1H, dd, *J* = 12.9, 4.4 Hz, *12b*), 1.25 (3H, s, *13* or *14*), 1.21 (3H, s, *14* or *13*), 0.24 (1H, ddd, *J* = 13.6, 6.3, 2.9 Hz, *8a*).

^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm = 158.7 (C, *4*), 133.3 (CH, *1*), 132.9 (CH, *2*), 121.9 (CH, *3*), 76.9 (HCOH, *9*), 61.5 (CH, *5*), 52.1 (CH, *10*), 43.8 (C, *6* or *11*), 41.0 (CH_2, *12*), 39.8 (CH_2, *8*), 37.7 (C, *6* or *11*), 33.1 (CH_3, *7*), 26.5 (CH_3, *13* or *14*), 26.3 (CH_3, *13* or *14*).

IR (neat film): ν = 3327(sb), 2950 (m), 1738 (s), 1447 (m), 1364 (s), 1216 (s), 1057 (m).

5.3 Preparation of Synthesis of (1*S*)-4-oxo-2-cyclopentenyl acetate 2.8.

5.31 Synthesis of (*cis*)-4-cyclopentene-1,3-diol 2.6.

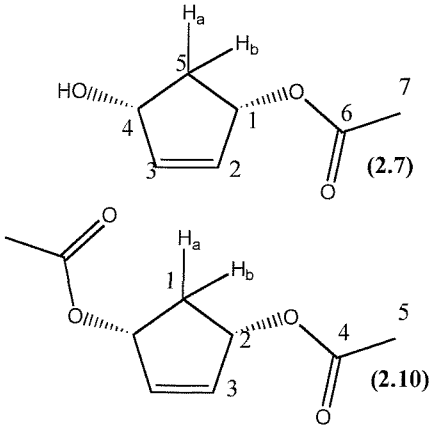


To a stirred solution of freshly distilled cyclopentadiene (66 g, 1 M), in methanol (500 mL) and dichloromethane at 0° C was added thiourea (52.3 g, 687.5 mmol) and tetraphenylporphyrin (280 mg). Oxygen was then bubbled vigorously through the solution for five minutes, after which time the reaction mixture was irradiated with a 400 W sodium lamp, cooled by a water jacket. Irradiation continued until all the cyclopentadiene had been consumed. At this point oxygen bubbling and irradiation were halted, and the reaction stirred for a further 12 hours in the dark. The reaction mixture was then concentrated, and the residue dissolved in water and washed with toluene, until a clear aqueous fraction had been obtained.. The water was then removed under vacuum, and the remaining material purified using flash column chromatography (20 % acetone in ethyl acetate R_f 0.3), to afford the product as a yellow oil (70.98 g, 136.6 mmol, 45%), NMR data for this compound was in good agreement with literature values.[93]

^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm = 6.01 (2H, s, *3* and *4*), 4.6 (m, 2H, *2* and *5*), 4.02 (bs, 2H, *OH*), 2.73 (1H, dt, *J* = 14.5, 7.3 Hz, *1a* or *1b*), 1.57 (dt, 1H, *J* = 14.5, 3.4 Hz, *1a* or *1b*).

^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm 136.4 (CH, *3*), 75.0 (CH, *2*), 43.4 (CH_2, *3*).

5.32 Synthesis of (1*S*,4*R*)-4-hydroxycyclopent-en-1-yl acetate (2.7) and (1*R*,4*S*)-4-(acetyloxy)cyclopent-2-en-1-yl acetate (2.10).



To a stirred solution of cis diol **2.6** (2.066g, 20 mmol in THF (100 mmol) at room temperature, was added triethylamine (2 mL), vinyl acetate (3 mL, 73 mmol) and pancreatin (10 g, 8 x U.S.P.). After five hours the reaction was filtered through celite and purified via flash column chromatography (50% ethyl acetate in petrol), to provide 1.37 g, (9.6 mmol, 50%) of

monoacetate **3** in high enantiomeric excess (>95%, GC method B), and 1.00 g of diacetate (27%). Both have NMR data that is in good agreement with literature values,[64,93] and the optical rotation for compound **2.7** is in good agreement with that found in the literature.

Data for **2.7**

$[\alpha]^{25}_{D}$ = +68.9° (*c* 1.066, $CHCl_3$). Lit. $[\alpha]^{25}_{D}$ = +66.9° (*c* 1.066, $CHCl_3$).[93]

^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm = 6.11 (1H, d, *J* = 4.0 Hz, *3*), 5.99 (1H, d, *J* = 4.5 Hz, *2*), 5.50 (1H,m, *1*), 4.7 (1H, *J* = Hz, *4*), 2.77 (1H, dt, *J* = 4, 4 Hz, *3 a* or *b*), 2.1 (3H, s, *7*), 1.61 (1H, dt, *J* = 4, 4 Hz, *3a* or *b*).

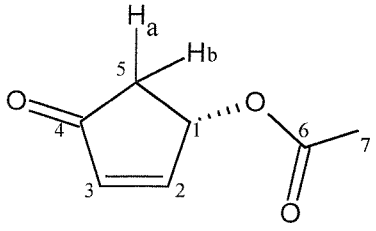
^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm = 171.1 (C=O, *6*), 138.7 (CH, *3*), 132.3 (CH, *2*), 74.6 (CH, *1*), 60.6 (CH, *4*), 40.4 (CH2, *5*), 21.3 (CH_3, *7*).

Data for **2.10**

^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm = 6.09 (2H, m, *3*), 5.54 (2H, dd, *J* = 7.5, 3.5 Hz, *2*), 2.87 (1H, m, *1a* or *b*), 2.06 (6H, s, *5*), 1.73 (1H, dt, *J* =15.1, 3.5 Hz, *1a* or *b*).

^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm = 170.9 (C=O, *4*), 134.7 (CH, *3*), 76.7 (CH, *2*), 37.2 (CH_3, *1*) 21.3 (CH_2, *5*).

5.33 Synthesis of (1*S*)-4-oxo-2-cyclopentenyl acetate 2.8.



To a stirred solution of monoacetate **2.7** (0.292 g, 2 mmol) in DCM (15 mL), was added PCC (1.29 g, 6 mmol). After 2 hours the reaction mixture was filtered through celite and the solvents removed. The resulting residue was chromatographed on silica (20% ethyl acetate in petrol) to furnish the product as a colourless oil (90 mg, 38%). NMR data for this compound is consistent with literature precedent[93] and the optical rotation is consistent with the literature for material of greater than 95 % e.e.[93]

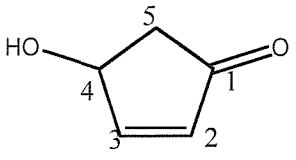
$[\alpha]^{295}_{D}$ = +101.9° (c 0.927, $CHCl_3$). Lit. $[\alpha]^{295}_{D}$ = +101° (c 0.927, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm = 7.59 (1H, dd, *J* = 5.7, 2.4 Hz, *3*), 6.34 (1H, d, *J* = 5.7, 1.1 Hz, *2*), 5.86 (1H, dd, *J* = 6.4, 1.1 Hz, *1*), 2.84 (1H, ddd, *J* = 18.8, 6.3, 1.3 Hz, *5a* or *b*), 2.32 (1H, dt, *J* = 18.8, 1.8 Hz, *5a* or *b*), 2.10 (3H, s, *7*).

^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm = 205.2 (C=O, *4*), 170.6 (C=O, *6*) 159.3 (CH, *2*), 137.0 (CH, *3*), 72.03 (CH, *1*), 41.0 (CH_2, *5*), 20.9 (CH_3, *7*).

5.4 Preparation of Preparation of racemic 4-butyl-2-cyclopenten-1-one 2.13.

5.41 Synthesis of *rac*-4-hydroxy-2-cyclopenten-1-one 2.11.[64]

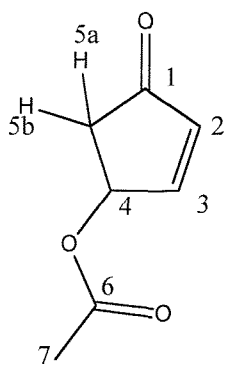


A solution of freshly distilled furfuryl alcohol (12.5 g, 127 mmol) and potassium hydrogen carbonate (0.65 g, 4.63 mmol) in water adjusted to pH 4.1 with orthophosphoric acid (meter), was stirred at reflux for 48 hours. The reaction mixture was then washed with DCM (2 x 50 mL), the organic layer was extracted with water (2 x 50 mL) and the aqueous fractions combined before being concentrated to give a brown oil. This was dissolved in DCM, dried over anhydrous magnesium sulphate and concentrated to afford the title product as dark red oil. CARE - oil stains all surfaces including skin (5.68 g, 57.2 mmol, 45%). ^{1}H and ^{13}C NMR data are in accordance with the literature values. [64]

^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm = 7.56 (1H, dd, *J* = 5.6, 2.0 Hz, *3*), 6.15 (1H, dd, *J* = 5.6, 1.0 Hz, *2*), 4.98 (1H, m, *4*) (3.70 (1H, bs, *OH*), 2.70 (1H, dd, *J* = 18.5, 6.3 Hz, *5a* or *b*), 2.20 (1H, dd, *J* = 18.5, 2.0 Hz, *5a* or *b*).

^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm = 207.9 (C=O, *1*), 164.5 (CH, *2*), 134.9 (CH, *3*), 70.3 (HCOH, *4*), 44.4 (CH_2, *5*).

5.42 Synthesis of racemic-4-oxo-2-cyclopentenyl acetate 2.8.

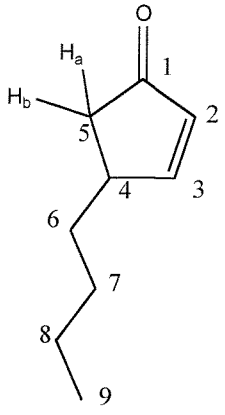


To a solution of hydroxyenone **2.11** (4.9 g, 50 mmol) in DCM (150 mL) at 0° C, was added pyridine (4.8 mL, 65 mmol) and acetic anhydride (4.4 mL, 60 mmol). This was then warmed to room temperature and stirred for 6 hours. The reaction mixture was then filtered through a layer of celite and concentrated to afford the crude product as a yellow oil which was purified using flash column chromatography (50% ethyl acetate in petrol). This provided the product (4.91g, 35 mmol, 70%) as a colourless oil, with analytical NMR data identical to that found in the published literature.[93]

^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm = 7.53 (1H, dd, *J* = 5.8, 2.4 Hz, *2*), 6.28 (1H, dd, *J* = 5.8 Hz, 1.1 Hz, *3*), 5.80 (1H, dd, *J* = 6.4, 1.1 Hz, *4*), 2.78 (1H, dd, *J* = 18.8, 6.3 Hz, *5a* or *5b*), 2.28 (1H, dd, *J* = 18.8, 2.2 Hz, *5a* or *5b*), 2.05 (3H, s, *7*).

^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm 205.0 (C=O, *1*), 170.5 (C=O, *6*), 159.1 (CH, *3*), 137.0 (CH, *2*), 72.0 (CH, *4*), 41.1 (CH_2, 5), 20.9 (CH_3, *6*).

5.43 Preparation of racemic 4-butyl-2-cyclopenten-1-one 2.13.[63]



To a suspension of copper cyanide (0.9 g, 10 mmol) in THF (30 mL) at –78 °C was added n-BuLi (2.5 M in hexanes, 8 mL, 20 mmol). The flask was allowed to warm until all CuCN was seen to dissolve and then cooled back to –78 °C. A solution of acetoxyenone **2.8** (0.7 g, 5 mmol) and chlorotrimethylsilane (TMSCl) (1.04 g) in THF (4 mL) was then added dropwise. The reaction was stirred for 45 mins, after which time GC (method A) showed the reaction to be complete. The whole was poured onto saturated ammonium chloride solution (25 mL), and the layers separated. The aqueous phase was extracted with ether (2 x 30 mL) and the combined ethereal fractions washed sequentially with saturated ammonium chloride solution water and brine (3 x 30 mL). The organic portion was then dried over anhydrous magnesium sulphate and concentrated to approximately half its original volume. A solution of potassium carbonate in methanol (2 M, 10 mL) was then added and stirred with

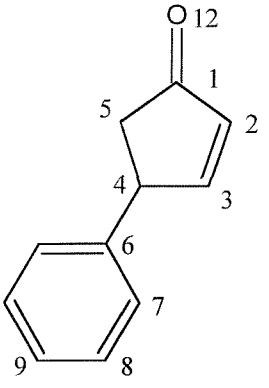
reaction monitoring by GC When deprotection and elimination were shown to be complete, brine (25 mL) was added and the layers separated. The aqueous phase was extracted with ether (25 mL) and the organic fractions were combined and washed with water (25 mL) and brine (25 mL). The ethereal phase was then dried over anhydrous magnesium sulphate and the solvents removed in vacuo to afford the crude product as a yellow oil. This was then purified using Kugelröhr distillation at 2 Torr, and 120 °C to give the desired compound as a colourless highly volatile oil with analytical data in excellent agreement with that found in the published literature (524 mg, 3.8mmol, 38%).[95]

^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm = 7.5 (1H, dd, *J* = 5.8, 2 Hz, *3*), 6.3 (1H, dd, *J* = 5.8, 2 Hz, *2*), 3.1 (1H, m, *4*), 2.50 (1H, dd, *J* = 18.7, 6.5, Hz, *5a* or *5b*), 2.0 (1H, dd, *J* = 18.7, 2.3 Hz, *5a* or *b*), 1.40-1.05 (6H, m, *6,7* and *8*), 0.91 (3H, t, *J* = 7 Hz, *9*).

^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm = 210.3 (C=O, *1*), 168.9 (CH, *2*), 133.7 (CH, *3*), 41.6 (CH, *4*), 41.2 (CH_2, *5*), 34.6 (CH_2, *6*), 29.9 (CH_2, *7*), 22.8 (CH_2, *8*), 14.1 (CH_3, *9*).

5.5 Preparation of 4-substituted cyclopentenones.

5.51 Synthesis of (4*R* and 4*S*)-4-phenyl-2-cyclopentenone 2.17.[65]



To a mixture of cinnamoyl chloride **2.15** (16.6 g, 100 mmol) and aluminium trichloride (14.0 g, 104 mmol) in DCM (175 mL) was added a solution of vinyltrimethylsilane **2.16** (12 g, 120 mmol) in DCM (25 mL). The reaction mixture was heated at reflux with stirring for 3 hours, after which time the reaction was shown to be complete by TLC (1% MeOH/$CHCl_3$). The reaction mixture was then poured onto an ice/water mix (200 g) containing ammonium chloride (25 g). The layers were then separated and the aqueous layer extracted with DCM (2 x 50 mL). The organic fractions were then combined, washed with water (50 mL) and brine (50 mL), dried over anhydrous magnesium sulphate and the solvents removed at reduced pressure to afford 13.45 g of the crude product as a yellow oil. The residue was then purified by column chromatography on silica (1% MeOH/$CHCl_3$) to afford (8.44 g, 53 mmol, 53 %) of the title

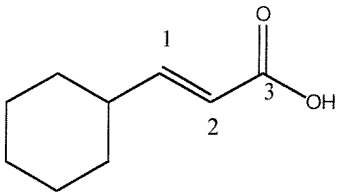
cyclopentenone as a pale yellow oil with ^{1}H and ^{13}C NMR data in accordance with the literature.[65]

^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm = 7.65 (1H, dd, *J* = 2.0, 5.5 Hz, *3*), 7.4-7.1 (5H, m, *phenyl ring*), 6.45 (1H, dd, *J* = 2.0, 5.5 Hz, *2*), 4.20 (1H, dd, *J* = 2.0, 6.8 Hz, *4*), 2.90 (1H, dd, *J* = 6.9, 18.9 Hz, *5a* or *5b*), 2.39 (1H, dd, *J* = 18.9, 2.3, Hz, *5a* or *5b*).

^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm = 210.1 (C, *1*), 166.9 (CH, *3*), 141.6 (C, *6*), 134.2 (CH, *2*), 129.2 (CH, *7*), 127.42 (CH, *9*), 127.3 (CH, *8*), 46.9 (CH, *4*), 44.2 (CH_2, *5*).

IR (neat film): ν = 2925 (m), 1736 (s), 1448 (w), 1365 (m), 1216 (m) 1091 (w) cm^{-1}.

5.52 Synthesis of (*E*)-3-cyclohexylpropenoic acid 2.22.[65]



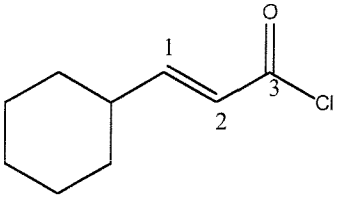
To a solution of malonic acid **2.21** (41g, 400 mmol) and cyclohexane carboxaldehyde **2.20** (56 g, 500 mmol) in pyridine (34 mL) was added piperidine (0.3 mL). The reaction was stirred for 72 hours after which time all the malonic acid had been consumed (10% Ether/Petrol). The reaction mixture was the poured onto a 50 % solution of sulphuric acid in water (200 mL), and the layers separated. The aqueous layer was extracted with ether (2 x 40 mL) and the organic fractions combined. The organic portion was then washed with water (40 mL) and brine (40 mL) and the solvents removed at reduced pressure. The residue was then dissolved in 10% K_2CO_3 solution (300 mL) and the excess cyclohexanecarboxaldehyde removed by washing with ether (2 x 40 mL). The aqueous layer was then acidified to pH 1 with dilute hydrochloric acid and the aqueous layer extracted with ether (2 x 100 mL). The organic layers were combined, washed with brine (50 mL), dried over anhydrous magnesium sulphate, and concentrated at reduced pressure to afford the desired material as a white solid with analytical data in good agreement with literature values (51.8 g, 332 mmol, 83%).[97]

Melting point: 47-48 °C, lit. m.pt. 49-50 °C.[96]

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 10.5 (1H, bs, *OH*), 6.96 (1H, dd, *J* = 16.0 Hz, 6.5 Hz, *1*), 5.70 (1H, dd, *J* = 16.0, 1.5 Hz, *2*) 2.10 (1H, m, cC_6H_{11}), 1.70 –1.10 (10H, m, cC_6H_{11}).

^{13}C NMR, (100 MHz, $CDCl_3$): δ/ppm = 172.9 (C, *3*), 157.61 (CH, *2*), 118.6 (CH, *1*), 43.3 (CH, cC_6H_{11}), 31.9 (CH_2, cC_6H_{11}), 26.3 (CH_2, cC_6H_{11}), 26.1 (CH_2, cC_6H_{11}).

5.53 Synthesis of (E)-3-cyclohexylpropenoyl chloride 2.19.

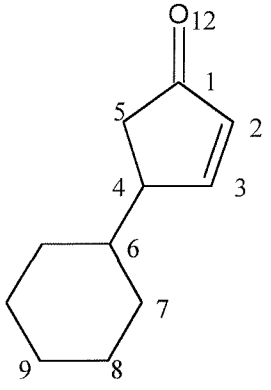


To a solution of 3-cyclohexylpropenoic acid **2.22** (15 g, 96 mmol), and oxalyl chloride (15 g, 124.2 mmol) in DCM (180 mL) at 0 °C was added DMF (40 mg). After stirring for 6 hours the reaction was complete by infrared spectroscopy, and so all solvents were removed at reduced pressure and the product (17.11 g, 106 mmol, 100%) was used immediately in the next step.

^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm =7.15 (1H, m, *2*) 6.0 (1H, m, *1*), 2.30 (1H, m, cC_6H_{11}), 2.0 – 1.5 (10H, m, cC_6H_{11}).

IR (neat film): ν = 2927 (m), 2854 (m), 1758 (s), 1621 (m), 1449 (m) 1270 (w), 1021 (m) cm^{-1}.

5.54 Synthesis of (4*R* and 4*S*)-4-cyclohexyl-2-cyclopenten-1-one 2.18.[65]



To a solution of 3-cyclohexylpropenoyl chloride **2.19** (15.4 g, 96 mmol) and aluminium trichloride (13.9 g, 104 mmol) in DCM (200 mL) was added a solution of vinylchlorotrimethylsilane **2.16** (11.52 g, 115.2 mmol) in DCM (mL). This was heated at reflux with stirring for 3 hours, after which time the reaction was shown to be complete by TLC (1% MeOH/$CHCl_3$). The reaction mixture was then poured onto an ice/water mix (200 g) containing ammonium chloride (25 g). The layers were then separated and the aqueous layer extracted with DCM (2 x 50 mL). The organic fractions were then

combined, washed with water (50 mL) and brine (100 mL), dried over anhydrous magnesium sulphate and the solvents removed at reduced pressure to afford 23.30 g of crude product as a yellow oil. The residue was then purified by column chromatography on silica (1% MeOH/$CHCl_3$) to afford (8.54 g, 51.7 mmol, 54 %) of the product as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.65 (1H, dd, *J* = 5.5, 2.5 Hz, *3*), 6.11 (1H, dd, *J* = 5.5, 2.0 Hz, *2*), 2.75 (1H, qt, *J* =6.5, 2.3 Hz, *4*), 2.37 (1H, dd, *J* = 19.0, 6.5 Hz, *5a* or *5b*), 2.06 (1H, dd, *J* = 19.0, 2.3 Hz, *5a* or 5b), 1.37 (1H, tdt, *J* = 11.5, 6.5, 3.3 Hz, *6*), 1.24-0.92 (10H, m, *cyclohexyl*).

^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 211.80 (C, *1*), 169.11 (CH, *3*), 135.90 (CH, *2*), 49.18 (CH, *4 or 6*), 43.52 (CH, *4 or 6*), 40.57 (CH_2, *5*), 32.53 (CH_2, *7*), 28.20 (CH_2, *9*), 28.04 (CH_2, *8*).

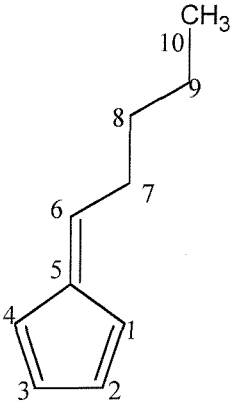
IR (neat film): ν = 2923 (s), 2851 (m), 1712 (s), 1448 (w), 1184 (w) cm^{-1}.

LRMS (EI mode): m/z 164.1 (M^+ 13%), 122.1 (20%), 82.1 (100%), 55.1 (59%).

HRMS: required 164.1201, found, 164.1204.

5.6 Preparation of Novel annulated cyclopentadienyl ligands.

5.61 Synthesis of 5-pentylidene-1,3-cyclopentadiene 2.26.[35]



To a solution of freshly prepared cyclopentadiene (16.4 mL, 200 mmol), in dry methanol (100 mL) at room temperature were added pyridine (7.5 mL, 120 mmol) and valeraldehyde **2.25** (6.89 g, 80 mmol). The reaction was then stirred for 12 hours. Acetic acid was then added and the reaction stirred for a further 30 mins. The reaction was quenched with water and diluted with diethyl ether (30 mL). The layers were separated and the aqueous layer extracted with ether (2 x 30 mL.) The organic fractions were combined washed with water (30

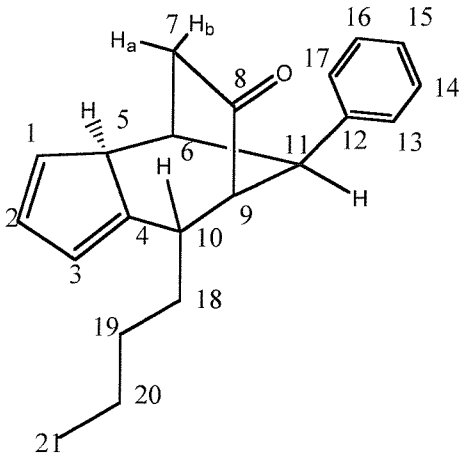
mL) and brine (30 mL) and dried over anhydrous magnesium sulphate. The solvents were removed, and the crude product (11.23 g) was purified using flash column chromatography on silica with petrol as the eluent to afford the product as a yellow oil (8.55g 64 mmol 80%.), with spectroscopic data in good agreement with literature values.[98]

^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm = 6.54 (2H, m, *2* and *3*), 6.45 (2H, m, *4* and 6), 6.22 (1H, dt, *J* = 5.1, 1.6 Hz, *1*), 2.55 (2H, dd, *J* = 15.0, 7.5, Hz, *7*), 1.55 (2H, quintet, *J* = 7.3 Hz, *8*), 1.4 (2H, sextet, *J* = 7.3 Hz, *9*), 0.90 (3H, t, *J* = 6.8 Hz, *10*).

^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm =146.0 (C, *5*), 143.6 (CH, *12,3* or *4*), 133.1 (CH, *12,3* or *4*), 130.8 (CH, *12,3* or *4*), 125.7 (CH, *12,3* or *4*), 119.3 (CH, *6*), 31.7 (CH_2, *7*), 30.9 (CH_2, *8*), 22.6 (CH_2, *9*), 14.1 (CH_3, *10*).

IR (neat film): ν = 2956 (w), 2930 (w), 1473 (w), 1380 (w), 1337 (w) cm^{-1}.

5.62 Synthesis of 10-butyl-11-phenyl[6.2.1.0^{2,6}]undeca-1,3-dien-8-one 2.27.



To a solution of diisopropylamine (0.4 mL, 2.8 mmol) in dry THF (15 mL) at –78 °C was added n-butyl lithium (n-BuLi) (1 mL, 2.5 M in hexanes, 2.5 mmol) and the solution was stirred for thirty minutes. A solution of 4-phenyl-2-cyclopentenone **2.17** (0.410 g, 2.5 mmol) in dry THF (10 mL) was added dropwise so that the temperature did not exceed –85 °C and stirred at -85 °C for I hour. A solution of 5-pentylidene-1,3-cyclopentadiene **2.26** (CARE- STENCH) (0.403 g, 3.3 mmol) in dry THF (10 mL) was added and the mixture warmed to –20 °C and stirred for ninety minutes. The reaction was quenched with distilled water and diluted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulphate and concentrated to provide 0.614 g of crude product as a yellow oil. Purification was achieved by flash column chromatography (5% ethyl acetate in petrol, R_f = 0.65) provided the title compound as a clear oil (0.480 g, 1.52 mmol, 60 %). The product was formed as single

diastereoisomer. The NMR data for the TBDMS ether of the reduced ketone is fully asssigned.

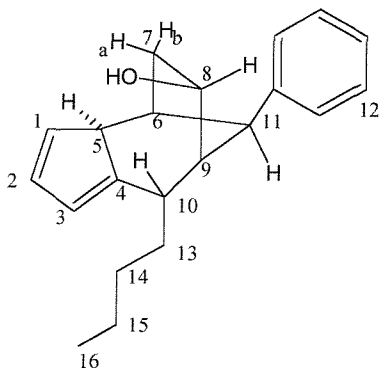
^{1}H NMR (400 MHz, $CDCl_3$): δ/*ppm* = 7.30 –7.10 (5H, m, *phenyl*), 6.39 (1H, dt, *J* = 2.3, 5.5 Hz, *1),* 6.15 (1H, d, *J* = 5.5 Hz, *2*), 6.05 (1H, m, *3*) 3.70 (1H, bs, *11*), 3.37 (1H, bs, *10*), 2.9 (2H, m, *5* and *6*), 2.63 (1H, bs, *9*), 1.70-1.62 (1H, dd, *J* = 19.8, 7.0 Hz, *7b*), 1.60-1.55 (2H, m, *18*), 1.30-1.20 (4H, m, *19* and *20*), 1.05 (1H, dd, J = 18.8, 1.5, *7a*), 0.8 (3H, m, *21*).

^{13}C NMR (100 MHz, CDCl*3*): δ/ppm = 148.4 (C, *4*), 142.41 (C, *13*), 134.7 (CH, *2*), 134.5 (CH, *1*) 129.1 (CH,), 127.1 (CH, *m-phenyl*), 127.6 (CH, *3*), 127.3 (CH, *p-phenyl*), 56.4 (CH, *5*), 55.5 (CH, *9*), 47.1 (CH, *11*), 43.8 (CH, *6*), 42.7 (CH, *10*), 34.8 (CH_2, *18*), 34.3 (*CH2, 7*), 29.8 (CH_2, *19*), 22.9 (CH_2, *20*), 14.4, (CH_3, *21*).

IR (neat film): ν =2955 (m), 2928 (m), 1739 (s), 1498 (w), 1450 (w), 1401 (w), 1147 (w), 1030 (w) cm^{-1}.

LRMS (EI mode): m/z 292 (M^+ 42 %), 193.2 (100%), 178 (62%), 165 (40%), 131 (92 %), 105 (70%).

5.63 Synthesis of rac-7-butyl-11-phenyltricyclo[6.2.1.0^{2,6}]undeca-3,5-dien-9-ol 2.29.



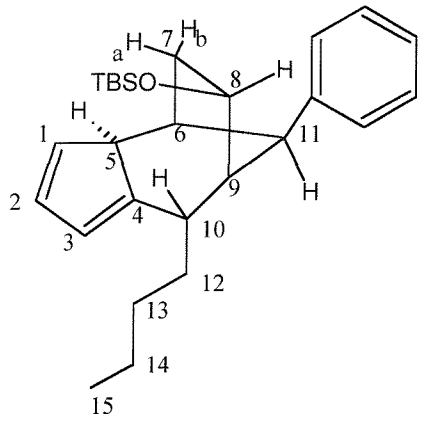
To a stirred solution of ketone **2.27** (1.168g, 4 mmol) in dry toluene (40 mL) at – 78 °C was added DIBAL-H (1.5 M in toluene, 3.2 mL, 5 mmol). After two hours the reaction was allowed to warm to room temperature and sodium bicarbonate (15 mL) was added and the reaction stirred for 45 minutes. The reaction was then diluted with ether (15 mL) and water (15 mL), and the organic phase extracted with ether (2 x 15 mL). The combined organic fractions were dried over anhydrous magnesium sulphate and the solvents removed to afford the product as a colourless oil (630 mg, 2.01 mmol, 53 %). It has not been possible to obtain pure samples, for HRMS or mass analysis; due to the difficulty in separation by

chromatography therefore spectroscopic analysis is incomplete. With this in mind this compound has been characterised as the TBDMS ether.

^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm = 7.35-7.25 (5H, *phenyl*), 6.45 (1H, dt, *J* = 5.0, 1.5 Hz, *1*), 6.20 (2H, m, *2* and *3*), 4.10 (1H, m, *8*), 3.54 (1H, s, *11*), 3.18 (1H, s, *10*), 3.05 (1H, t, *J* = 7.0 Hz, *5*), 2.92 (1H, s, *6*), 2.50 (1H, bd, *J* = 4.8 Hz, *9*), 1.90 (1H, ddd, J = 14.3, 10.7, 7.0 Hz *7b*), 1.70 (2H, m, *13*), 1.45-1.30 (4H, m, *14* and *15*), 1.0-0.90 (3H, m, *16*). 0.03 (1H, dd, J = 14.0, 4.0 Hz, *7a*).

LRMS (EI mode): m/z = 294 (M^+, 88%).

5.64 Synthesis of rac-1-(tert-butyl)-1,1-dimethylsilyl(7-butyl-11-phenyltricyclo[6.2.1.0^{2,6}]undeca-3,5-dien-9-yl) ether 2.31.



A mixture of alcohol **2.29** (588 mg, 2 mmol), 2,6-lutidine (428 mg, 4 mmol)) and freshly distilled DCM (30 mL) was cooled under argon to 0° C and to it was added TBDMSOTf (800 mg, 3 mmol) dropwise via a syringe. The reaction was stirred at room temperature for 30 min after which time water (20 mL) was added and the organic layer separated. The aqueous phase was extracted with diethyl ether (3 x 10 mL) and the combined ether/DCM extracts were dried over anhydrous magnesium sulphate and concentrated to provide the crude product as a colourless oil. This was purified by flash column chromatography (10 % EtOAc/petrol). The title compound was isolated in 81% yield as a single diastereoisomer and as a colourless oil (526 mg, 1.4 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.50-7.35 (5H, *phenyl*), 6.55 (1H, dt, *J* = 5.3, 1.8 Hz, *1*), 6.190 (1H, dt, *J* = 5.3, 1.8 Hz, *2*), 6.25 (1H, bs, *3*), 4.06 (1H, dt, *J* = 10.3, 5.7 Hz, *8*), 3.48 (1H, bs, *11*), 3.13 (1H, td, *J* = 7.5, 2.4 Hz, *10*), 3.07 (1H, bs, *5*), 2.89 (1H, dd, *J* = 7.0, 3.3 Hz, *6*), 2.30 (1H, d, *J* = 5.8 Hz, *9*), 1.80 (1H, ddd, *J* = 13.5, 10.0, 7.0 Hz, *7b*), 1.65 (2H,

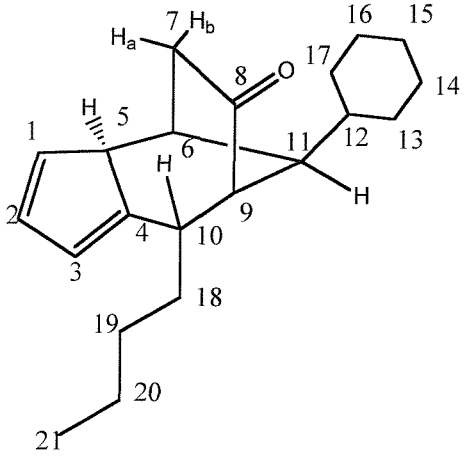
m, *12*) 1.45-1.40 (4H, m, *13* and *14*), 0.96 (3H, m, *15*), 0.86 (9H, s, $SiC(CH_3)_3$), 0.31 (1H, dddd, J = 14.0, 5.0, 1.3, 0.9 Hz, *7a*), -0.08 (3H, s, *Si* CH_3), -0.11 (3H, s, *Si* CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 150.9 (C, 4), 142.3 (C, *phenyl*), 133.3 (CH, *2*), 132.6 (CH, *1*), 127.3 (CH, *o-phenyl*), 126.5 (CH, *3*), 125.6 (CH, *m-phenyl*), 124.8 (CH, *p-phenyl*), 71.1 (CH, *8*), 56.6 (CH, *5*), 51.2 (CH, *9*), 48.2 (CH, *11*), 40.2 (CH, *6*), 36.9 (CH, *10*), 34.0 (CH_2, *12*), 30.3 (CH, *7*), 28.1 (CH_2, *13*), 24.8 (CH_3, $SiC(\underline{C}H_3)_3$), 21.8 (CH_2, *14*), 17.1 (C, $Si\underline{C}CH_3$), 13.1 (CH_3, *15*), -3.9 (CH_3, $SiCH_3$), -4.0 (CH3, $SiCH_3$).

IR (neat film), ν = 2954 (m), 2926 (m), 2855 (w), 1471)w), 1256 (m), 1144 (m), 1096 (s), 890.54 (m) cm^{-1}.

LRMS (ACPI, AP+, 400 °C): m/z 409.1 (M^+, 50 %), 277.0 (100%).

5.65 Synthesis of 7-butyl-11-cyclohexyltricyclo[6.2.1.$0^{2,6}$]undeca-3,5,-dienone 2.28.



To a solution of diisopropylamine (0.4 mL, 2.8 mmol) in dry THF (15 mL) at –78 °C was added n-butyl lithium (n-BuLi) (1 mL, 2.5 M in hexanes, 2.5 mmol) and the solution was stirred for thirty minutes. A solution of 4-cyclohexyl-2-cyclopentenone **2.18** (0.410 g, 2.5 mmol) in dry THF (10 mL) was added dropwise so that the temperature did not exceed –85 °C and stirred at -85 °C for 1 hour. A solution of 5-pentylidene-1,3-cyclopentadiene **2.26** (CARE- STENCH) (0.403 g, 3.3 mmol) in dry THF (10 mL) was added and the mixture warmed to –20 °C and stirred for ninety minutes. The reaction was quenched with distilled water and diluted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulphate and concentrated to provide 0.614 g of crude product as a yellow oil. Purification was achieved by flash column chromatography (5% ethyl acetate in petrol, R_f = 0.65) provided the title compound as a clear oil (0.320g, 1.01 mmol, 40 %). The product was formed as single diastereoisomer in a complex mixture of other compounds, which has made structural

determination difficult. As a result the NMR data for this molecule has been assigned as the TBDMS ether.

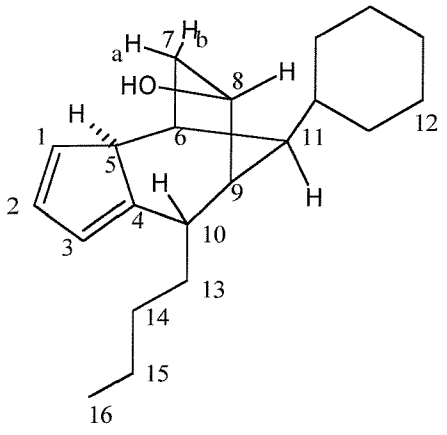
^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm = 6.46 (1H, ddd, *J* = 1.6, 1.6, 5.0 Hz, *1*), 6.18 (1H, d, *J* = 5.2 Hz, *2*), 6.04 (1H, *d*, 7.4 Hz, *3*), 3.1 (1H, m, *10*), 2.98 (1H, m, *5*), 2.35 (1H, m, *6*), 2.20 (1H, d, *J* = Hz, *9*), 1.95 (1H, *J* = Hz, *11*) 1.75 (1H, m, *12*), 1.65 (1H, m, *7b*), 1.55 (2H, m, *18*) 1.40-1.05 (15H, m, *cC$_6$H$_{11}$, 7a, 19* and *20*), 0.80 (3H, m, *21*).

IR (neat film): ν = 2925 (s), 2852 (m), 1742 (s) cm^{-1}.

LRMS (CI mode): m/z 298 (M+H, 100%), 242 (42%), 117.1 (72%).

HRMS: required 298.2297, actual 298.2304.

5.66 Synthesis of rac-7-butyl-11-cyclohexyltricyclo[6.2.1.0^{2,6}]undeca-3,5,-dienol 2.30.



To a stirred solution of ketone **2.28** (596 mg, 2 mmol) in dry toluene (20 mL) at – 78 °C was added DIBAL-H (1.6 mL, 1.5 M in toluene, , 2.4 mmol). After two hours the reaction was allowed to warm to room temperature and sodium bicarbonate (15 mL) was added and the reaction stirred for 45 minutes. The reaction was then diluted with ether (15 mL) and water (15 mL), and the organic phase extracted with ether (2 x 15 mL). The combined organic fractions were dried over anhydrous magnesium sulphate and the solvents removed to afford the product as a colourless oil contaminated with other materials. Due to the difficulties in obtaining pure material by column chromatography the NMR data has been more fully assigned for the TBDMS ether (240 mg, 0.8 mmol, 34%).

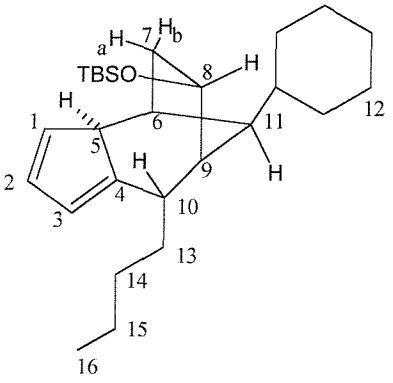
^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm = 6.48 (1H, dt, *J* = 5.5, 1.5 Hz, *1*), 6.19 (2H, m, *2* and *3*), 4.19 (1H, ddd, *J* = 10.3, 5.1, 5.1 Hz, *8*), 2.95 - 2.85 (2H, m, *10* and *5*), 2.51 (1H, dd, J = 6.4, 3.3 Hz, *6*), 2.20 (1H, d, *J* = 4.4 Hz, *9*), 1.90 (1H, m, *11*), 1.85-1.70 (5H, m, *7b, 13, 14* and *15*), 1.60-1.40 (14H, m, *16*, *cC$_6$H$_{11}$*), 0.30 (1H, ddd, *J* = 14.2, 4.5, 1.1 Hz, 7a).

IR (neat film), ν = 2982, (m), 2972 (m), 2840 (w), 1471 (w), 1256 (m), 1212 (w)1123 (m), 1096 (s), 952 (m),898 (m), 896 (m) cm^{-1}.

LRMS (CI mode): m/z = 301 (MH^+, 100%), 283 (40%), 199 (12%).

HRMS: required 300.2453, actual 300.2452.

5.67 Synthesis of rac-tert-butyl[(7-butyl-11-cyclohexyltricyclo[6.2.1.$0^{2,6}$]undeca-3,5-dien-9-yl)oxy]dimethylsilane 2.32.



A mixture of alcohol **2.30** (150mg, 0.5 mmol), 2,6-lutidine (107 mg, 1 mmol) and freshly distilled DCM (10 mL) was cooled under argon to 0° C and to it was added TBDMSOTf (200 mg, 0.75 mmol) dropwise via a syringe. The reaction was stirred at room temperature for 30 min after which time water (20 mL) was added and the organic layer separated. The aqueous phase was extracted with diethyl ether (3 x 20 mL) and the combined ether/DCM extracts were dried over anhydrous magnesium sulphate and concentrated to provide the crude product as a colourless oil. This was purified by flash column chromatography (10 % EtOAc/petrol). The compound was isolated as a colourless 81% yield oil (152 mg, 0.34 mmol, 69%).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 6.40 (1H, d, *J* = 5.3 Hz, *1*), 6.05 (1H, d, *J* = 4.0 Hz, *2*), 6.00 (1H, bs, *3*), 4.15 (1H, dt, *J* = 10.0, 4.5 Hz, *8*), 2.93 (1H, dt, *J* = 10.0, 3.0 Hz, *10*), 2.80 (1H, s, *5*), 2.40 (1H, d, *J* = 4.0 Hz, *6*), 2.00 (1H, d, *J* = 4.5 Hz, *9*), 1.90 (1H, d, *J* = 11.8, *11*) 1.70 (2H, m, *13*), 1.55 (1H, m, *7b*), 1.50-1.13 (6H, m, *13*, *14* and *Cy*), 1.00-0.80 (16H, m, *15*, *SiC(CH$_3$)$_3$* and *cC$_6$H$_{11}$*) 0.12 (1H, dd, *J* = 13.54.5Hz, *7a*) –0.03 (3H, s, *SiCH$_3$*), -0.05 (1H, s, *Si CH$_3$*).

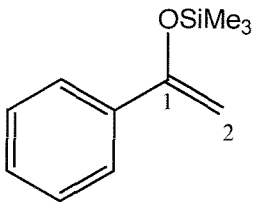
^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 151.6 (C, *4*), 132.80 (CH, *1* or *2*), 132.6 (CH, *1* or *2*), 125.9 (CH, *3*), 71.6 (CH, *8*), 56. (CH, *5*), 50.6 (CH, *Cy*), 45.5 (CH, *9*), 37.6 (CH, *6*), 36.8 (CH, *10*), 35.9 (CH, *11*), 33.8 (CH, *12*), 31.5 (CH_2, *7*), 30.8 (CH*2*, *13*), 30.0 (CH_2,

cC$_6H_{11}$), 29.1 (CH_2, *13*), 25.6 (2 x CH_2, *cC*$_6H_{11}$), 25.4 (2 x CH_2, *cC*$_6H_{11}$), 24.9 (CH3, $SiC(CH_3)_3$), 21.7 (CH_2, *15*), 17.0 (C, *SiC(CH*$_3$*)*$_3$), 13.1 (CH_3, *16*), -3.9 (CH_3, *Si CH*$_3$), -4.9 (CH_3, *Si CH*$_3$).

LRMS (ACPI, AP+, 400 °C): m/z 415.1 (M^+, 65 %) 375.2 (20%), 283.0 (100%).

5.7 Preparation of (4*R*,7*R*)-4,7-diphenyl-4,5,6,7-tetrahydro-3aH-indene 3.1a.

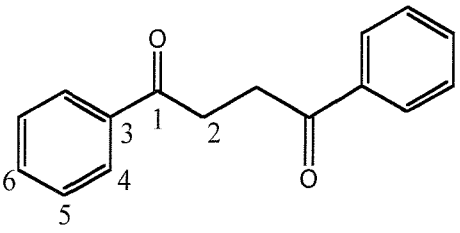
5.71 Synthesis of trimethyl-(1-phenylvinyloxy)-silane 3.9.[68]



To a mixture of cyclpentenone (12.0 g, 100 mmol, 11.6 mL) and triethylamine (10.12 g, 100 mmol, 13.98 mL) and TMSCl (10.86 g, 100 mmol) was added sodium iodide (14.90 g, 100 mmol) in acetonitrile (100 mL). This was stirred for 25 mins at which time a thick white precipitate was formed. Pentane (50 mL) followed by ice-water (30 mL). The layers were separated and the aqueous layer was extracted with pentane (20 mL). The combined organic fractions were then washed with aliquots of ice/water (30 mL) until the pH was neutral. The organic phase was then dried over anhydrous magnesium sulphate and concentrated at reduced pressure. NMR spectroscopy showed that the desired product was present only as 20% of the product with the remainder the starting material. (10.37g, 60% recovered mass in total, 2.074g, 11mmol, 10%).

^{1}H NMR: (300 MHz, $CDCl_3$) δ/ppm: 7.72-7.08 (5H, m, *Ph*), 4.86 (1H, d, *J* = 1.5 Hz, *2a* or *2b*), 4.30 (1H, d, *J* = 1.5 Hz, *2a* or *2b*), 0.2 (3H, s, *SiCH*$_3$).

5.72 Synthesis of 1,4-diphenyl-butane-1,4,-dione 3.6.[69]



To a suspension of CAN (17.54g, 32 mmol) and sodium bicarbonate (5.2 g, 62 mmol) in dry, acetonitrile (210 mL) freshly distilled from calcium hydride was added trimethyl-(1-phenylvinyloxy)-silane (6 g, 31.0 mmol) at which time the reaction mixture turned an orange colour. This was stirred for 30 minutes at which time all the orange colouration at disappeared. The reaction was the poured onto ice/water and the

layers separated. The aqueous layer was then extracted with chloroform (3 x 50 mL) and the combined organic fractions dried over anhydrous magnesium sulphate and concentrated at reduced pressure. The residue was then recrystallised from ethanol/pentane. (1.384g, 5.7 mmol, 18%.) The product had spectral data in good agreement with literature precedent.[99]

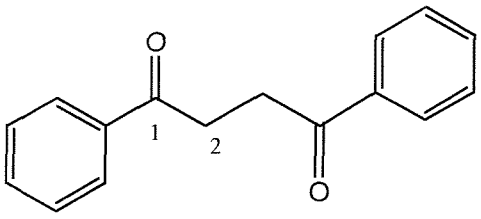
M. Pt. 141-143 °C, (benzene). Lit. M. Pt. 142-144 °C.[100]

^{1}H NMR: (300 MHz, $CDCl_3$) δ/ppm: 8.0-7.35 (5H, m, *Ph*), 3.42 (2H, s, *2*).

^{13}C NMR: (75 MHz, $CDCl_3$) δ/ppm: 198.9 (C=O, *1*), 136.9 (ArC, *3*), 133.4 (ArCH, *6*), 128.7 ($ArCH_2$, *4* or *5*), 128.3 ($ArCH_2$, *4* or *5*), 32.7 (CH_2, *2*).

LRMS (CI mode): m/z 239 (100% M+H), 105 (100%).

5.73 Synthesis of 1,4-diphenyl-2-butan-1,4-dione 3.6.[70]

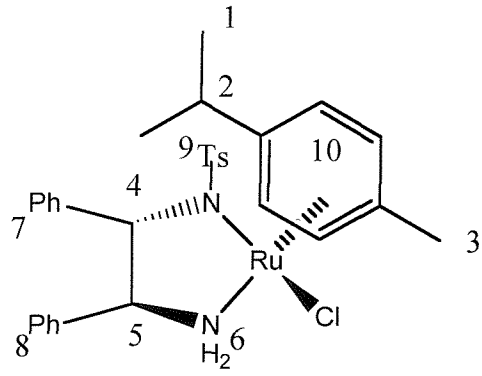


To a suspension of zinc chloride (108.8 g, 800 mmol), flame dried under vacuum, in benzene (400 ml) was added diethylamine (40 mL) and ^{t}BuOH (5.4 mL, 60 mmol. The suspension was stirred at room temperature for 2 hours and then acetophenone (68 mL, 600 mmol) and phenacyl bromide (79.2 g, 400 mmol) were added. The reaction was stirred for a further hour and then allowed to stand with no agitation for 1 week. At this time sulphuric acid (100 mL, 2N) was added and the reaction mixture filtered at reduced pressure. The solid residue was then washed with benzene (50 mL), water (50 mL) and methanol (50 mL) and solid dried under vacuum. Meanwhile the filtrate was separated and the aqueous layer extracted with ether (3 x 50 mL). The combined organic layers were then washed with sulphuric acid (100 mL, 2 N), water (50 mL) and brine (100 mL), dried over anhydrous magnesium sulphate and concentrated *in vacuo*. The residue of this was combined with the earlier isolated solid and recrystallised from the minimum quanitity of hot ethanol to afford the desired product as a crystalline white solid (131.37 g, 552 mmol, 69%). NMR and melting point data is consistent with literature values. (See above for data).

5.74 X-ray Crystallography of 1,4-diphenylbutane-1,4-dione 4.4 (03paw003).[107]

A summary of crystal data, intensity collection, and refinement parameters are reported in appendix 1. A single crystal of **(4.4)** was mounted on a glass fibre and data collections performed at 150K using an Enraf Nonius Kappa CCD area detector (λ Mo Ka = 0.71073 Å).[108] The data were corrected for absorption effects using SORTAV[109] and the structures solved by direct methods using SHELXS97[110] Hydrogen atoms were included in calculated positions and all heavy atoms were refined anisotropically using full–matrix least–squares refinement on F^2 (*SHELXL97*[111]) to give R1 = 0.0451 and wR2 = 0.1063 for I>2σ(I). All operations were carried out within the WinGX environment.[112]

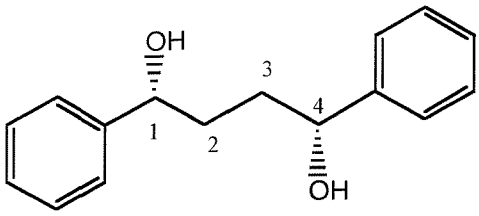
5.75 Synthesis of Noyori's catalyst 3.11.[101]



A mixture of [{$RuCl_2(\eta^6$-*p*-cymene)$\}_2$] (200mg, 0.34 mmol), (*S,S*)-TsDPhEN (250 mg, 0.68 mmol), and triethylamine (0.2 mL, 1.4 mmol) in IPA was heated at 80 °C for 1 hour. The orange solution was concentrated and the resulting solid collected by filtration. The crude compound was washed with water and dried under reduced pressure to afford the desired complex. This was recrystallised from methanol to give orange/brown crystals (402 mg, 0.61 mmol, 90%). NMR data was in accordance with literature values.[101]

^{1}H NMR: (300 MHz, $CDCl_3$) δ/ppm: 7.02-6.29(14H, m, *7,8* and *9 Ar*), 6.61 (1H, m, *6*), 5.86-5.68 (4H, m, *10*), 3.66 (1H, d, *J* = 11 Hz, *4*), 3.54 (1H, m, *5*), 3.26 (1H, m, *6*), 3.07 (1H, m, *2*), 2.28 (3H, s, *TsMe*), 2.19 (3H, s, *3*), 1.34 (3H, d, *J* = 7 Hz, *1a* or *b*), 1.32 (3H, d, *J* = 7 Hz, *1a* or *b*).

5.76 Synthesis of (1*R*, 4*R*)-1,4-diphenyl-2-butan-1,4-diol 3.5.[81]



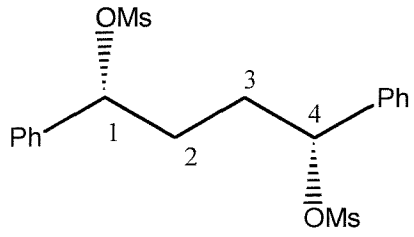
A solution of TsDPhEN (182 mg, 0.5 mmol), [RuCymeneCl_2] (152 mg, 0.25 mmol), and 1,4-diphenyl-2-butan-1,4-dione (11.95 g, 50 mmol) in degassed DCM (250 mL) under a nitrogen atmosphere was stirred for 3 minutes. The reaction was heated to 40 °C and TEAF (32 mL) was added in aliquots every 12 hours until all starting material was consumed. Water was then added (50 mL) and the layers were separated. The aqueous layer was extracted with DCM (2 x 30 mL) and the combined organic layers washed repeatedly with saturated brine/water (50:50) (8 x 40 mL). The organic fraction was dried over anhydrous magnesium sulphate and the solvents removed at reduced pressure. The resulting brown oil was purified using flash column chromatography on silica (50 % hexanes/ether) to afford the desired product as a clear oil which solidified following tituration (10.74 g, 44.4 mmol, 90%). NMR, melting point and optical rotation data is consistent with literature values.[84]

$[\alpha]^{295}_{D}$ = -57.9 (c = 1.113, $CHCl_3$). Lit $[\alpha]^{298}_{D}$ = 58.5 (c = 1.113, $CHCl_3$).[84]

M.Pt. 73-75 °C (DCM/hexane). Lit M.Pt. 74.6-75.2 °C.[84]

^{1}H NMR: (300 MHz, $CDCl_3$) δ/ppm: 7.25-7.11 (10H, m, *Ph*) 4.46 (2H, bs, *OH*), 4.05 (2H, d, *J* = 3.5 Hz, *1* and *4*), 1.86-1.62 (4H, m, *2* and *3*).

5.77 Synthesis of (1*R*,4*R*)-methanesulphonic acid 4-methanesulphonoxy-1,4-diphenyl-butyl ester 3.4.[84]

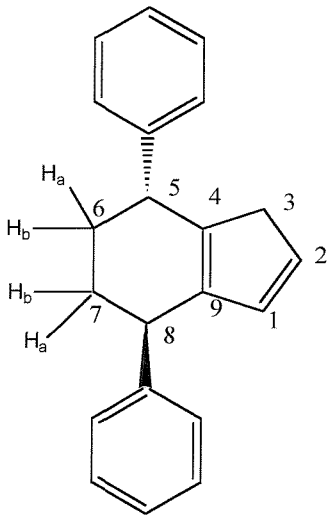


To a solution of (*R*, *R*)-1,4-diphenyl-2-butan-1,4-diol (720 mg, 3 mmol) and triethylamine (1.26 mL) in DCM (57 mL) at –30 °C was added methanesulphonyl chloride (0.6 mL, 7.8 mmol) dropwise. The reaction was stirred at room temperature for two hours at –30 °C. Saturated ammonium chloride solution (12 mL) was then added and the reaction allowed to warm to room temperature. Ethyl acetate (99 mL) was added and the layers were separated. The

organic layer was then washed with a 1:2:1 mixture of water, brine and sodium hydrogen carbonate (4 x 20 mL). The organic layer was then dried over anhydrous magnesium sulphate, filtered through celite and concentrated until 2 mL of solution remained. The residue was then cooled to 0 °C and hexane added to precipitate the desired dimesylate. The precipitate was suction filtered and washed repeatedly with hexanes under suction to remove all traces of ethyl acetate. The white solid was the used immediately in the next reaction (1.340 g, 3.2 mmol, 100%). ^{1}H NMR is in good agreement with literature values.[84]

^{1}H NMR: (400 MHz, $CDCl_3$) δ/ppm: 7.22-6.99 (10H, m, *Ph)*, 5.76-5.72 (2H, m, *1* and *4*), 2.09-1.88 (4H, m, *2* and *3*), 2.03 (6H, s, *SO_2Me*).

5.78 (4*R*,7*R*)-4,7-diphenyl-4,5,6,7-tetrahydro-3aH-indene 3.1a.



To a suspension of petrol washed sodium hydride (400mg, 10 mmol of 60% dispersion in mineral oil) in THF (20 mL) at 0 °C was added freshly distilled cyclopentadiene (0.50 mL, 10 mmol) added. This was stirred for 30 minutes at 0 °C, then cooled to -78 °C and a solution of dimesylate (2.0 g, 4 mmol) in THF (10mL) was added dropwise. This was then allowed to warm to room temperature and stirred overnight. Water (20 mL) was added and the layers were separated. The aqueous layer was extracted was ether (2 x 10 mL) and the combined organic fractions washed with brine (2 x 10mL) and dried over anhydrous magnesium sulphate. The organic fraction was the concentrated at reduced pressure to give the crude product as a viscous colourless oil (150 mg). This was then purified by flash column chromatography with 100% petrol as the eluent, to give the final compound as a colourless oil which solidified upon cooling to give a white amorphous solid (272 mg, 0.37 mmol, 40%).

M. Pt. 64-66 °C (hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ/ppm: 7.30-7.05 (10H, m, *Phenyl*), 6.14 (1H, d, J = 5.5 Hz, *1*), 6.03 (1H, dt, J = 5.4, 1.5 Hz, *2*), 3.78-3.70 (2H, m, *5* and *8*), 2.74 (2H, dd, J = 3.0, 1.5 Hz, *3*), 2.12-2.04 (2H, m, *6a* or *b* or *7a* or *b*)1.70-1.60 (2H, m, *6a* or *b* or *7a* or *b*).

^{13}C NMR: (100 MHz, $CDCl_3$) δ/ppm: 145.6 (C, *phenyl*), 144.5 (C, *phenyl*), 144.5 (C, *4* or *9*), 140.8 (C, *4* or *9*), 132.1 (CH, 2), 129.9 (CH, 3), 127.3 (CH, *phenyl*), 127.2 (CH, *phenyl*), 127.1 (CH, *phenyl*), 125.1, (CH, *phenyl*) 43.6 (CH, *5* or *8*), 42.7 (CH_2, *3*), 42.5 (CH, 5 or 8), 32.6 (CH_2, *6* or *7*), 32.5 (CH2, *6* or *7*).

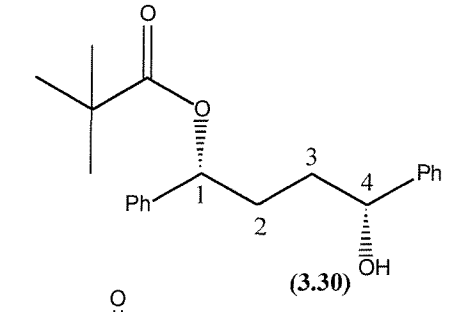
IR (neat film), ν = 3049 (w), 3015 (w), 2930 (w), 2840 (w) cm^{-1}.

LCMS (Cl mode): m/z 273 (M+H, 100%), 168 (82%).

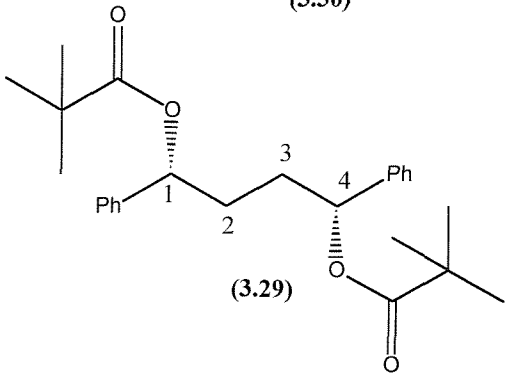
HRMS: required 272.1565, actual 272.1564.

5.8 Preparation of Ester Protected Alcohols and a Novel Cp.

5.81 Synthesis of (1*R*,4*R*)-2,2-dimethyl-propionic acid 4-hydroxy-1,4-diphenyl-butyl ester 3.30 and (1R,4R)-2,2dimethylpropionic acid-(2,2-dimethyl-propionoxyloxy)-1,4-diphenyl-butyl ester 3.29.



(3.30)



(3.29)

To a suspension of sodium hydride (400 mg, 60 % dispersion in mineral oil, 10 mmol) in THF was added diol (717 mg, 3 mmol). The reaction was stirred for thirty minutes and then pivaloyl chloride (960 mg, 8 mmol). The reaction was then allowed to stir at room temperature overnight at which time (TLC 40% ether/petrol) showed that a mixture of the bis pivaloyl ester and the mono pivaloyl esters had formed (R_F = 0.9, 0.5 respectively). The reaction was then quenched with water CARE: Vigorous effervescence, and the layers separated, the aqueous layer was

extracted with diethyl ether (2 x 8 mL) and the combined organic extracts washed with brine (10 mL). The organic portion was then dried over anhydrous magnesium sulphate and the solvents removed at reduced pressure to afford the crude product as a colourless oil. Purification was achieved via column chromatography (40% ether/petrol) to afford bis ester **3.29** as a white solid (147 mg, 0.35 mmol, 11%) and the monoester **3.30** as a colourless oil (632 mg, 1.93 mmol, 64%).

Data for **3.30**

^{1}H NMR: (300 MHz, $CDCl_3$) δ/ppm: 7.38-7.26 (10H, m, *phenyl*), 5.76 (1H, dd, J = 8, 5.2 Hz, *1*), 4.68 (1H, dd, J = 7.4, 5.2, *4*), 2.10-1.65 (4H, m, *2* and *3*), 1.21 (18H, s, 2 x $C(CH_3)_3$).

^{13}C NMR: (75 MHz, $CDCl_3$) δ/ppm: 177.8 (C=O, *5*), 144.5 (C, phenyl), 141.1 (C, phenyl), 128.7 (CH, *phenyl*), 128.6 (CH, *phenyl*), 127.8 (CH, *phenyl*), 126.3 (CH, *phenyl*), 126.0 (CH, *phenyl*) 75.4 (CH, *1*), 74.2 (CH, *4*), 39.0 (C, $\underline{C}(CH_3)_3$), 34.6 (CH_2, *2* or *3*), 33.0 (CH_2, *2* or *3*), 27.3 (CH_3, $C(\underline{C}H_3)_3$).

IR (neat film) ν = 3453 (mb), 2969 (s), 1725 (s), 1453 (m), 1281 (s) cm^{-1}.

LRMS (ES^+ mode): m/z 390.2 $((M+Na+MeCN))^+$ 50%), 349.1 $((M+Na))^+$ (100%).

HRMS required $(M+Na)^+$ 349.1774, found 349.1774, required for $(M+Na+MeCN)^+$ 390.2040, found 390.2041.

Microanalysis: found, C, 77.35 H, 8.31. $C_{21}H_{26}O_3$ (326.19) requires C, 77.27 H, 8.03%.

Data for **3.29**

M. Pt. 58-60 °C (hexane/DCM)

^{1}H NMR: (300 MHz, $CDCl_3$) δ/ppm: 7.52-7.25 (10H, m, *phenyl*), 5.75 (2H, dd, J = 7.4, 5.1 Hz, *1* and *4*), 2.04 –1.74 (4H, m, *3* and *4*), 1.23 (9H, s, $C(CH_3)_3$).

^{13}C NMR: (75 MHz, $CDCl_3$) δ/ppm: 177.7 (C=O, *5*), 140.8 (C, phenyl), 128.6 (CH, phenyl), 128.0 (CH, *phenyl*), 126.2 (CH, *phenyl*), 75.1 (CH, *1* and *4*), 39.0 (C, $C(CH_3)_3$), 32.7 (CH_2, *2* and *4*), 32.3 (CH_3, $C(CH_3)_3$).

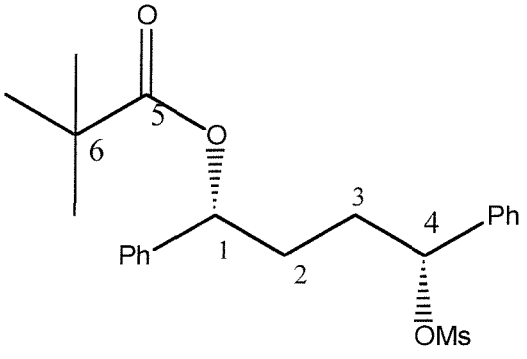
IR (solid), ν = 2978 (m), 2956(m), 1723 (s), 1473 (a), 1277 (s) cm^{-1}.

LRMS (ES^+ mode): m/z 843.6 $((M_2+Na))^+$ 40%), 433.2 $((M+Na))^+$ (100%).

HRMS required for $(M+Na)^+$ 433.2349, found 433.2352.

Microanalysis: Found C, 75.66, H, 8.13, $C_{26}H_{34}O_4$ (410.25) requires C, 76.06, H, 8.35%.

5.82 Synthesis of (1*R*,4R)-2,2-dimethyl-propionic acid 4-methanesulphonoxy-1,4-diphenyl-butyl ester 3.32.



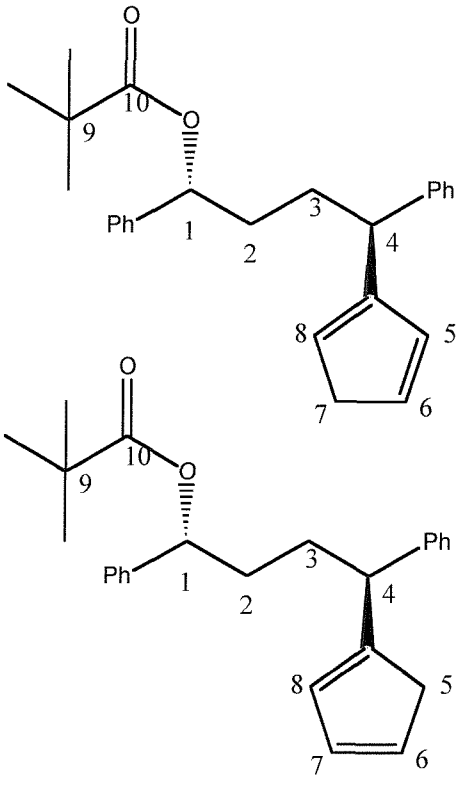
To a solution of (1*R*,4*R*)-2,2-dimethyl-propionic acid 4-hydroxy-1,4-diphenyl-butyl ester 3.30 (311 mg, 1 mmol) and triethylamine (0.42 mL) in DCM (10 mL) at –30 °C was added methanesulphonyl chloride (0.1 mL, 1.3 mmol) drop wise. The reaction was stirred at room temperature for two hours at –30 °C. Saturated ammonium chloride solution (5 mL) was then added and the reaction allowed to warm to room temperature. Ethyl acetate (33 mL) was added and the layers were separated. The organic layer was then washed with a 1:2:1 mixture of water, brine and sodium hydrogen carbonate (4 x 10 mL). The organic layer was then dried over anhydrous magnesium sulphate, filtered through celite and concentrated until 1 mL of solution remained. The residue was then cooled to 0 °C and hexane added to precipitate the desired mesylate. The precipitate was suction filtered and washed repeatedly with hexanes under suction to remove all traces of ethyl acetate. The white solid was the used immediately in the next reaction (402 mg, 1 mmol, 100%).

M. Pt. 62-64 °C (hexane).

^{1}H NMR: (300 MHz, $CDCl_3$) δ/ppm: 7.45-7.25 (10H, phenyl), 5.79 (1H, dd, J = 8.1, 5.1 Hz, *4*), 5.53 (1H, dd, J = 8.0, 5.1 Hz, *1*), 2.62 (3H, s, SO_2CH_3), 2.20-1.80 (4H, m, *2* and *3*), 1.21 (9H, s, CCH_3).

^{13}C NMR: (75 MHz, $CDCl_3$) δ/ppm: 177.7 (C=O, *5*), 140.6 (C, phenyl), 138.2 (C, phenyl) 129.4 (CH, *phenyl*), 129.2 (CH, *phenyl*), 128.7 (CH, *phenyl*), 128.1 (CH, *phenyl*), 126.8 (CH, *phenyl*), 126.2 (CH, *phenyl*), 84.5 (CH, *1*), 74.6 (CH, 4), 39.2 (CH_3, $SO_2\underline{C}H_3$), 39.0 (C, *6*), 33.2 (CH_2, *2* or *3*), 32.7 (CH_2, *2* or *3*), 27.3 (CH_3, $C\underline{C}H_3$).

5.83 (1*R*,4*S*)-4-(1,3-cyclopentadienyl)-1,4-diphenylbutyl pivalate.



To a suspension of petrol washed sodium hydride (40mg, 1 mmol of 60% dispersion in mineral oil) in THF (2 mL) at 0 °C was added freshly distilled cyclopentadiene (0.03 mL, 0.6 This was stirred for 30 minutes at 0 °C and then cooled to -78 °C and a solution of mesylate (180 mg, 0.5 mmol) in THF (1 mL) was added drop wise. This was then allowed to warm to room temperature and stirred overnight. Water (2 mL) was added and the layers were separated. The aqueous layer was extracted was ether (2 x 1 mL) and the combined organic fractions washed with brine and dried over anhydrous magnesium sulphate. The residue was the concentrated at reduced pressure to give the crude product as a viscous colourless oil (150 mg). This was then purified by flash column chromatography with 100% petrol as the eluent, to give the final compound as a colourless oil, (101 mg, 0.37 mmol, 74%). The compound was formed a mixture of tautomers, which has made accurate NMR assignment difficult.

^{1}H NMR: (400 MHz, $CDCl_3$) δ/ppm: 7.24-7.04 (10H, m, *Ph*), 6.32-6.27 (1H, m, *Cp, alkenyl*), 6.22 (1H, dd, *J* = 5.5, 1.5 Hz, *Cp, alkenyl*), 6.1-6.08 (1H, m, *Cp, alkenyl*), 5.65,

(1H, dd, J = 7.5, 6.0 Hz, *1*), 3.55 (2 x ½H, 2 x t, *J* = 8Hz, *4*), 2.86 (2H, bs, *Cp, alkyl*), 2.65 (2H, bs, *Cp, alkyl*), 1.99-1.76 (4H, m, *2* and *3*), 1.22 (9H, s, $C(CH_3)_3$).

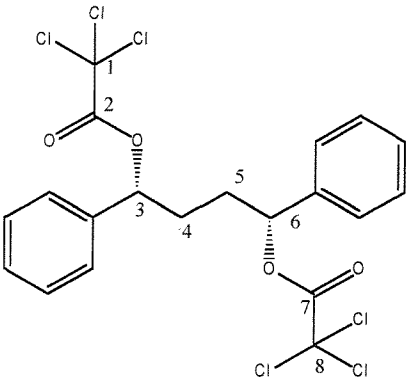
^{13}C NMR: (100 MHz, $CDCl_3$) δ/ppm: 176.6 (C=0, *10*), 151.2(C, Cp), 148.6 (CH, Cp), 142.7 (C, phenyl), 140.1 (C, phenyl), 132.8, 132.7, 131.0, 130.5, 127.4, 127.4, 127.3, 126.9, 126.7, 126.6, 126.6, 125..2, 125.2, 125.1, 125.1, 125.0 (All CH, *Cp or phenyl*), 74.4 (CH, *1*), 46.0 and 45.0 (CH, *4*), 41.1 and 40.0 (CH_2, Cp, alkyl), 37.8 (C, $\underline{C}(CH_3)_3$), 33.9 and 33.8 (CH_2, 2), 30.0 and 29.5 (CH_2, 3), 26.1 (CH3, $C(\underline{C}H_3)_3$).

IR (neat film), ν = 2969 (w), 2955 (w), 1726 (s), 1478 (w), 1365 (w), 1280 (m) cm^{-1}.

LRMS (ES^+ mode): m/z 397.2 $((M+Na))^+$, 100%).

HRMS: required $(M+Na)^+$ 397.2138, actual 397.2145.

5.84 Synthesis of (1*R*,4*R*)-1,4-diphenyl-4-[(trichloroacetyl)oxy]butyl trichoroacetate 3.28.



To a solution of (1*R*,4*R*)-1,4-diphenyl-2-butan-1,4-diol **3.5** (1.210 g, 5 mmol) in DCM (20 mL) at 0 °C was added aluminium chloride (792 mg, 6 mmol) and trichloroacetyl chloride (1.00 g, 5.5 mmol). After stirring for two hours, TLC showed that all starting material had been consumed. The reaction mixture was poured onto ice/water and the two phases separated. The organic phase was extracted by ether (2 x 10mL) and the combined organic portions were washed with brine and a saturated $NaHCO_3$ solution. The solvents were removed *in vacuo* and NMR analysis revealed that the desired compound had formed as a yellow/white solid (2.025 g, 3.8 mmol, 76%).

M. Pt. 63-65 °C (hexane)

^{1}H NMR: (400 MHz, $CDCl_3$) δ/ppm: 7.23- 7.14 (10H, m, *phenyl*), 5.68 (2 x 1H, dd, J= 7.0, 5.5 Hz, *3* and *6*), 2.10-1.75 (4H, m, *4* and *5*).

^{13}C NMR: (100 MHz, $CDCl_3$) δ/ppm: 161.4 (C=O, *2* and *7*), 138.2 (C, *phenyl*), 129.3 (CH, *phenyl*), 129.3 (CH, *phenyl*), 126.7 (CH, *phenyl*), 90.4 (C, *1* and *8*), 81.2 (CH, *3* and *6*), 32.3 (CH_2, *4* and *5*).

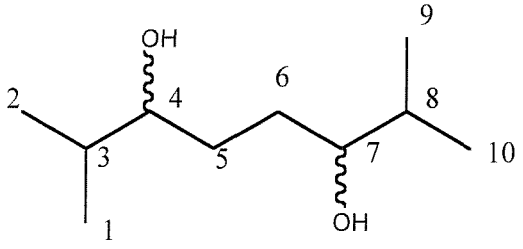
IR (solid), ν = 2959 (w), 1752 (s) (w), 1453 (w), 1301 (w)., 1235 (s) cm^{-1}.

LRMS (ES^+ mode), 554.9 $((M+Na))^+$ 20%.

Microanalysis: Found C, 45.13 H, 3.04 Cl, 39.49 $C_{20}H_{16}Cl_6O_4$ (529.92) requires C, 45.06, H, 3.04 Cl, 39.90%.

5.9 Preparation of methanesulphonic acid 1-isopropyl-4-methanesulphonoxy-5-methyl-hexyl ester 3.36.

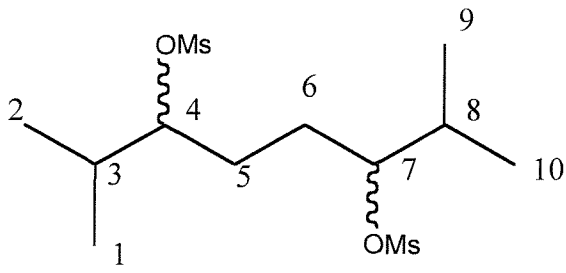
5.91 Synthesis of 2,7-dimethyl-octane-3,6-diol 3.35.



To a solution of succinaldehyde (4g, 43 mmol) in THF (40 mL) at 0 °C was added isopropyl magnesium chloride (60 mL, 2 M, 120 mmol). This was stirred for 72 hours. The reaction mixture was then cooled to 0 °C and water added dropwise to quench the reaction. CARE: vigourous effervescence. The layers were separated and aqueous layer was extracted with ether (3 x 30 mL). The combined ethereal extracts were combined washed with brine (30 mL) and dried over anhydrous magnesium sulphate. The filtrate was then concentrated at reduced pressure. The residue was then purified by flash column chromatography on silica with 50 % petrol/ether as the eluent to afford the desired product as a white solid (1.125g, 8 mmol, 17%). NMR data was consisitent with literature values, and showed that the product had formed as a mixture of diastereoisomers.[102]

^{1}H NMR: (300 MHz, $CDCl_3$) δ/ppm: 3.40-1.30 (2H m, *4 and 7*), 2.69 (2H, bs, *OH)*, 1.72-60 (4H, m, *5 and 6*), 1.53 (4H, m, *3* and *8*), (12H, m, *1, 2, 9* and *10*).

5.92 Synthesis of methanesulphonic acid 1-isopropyl-4-methanesulphonoxy-5-methyl-hexyl ester 3.36.[105]

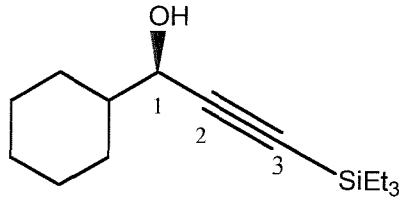


To a solution of diisopropyl diol in DCM (9 mL) at – 30 °C was added triethylamine (0.42 mL) and then methanesulphonyl chloride (0.20 mL, 2.6 mmol) as solution in DCM (10 ml). The reaction was stirred at –30 °C for 2 hours and then saturated ammonium chloride solution (4 mL) was added and the reaction allowed to warm to room temperature. Ethyl acetate (33 mL) was added and the layers separated. The organic fraction was washed with a 1:2:1 mixture of water, brine and sodium bicarbonate, (3 x 20 mL) and then dried over anhydrous magnesium sulphate, filtered and concentrated. This provided the product as a white powder and as a mixture of diastereoisomers (170 mg, 0.5 mmol, 50%). It was then used immediately in the next reaction.

^{1}H NMR: (300 MHz, $CDCl_3$) δ/ppm: 4.62-4.53 (2H, m, *4* and *7*), 3.03 (6H, s, $SO_2\underline{Me}$), 2.04-1.99 (2H, m, *3* and *7*), 1.87-1.77 (4H, m, *5* and *6*) 0.98 (12H, dd, J = 6.5, 4.4 Hz, *1, 2, 9* and *10*).

5.10 Preparation of 1,4-dicyclohexylbutane-1,4-diol 3.46.

5.101 Synthesis of (*R*)-1-cyclohexyl-3-triethylsilyl-2-propyn-1-ol 3.44.[104]



A 50 mL 3-necked flask charged with zinc triflate (3.60 g, 10 mmol) was heated under vacuum at 125 °C for 4 hours. The flask was then cooled to room temperature, refilled with nitrogen and (+)-N-methylephedrine (1.98g, 11 mmol) was added. The flask was stirred under vacuum for 30 minutes and then refilled with nitrogen. Toluene (3 mL) and triethylamine (2.53 g, 25 mmol) were added and the reaction mixture stirred at room temperature for 2 hours. At this time triethylsilylacetylene (1.68g, 12 mmol) was added and the reaction stirred for a further 15 minutes. Cyclohexane carboxaldehyde (1.12g, 10 mmol) was added and the reaction heated to 60 °C overnight.

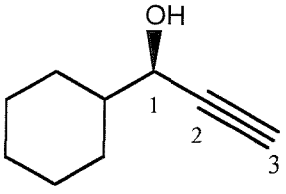
Saturated ammonium chloride solution (3mL) was added and the layers separated. The aqueous layer was extracted with ether (3 x 5 mL) and the combined organic layers washed with brine, dried over anhydrous magnesium sulphate and concentrated *in vacuo* to afford the cruded product as a colourless oil. This was then purified using flash column chromatography on silica (40% DCM/pentane) to give the desired product as a colourless oil (1.84 g, 7.3 mmol, 73 %). ^{1}H NMR data and optical rotation is consistent with literature precedent.[106]

$[\alpha]^{296}_D$ –5.2° (c = 1.1, $CHCl_3$). Lit $[\alpha]^{298}_D$ – 5.4° (c = 1.1, $CHCl_3$)[106]

^{1}H NMR: (300 MHz, $CDCl_3$) δ/ppm: 4.17 (1H, d, *J* = 5.9 Hz, *1*), 1.90-1.10 (11H, m, cC_6H_{11}), 0.99 (9H, t, *J* = 7.8 Hz, $SiCH_2\underline{C}H_3$), 0.60 (6H, q, *J* = 7.8 Hz, $Si\underline{C}H_2CH_3$).

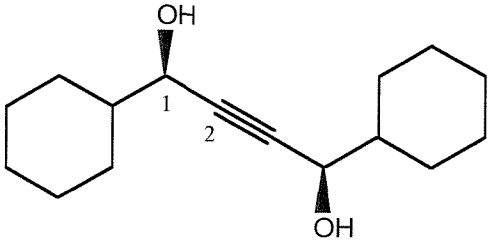
^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm 107.2 (C, *2*), 87.6 (C, 3), 67.8 (CH, *1*), 44.2 (CH, cC_6H_{11}), 28.7 (CH_2, cC_6H_{11}), 28.0 (CH_2, cC_6H_{11}), 26.6 (CH_2, cC_6H_{11}), 26.0 (CH_2, cC_6H_{11}), 26.0 (CH_2, cC_6H_{11}), 7.6 (CH_3, $SiCH_2\underline{C}H_3$), 4.5 (CH_2, $Si\underline{C}H_2CH_3$).

5.102 Synthesis of (*R*)-1-cyclohexyl-2-propyn-1-ol 3.42.[88]



To a solution of (*R*)-1-cyclohexyl-3-triethylsilyl-2-propyn-1-ol (1.25g, 5 mmol) in methanol (10 mL) was added sodium hydroxide as a 10 % solution in water (10 mL). This was stirred overnight. At this time ether (50 mL) was added, and the layers were separated. The aqueous phase was extracted with ether (2 x 20 mL) and the combined organic fractions washed with brine and dried over anhydrous magnesium sulphate. Solvents were then removed at reduced pressure to give the crude product as a colourless oil. This was used without further purification and so NMR data is very unclear.

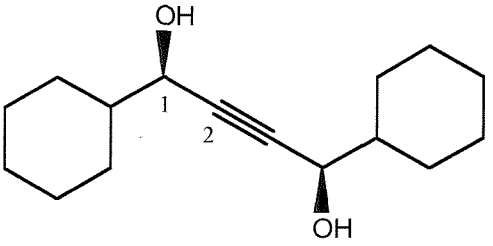
5.103 Synthesis of (1*R*, 4*R*)-1,4-diphenyl-2-butyn-1,4-diol 3.45[104].



A 50 mL 3-necked flask charged with zinc triflate (0.36 g, 1 mmol) was heated under vacuum at 125 °C for 4 hours. The flask was then cooled to room

temperature, refilled with nitrogen and (+)-N-methylephedrine (0.198, 1.1 mmol) was added. The flask was stirred under vacuum for 30 minutes and then refilled with nitrogen. Toluene 3 mL and triethylamine (0.253 g, 2.5 mmol) were added and the reaction mixture stirred at room temperature for 2 hours. At this time (R)-1-cyclohexyl-2-propyn-1-ol (1.68g, 12 mmol) was added and the reaction stirred for a further 15 minutes. Cyclohexane carboxaldehyde (1.12g, 10 mmol) was added and the reaction heated to 60 °C overnight. Saturated ammonium chloride solution (3mL) was added and the layers separated. The aqueous layer was extracted with ether (3 x 5 mL) and the combined organic layers washed with brine, dried over anhydrous magnesium sulphate and concentrated *in vacuo* to afford the crude product as a colourless oil. This was then purified using flash column chromatography on silica (40% DCM/pentane) to give the desired product as a colourless oil (1.84 g, 7.3 mmol, 73 %). ^{1}H NMR, melting point data and optical rotation data are is consistent with literature precedent.[105] See below for spectral data

5.104 Alternate synthesis for the synthesis of 1,4-diphenyl-2-butyn-1,4-diol.



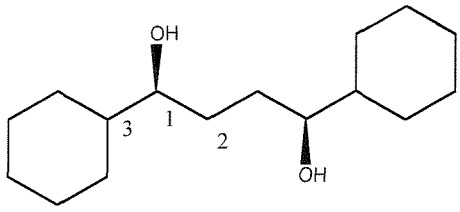
A 50 mL 3-necked flask charged with zinc triflate (0.36 g, 1.1 mmol) was heated under vacuum at 125 °C for 4 hours. The flask was then cooled to room temperature, refilled with nitrogen and (+)-N-methylephedrine (0.198g, 1.1 mmol) was added. The flask was stirred under vacuum for 30 minutes and then refilled with nitrogen. Toluene 3 mL and triethylamine (0.253 g, 2.5 mmol) were added and the reaction mixture stirred at room temperature for 2 hours. At this time cyclohexane carboxaldehyde (0.112g, 1.0 mmol) and acetylene gas (12 mL, 0.5 mmol) were added and the sealed reaction stirred at room temperature for 14 days. Saturated ammonium chloride solution (3mL) was added and the layers separated. The aqueous layer was extracted with ether (3 x 5 mL) and the combined organic layers washed with brine, dried over anhydrous magnesium sulphate and concentrated *in vacuo* to afford the crude product as a colourless oil. This was then purified using flash column chromatography on silica (40% DCM/pentane) to give the desired product as a colourless oil (0.76 g, 0.3 mmol, 60 %). ^{1}H NMR, melting point data and optical rotation data are is consistent with literature precedent.[105]

$[\alpha]^{298}_{D}$ –5.5° (c = 0.84, $CHCl_3$). Lit. $[\alpha]^{298}_{D}$ –5.7° (c = 0.84, $CHCl_3$).[105]

M. Pt. 125-127 °C (toluene). Lit. M. Pt., 126-128.[105]

^{1}H NMR: (300 MHz, $CDCl_3$) δ/ppm: 4.15 (2H, s, *1*), 1.98 (22H, m, cC_6H_{11}).

5.105 Synthesis of (1*R*, 4*R*)-1,4-dicyclohexylbutane-1,4-diol 3.46.[89]



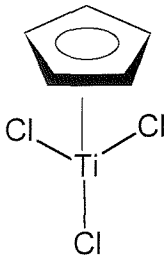
To a round bottomed flask equipped with a hydrogen balloon was added diol(1.0 g, 4 mmol), methanol (10 mL) and 5% Pt/C (40 mg). This was then stirred overnight and filtered through a pad of celite. The filtrate was then concentrated at reduced pressure to give the desired product as a white solid (1.03 g, 100%). Both melting point data and proton NMR data was in good agreement with literature precedent.[89]

M. Pt. 148-149 °C (DCM). Lit. M. Pt. 149.2-149.8 °C. [100]

^{1}H NMR: (300 MHz, $CDCl_3$) δ/ppm: 3.37 (2H, dd, *J* = 5.7 Hz, *1*), 2.20 (2H, bs, *OH*), 1.78 (26H, dm, *2* and cC_6H_{11}).

5.11 Preparation of η-5-cyclopentadienyl[(4*R*,7*R*)-4,7-diphenyl-5,6,7,7a-tetrahydro-4*H*-indenyl]titanocene dichloride.

5.111 Synthesis of cyclopentadienyl titanium chloride.[106]

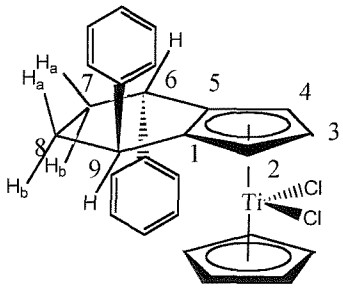


Bis-(cyclopentadienyl) titanium trichloride (6.0 g, 24.0 mmol, 1.0 equivalent) was placed under an argon flush in a 100 mL three-neck round bottomed flask equipped with a reflux condenser and internal thermometer, which had been previously flame-dried under vacuum. Xylene (50 mL) was added to slurry the metallocene, and $TiCl_4$ (7.4 mL, 65.0 mmol, 2.7 equivalents) was added via syringe. The reaction mixture was then stirred with refluxing conditions (140 °C), for 6 hours before cooling to room temperature overnight, during

which time dirty crystals formed below the black solution. The liquor was decanted, and the crystals washed with hexane (6 x 15 mL), to give the crude product as an orange/brown solid. Recrystallisation from hot benzene gave the title compound in 74 % yield (3.931g, 17.8 mmol) as a yellow crystalline solid. ^{1}H NMR data was in good agreement with literature values.

^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm = 7.07 (5H, s, *Cp ring*).[106]

5.112 Synthesis of Synthesis of η-5-cyclopentadienyl[(4*R*,7*R*)-4,7-diphenyl-5,6,7,7a-tetrahydro-4*H*-indenyl]titanocene dichloride 4.4.[92]



To a solution of Cp ligand **3.1** (272 mg, 1 mmol) in ethanol (2 mL) at room temperature was added thallium ethoxide (275 mg). After stirring at room temperature for two hours a grey/white precipitate of the thallium Cp had formed and so the ethanol was removed via syringe and the residue washed with ether, ethanol and hexane and dried *in vacuo*. Toluene (2.5 mL) and a solution $CpTiCl_3$ (217 mg, 1 mmol) in toluene (2.5 mL) were added and the reaction heated at 72°C for 4 hours at which analysis by 1H NMR showed that the desired complex had formed. The reaction mixture was filtered through celite then concentrated at reduced pressure to give the crude compound as a red solid, which was recrystallised by slow evaporation from hexane layered onto a solution of crude material in the lowest quantity of DCM, stored at –20 °C for 1 week to afford the title compound (91mg, 0.2 mmol) in a 20% overall yield.

M. Pt. 266-267 °C (hexane).

^{1}H NMR (400 MHz, C_6D_6): δ/ppm = 7.38-7.16 (10H, m, *phenyl*), 6.39 (1H, m, *2* or *4*), 6.12 (1H, t, *J* = 2.5 Hz, *2* or *4*) 5.88 (5H, s, *Cp*), 5.57 (1H, m, *3*), 4.77 (1H, dd, *J* = 12.3, 5.0 Hz, *9*), 3.88 (1H, dd, *J* = 12.6, 5.0 Hz, *6*), 2.71 (1H, qd, *J* = 12.9, 2.0 Hz, *7b*), 2.35 (1H, m, *8b*), 1.94 (1H, qd, *J* = 13, 2.5 Hz, *8a*), 1.89 (1H, m, *7a*).

^{13}C NMR (100 MHz, C_6D_6): δ/ppm = 142.6 (C, *phenyl*), 139.3 (C, *phenyl*), 138.6 (C, *1* or *5*), 133.6 (C, *1* or *5*), 132.6 (CH, *2* or *4*), 127.0 (2 x CH, *phenyl*), 126.9 (2 x CH, *phenyl*), 126.8 (2 x CH, *phenyl*), 126.7 (2 x CH, *phenyl*), 125.6 (CH, *phenyl*), 124.8 (CH, *phenyl*), 117.6 (5 x CH, *Cp*), 109.1 (CH, *2* or *4*), 105.3 (CH, *3*), 44.6 (CH, *6* or *9*), 40.7 (CH, *6* or *9*), 31.0 (CH_2, *7* or *8*), 24.6 (CH_2, *7* or *8*).

IR (solution in DCM): ν = 3101 (w), 2907 (w), 2358 (m), 2335 (m), 1436 (w).

MS: compound resisted all attempts to obtain a mass spectrum, despite the use of multiple techniques.

5.113 X-ray Crystallography of η-5-cyclopentadienyl[(4*R*,7*R*)-4,7-diphenyl-5,6,7,7a-tetrahydro-4*H*-indenyl]titanocene dichloride (03paw002).[107]

A summary of crystal data, intensity collection, and refinement parameters are reported in appendix 1. A single crystal of **(4.4)** was mounted on a glass fibre and data collections performed at 150K using an Enraf Nonius Kappa CCD area detector (λ Mo Ka = 0.71073 Å).[108] The data were corrected for absorption effects using SORTAV[109] and the structures solved by direct methods using SHELXS97[110] Hydrogen atoms were included in calculated positions and all heavy atoms were refined anisotropically using full–matrix least–squares refinement on F^2 (*SHELXL97*[111]) to give R1 = 0.0451 and wR2 = 0.1063 for I>2σ(I). All operations were carried out within the WinGX environment.[112]

Appendix 1

X-ray structure for compound 3.6

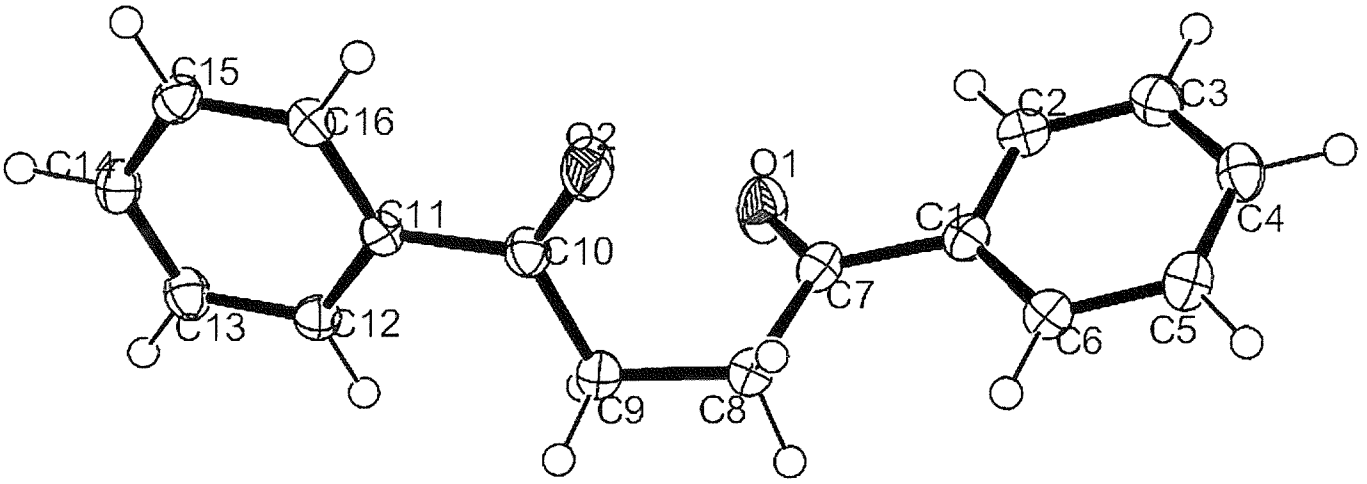


Table 1. Crystal data and structure refinement for 03paw003.

Identification code	03paw003	
Empirical formula	C16 H14 O2	
Formula weight	238.27	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P212121	
Unit cell dimensions	a = 8.2509(4) Å	α= 90°.
	b = 10.5175(5) Å	β= 90°.
	c = 14.0364(7) Å	γ = 90°.
Volume	1218.06(10) $Å^3$	
Z	4	
Density (calculated)	1.299 Mg/m^3	
Absorption coefficient	0.085 mm^{-1}	
F(000)	504	
Crystal size	0.6 x 0.25 x 0.25 mm^3	
Theta range for data collection	3.14 to 27.46°.	
Index ranges	-9<=h<=10, -13<=k<=12, -18<=l<=18	
Reflections collected	11597	
Independent reflections	2791 [R(int) = 0.0655]	
Completeness to theta = 27.46°	99.6 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2791 / 0 / 219	
Goodness-of-fit on F^2	1.061	
Final R indices [I>2sigma(I)]	R1 = 0.0451, wR2 = 0.1063	
R indices (all data)	R1 = 0.0574, wR2 = 0.1130	
Absolute structure parameter	0.1(15)	
Largest diff. peak and hole	0.171 and -0.225 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 03paw003. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(2)	1777(2)	4072(1)	2611(1)	40(1)
C(11)	1130(2)	3560(2)	4202(1)	20(1)
O(1)	-1914(2)	3966(1)	1848(1)	39(1)
C(9)	93(2)	2245(2)	2762(1)	26(1)
C(7)	-1087(2)	3330(2)	1311(1)	24(1)
C(6)	-324(2)	2790(2)	-392(1)	24(1)
C(2)	-1907(2)	4672(2)	-68(1)	25(1)
C(13)	317(2)	3067(2)	5816(1)	26(1)
C(14)	1283(2)	4050(2)	6156(1)	24(1)
C(4)	-1165(2)	4150(2)	-1684(1)	27(1)
C(12)	240(2)	2824(2)	4840(1)	24(1)
C(15)	2189(2)	4779(2)	5524(1)	24(1)
C(1)	-1096(2)	3588(2)	262(1)	21(1)
C(10)	1059(2)	3357(2)	3143(1)	23(1)
C(8)	-32(2)	2260(2)	1680(1)	25(1)
C(3)	-1937(2)	4947(2)	-1033(1)	28(1)
C(5)	-363(2)	3073(2)	-1365(1)	27(1)
C(16)	2117(2)	4536(2)	4552(1)	23(1)
H(15)	2840(20)	5448(17)	5773(12)	26(5)
H(8A)	-490(20)	1432(18)	1442(14)	26(5)
H(2)	-2500(20)	5703(19)	-1284(14)	30(5)
H(12)	-380(20)	2123(19)	4594(15)	31(5)
H(5)	240(20)	2026(19)	-151(15)	29(5)
H(9B)	600(20)	1424(19)	2964(15)	28(5)
H(1)	-2430(20)	5210(17)	381(14)	24(5)
H(3)	-1220(30)	4350(20)	-2376(16)	39(6)
H(13)	-310(20)	2538(18)	6282(15)	28(5)
H(8B)	1070(20)	2350(18)	1385(13)	25(5)
H(16)	2730(20)	5067(17)	4105(12)	25(5)
H(9A)	-1030(30)	2200(20)	3058(15)	35(5)
H(14)	1390(20)	4236(18)	6885(13)	25(5)
H(4)	110(30)	2460(20)	-1799(16)	38(6)

Appendix 2

X-ray for compound 4.4

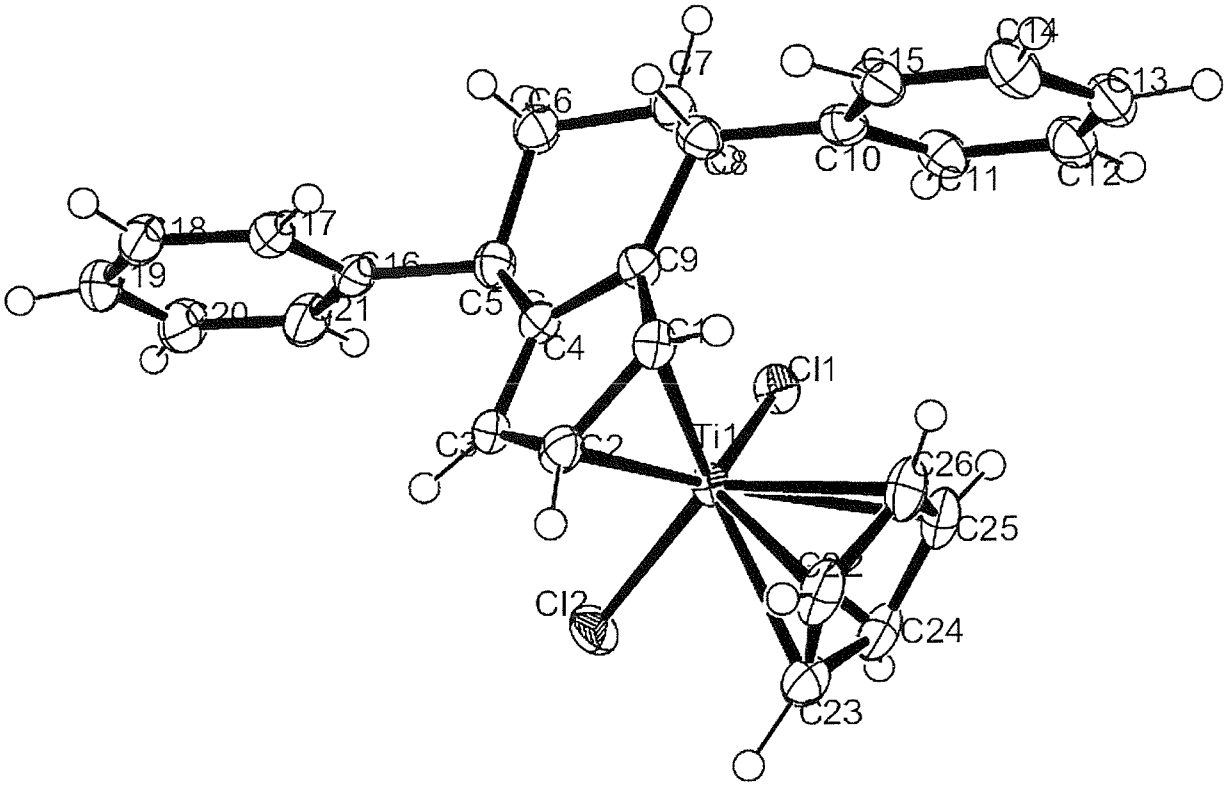


Table 1. Crystal data and structure refinement for 03paw002.

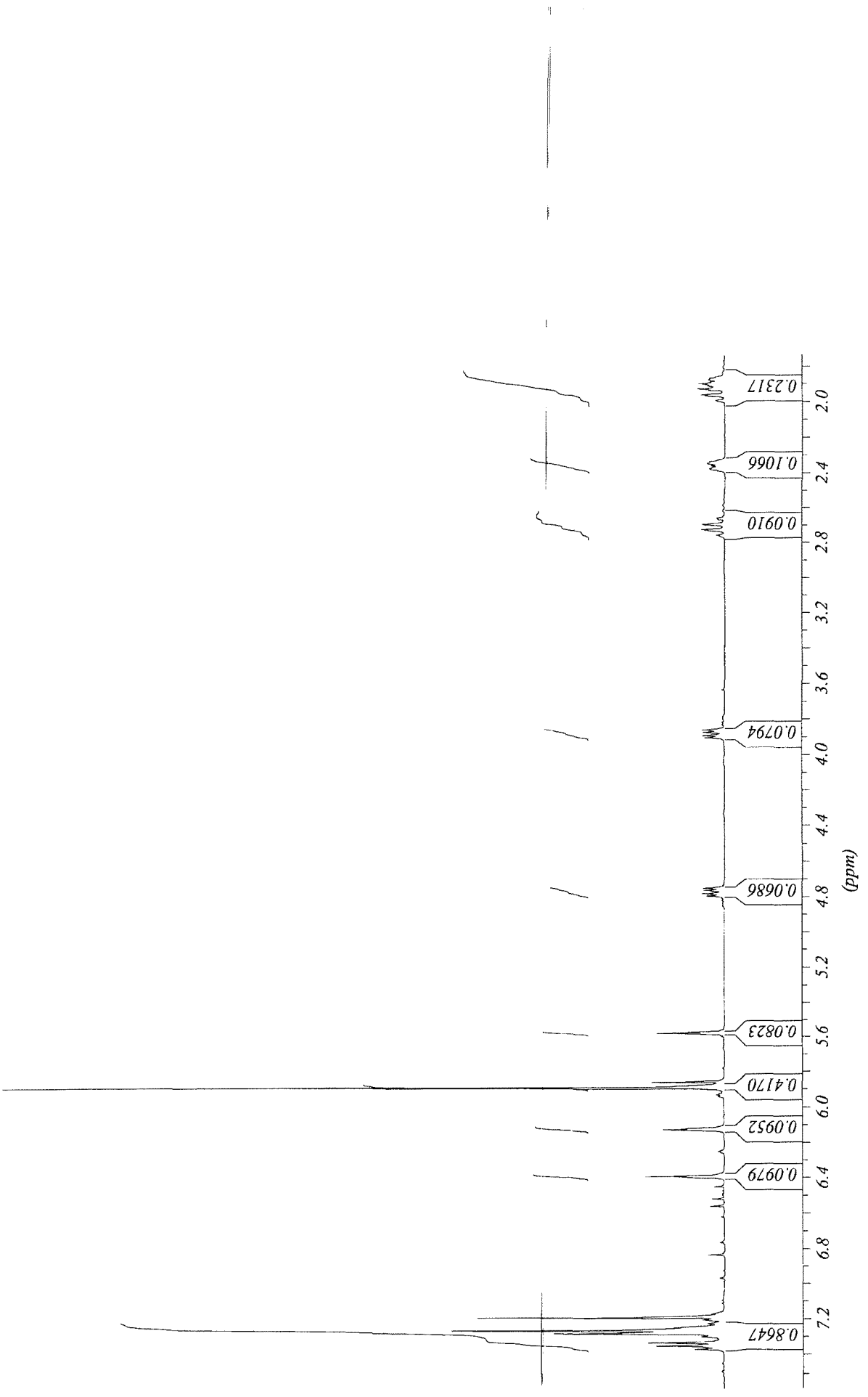
Identification code	03paw002	
Empirical formula	C26 H24 Cl2 Ti	
Formula weight	455.25	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P212121	
Unit cell dimensions	a = 6.8297(2) Å	α= 90°.
	b = 14.7988(5) Å	β= 90°.
	c = 21.1067(8) Å	γ = 90°.
Volume	2133.28(13) $Å^3$	
Z	4	
Density (calculated)	1.417 Mg/m^3	
Absorption coefficient	0.662 mm^{-1}	
F(000)	944	
Crystal size	0.25 x 0.14 x 0.08 mm^3	
Theta range for data collection	2.92 to 27.49°.	
Index ranges	-8<=h<=8, -17<=k<=19, -21<=l<=27	
Reflections collected	17876	
Independent reflections	4793 [R(int) = 0.0623]	
Completeness to theta = 27.49°	99.4 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4793 / 0 / 262	
Goodness-of-fit on F^2	1.046	
Final R indices [I>2sigma(I)]	R1 = 0.0377, wR2 = 0.0807	
R indices (all data)	R1 = 0.0489, wR2 = 0.0848	
Absolute structure parameter	-0.01(2)	
Largest diff. peak and hole	0.219 and -0.268 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 03paw002. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Ti(1)	3898(1)	3874(1)	998(1)	19(1)
Cl(2)	6076(1)	3045(1)	348(1)	32(1)

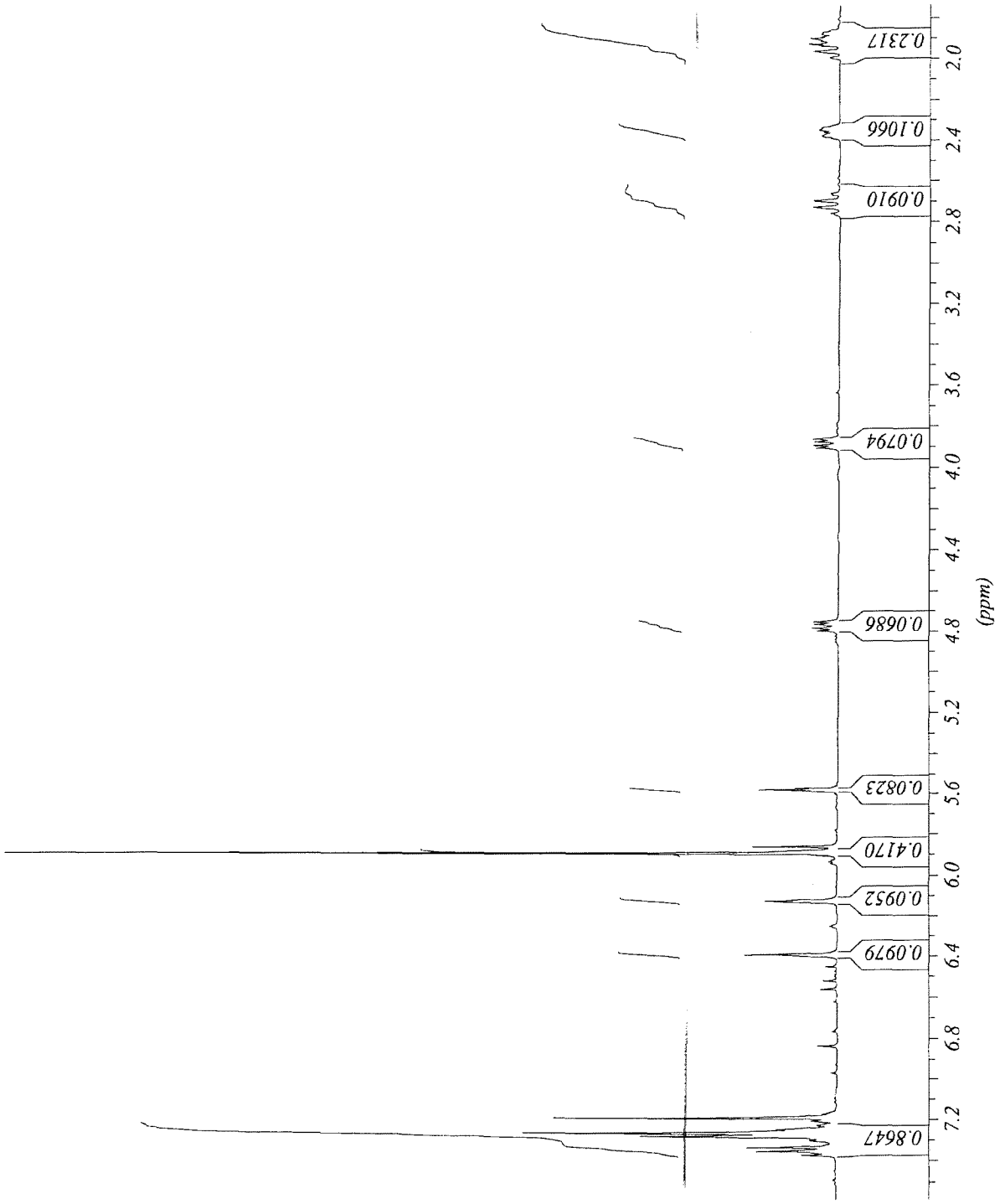
Cl(1)	6552(1)	4511(1)	1548(1)	26(1)
C(5)	6011(4)	5821(2)	222(1)	24(1)
C(3)	3423(3)	4551(2)	-27(1)	22(1)
C(15)	134(4)	6243(2)	2003(1)	27(1)
C(9)	2826(3)	5456(2)	829(1)	21(1)
C(1)	1260(3)	4847(2)	766(1)	22(1)
C(8)	3000(3)	6274(2)	1262(1)	24(1)
C(13)	344(4)	5812(2)	3094(1)	30(1)
C(4)	4186(3)	5266(2)	335(1)	22(1)
C(6)	5833(4)	6736(2)	571(1)	30(1)
C(7)	5089(3)	6645(2)	1254(1)	28(1)
C(10)	2132(3)	6116(2)	1917(1)	23(1)
C(11)	3217(4)	5829(2)	2436(1)	28(1)
C(16)	6390(3)	5966(2)	-482(1)	24(1)
C(14)	-759(4)	6097(2)	2583(1)	33(1)
C(20)	8539(4)	5957(2)	-1390(1)	38(1)
C(2)	1637(3)	4285(2)	241(1)	24(1)
C(21)	8219(4)	5796(2)	-747(1)	34(1)
C(26)	1605(4)	3535(2)	1808(1)	31(1)
C(22)	1180(4)	2966(2)	1292(1)	32(1)
C(19)	7068(4)	6298(2)	-1767(1)	35(1)
C(24)	4193(4)	2606(2)	1673(1)	32(1)
C(17)	4920(4)	6299(2)	-871(1)	27(1)
C(18)	5252(4)	6470(2)	-1509(1)	33(1)
C(23)	2781(4)	2390(2)	1209(1)	34(1)
C(12)	2332(4)	5684(2)	3019(1)	31(1)
C(25)	3430(4)	3301(2)	2048(1)	31(1)
H(5)	7129	5492	401	29
H(3)	4005	4297	-383	26
H(15)	-624	6433	1662	33
H(1)	163	4820	1026	26
H(8)	2188	6744	1067	29
H(13)	-246	5708	3484	37
H(6A)	7106	7027	576	36
H(6B)	4945	7123	336	36
H(7A)	5943	6242	1488	33
H(7B)	5116	7232	1459	33
H(11)	4556	5733	2392	34

H(14)	-2099	6189	2628	39
H(20)	9758	5833	-1566	45
H(2)	839	3819	97	29
H(21)	9228	5575	-496	40
H(26)	799	3991	1962	37
H(22)	42	2972	1050	39
H(19)	7300	6413	-2193	42
H(24)	5412	2334	1721	38
H(17)	3687	6410	-702	33
H(18)	4253	6699	-1762	39
H(23)	2896	1943	901	41
H(12)	3085	5498	3362	38
H(25)	4039	3561	2397	37


0.8647
0.0979
0.0952
0.4170
0.0823
0.0686
0.0794
0.0910
0.1066
0.2317
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
(ppm)

Appendix 4

NMR for complex 4.4



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