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Multi-Component Synthesis using Zirconium

By

Andreina Pacheco Pita

Thesis for the Degree of Doctor of Philosophy (PhD)

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Abstract

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The research described in this thesis focuses on different areas of organozirconium chemistry.

Firstly, four compounds with a *cis*-bicyclo[3.3.0]oct-2-ene backbone were synthesised to target orphan nuclear receptors LRH-1 and SF-1. The key reaction to construct the bicyclo[3.3.0]oct-2-ene involved the zirconocene-mediated cyclisation of 1,6-enynes (prepared *via* multi-step synthetic routes) followed by further elaboration with the insertion of a 1,1-dihalide alkyl carbenoid and a lithium phenyl acetylide.

Secondly, a wide range of benzyl carbenoids were inserted into unsaturated zirconacycles which afforded the corresponding alkene product after a low temperature quench. For the clean synthesis of dienes from the reaction, efficient zirconocene traps were discovered (chloroform and benzyl chloride), the former of which was used for the synthesis of a range of diene compounds. The traps were found to facilitate the decomplexation of zirconocene from zirconocene η^2-alkene complexes which are formed after endocyclic cyclometallation of the benzyl-inserted zirconacycle.

Finally, the novel reactivity of benzyl chloride with zirconocene η^2-alkene complexes was explored, the scope of the reaction examined and mechanistic investigations undertaken. Ultimately the reaction allowed for the development of a novel one-pot three-component coupling reaction synthesising tri-substituted alkenes with a benzyl substituent. The reaction involved the insertion of alkenyl carbenoids into benzylzirconocene followed by transmetallation to zinc for addition of an aldehyde or for coupling with an aryl halide.

Contents

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List of Abbreviations

Techniques

APPI	Atmospheric Pressure Photoionisation
CI	Chemical Ionisation
^{13}C-NMR	Carbon-13 Nuclear Magnetic Resonance
COSY	^{1}H-^{1}H Correlated Spectroscopy
DEPT	Distortionless Enhancement by Polarisation Transfer
EI	Electron Ionisation
ESI^{+}	Electrospray Ionisation (Positive)
FID	Flame Ionisation Detector
GC	Gas Chromatography
GCMS	Gas Chromatography Mass Spectrometry
^{1}H-NMR	Proton Nuclear Magnetic Resonance
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
HSQC	Heteronuclear Single Quantum Coherence Spectroscopy
IR	Infra-Red Spectroscopy
LRMS	Low Resolution Mass Spectrometry
NMR	Nuclear Magnetic Resonance
TLC	Thin Layer Chromatography

Reagents

Bibn	Bibenzyl
BnCl	Benzyl chloride
n-BuLi	*n*-Butyllithium
DCM	Dichloromethane
DMEDA	1,2-Dimethylethylenediamine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
Dppf	1,1'-Bis(diphenylphosphino)ferrocene
HMPA	Hexamethylphosphoroamide
IPA	Isopropyl alcohol
LDA	Lithium diisopropylamide
LiTMP	Lithium 2,2,6,6-tetramethylpiperidide
MsCl	Methanesulfonyl chloride
MTBE	Methyl *tert*-butyl ether
TBAF	Tetrabutylammonium fluoride
TEBA	Benzyltriethylammonium
THF	Tetrahydrofuran
TMEDA	*N*,*N*,*N*,*N*-Tetramethylethylenediamine
TBDMS	*tert*-Butyldimethylsilyl chloride
TBDPS	*tert*-Butyldiphenylsilyl chloride
TIPSCl	Triisopropylsilyl chloride
TIPSF	Triisopropylsilyl fluoride
TMP	2,2,6,6-Tetramethylpiperidine
TMSCl	Trimethylsilyl chloride
TMSOTf	Trimethylsilyl triflate
TsCl	Toluene-*p*-sulfonyl chloride

Chemical Groups

Ar	Aryl
Bn	Benzyl
Bz	Benzoyl
Cp	Cyclopentadienyl
MOM	Methoxymethyl
Ms	Methanesulfonyl
OTf	Trifluoromethanesulfonate
Py	Pyridine
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
Ts	Toluenesulfonyl

Biological

AF	Activation Function domain
Arg	Arginine
CYP	Cytochrome P450
Cys	Cysteine
DBD	DNA-Binding Domain
DLPC	Phospholipid Dilauroylphosphatidylcholine
DUPC	Diundecanoylphosphatidylcholine
EC_{50}	Half Maximal Effective Concentration
FRET	Fluorescence Resonance Energy Transfer
FXR	Farnesoid X Receptor
Gln	Glutamine
HepG2	Hepatoma G2
His	Histamine
HNF	Hepatocyte Nuclear Factor-4
HRE	Hormone Response Elements
HTS	High-Throughput-Screen
Huh-7	Human Liver-7
IC_{50}	Half Maximal Inhibitory Concentration
LBD	Ligand-Binding Domain
LRH-1	Liver Receptor Homolog-1
NR	Nuclear Receptor
ONR	Orphan Nuclear Receptor
PIP_3	Phosphatidyl (3,4,5) Inositol Triphosphate
SAR	Structure-Activity Relationship
SF-1	Steroidogenic Factor-1
Thr	Threonine
Val	Valine

Others

AD-H	Amylose tris(3,5-dimethylphenylcarbamate)
aq.	Aqueous
°C	Degrees celcius
Cat.	Catalytic
Conc.	Concentrated
d.r.	Diastereoisomeric ratio
eq	Equivalents(s)
h	Hour(s)
M	Moles per dm^3
mg	Milligram(s)
mL	Millilitre (s)
mins	Minutes
mmol	Millimole(s)
m.p.	Melting point
m/z	Mass charge tatio
OD-H	Cellulose tris(3,5-dimethylphenylcarbamate)
ppm	Parts per million
Rt	Retention time
RT	Room temperature

Chapter 1 – Introduction

1.1– Overview

The results discussed in this thesis are divided into three chapters. Chapter two looks at the synthesis of compounds with a *cis*-bicyclo[3.3.0]oct-2-ene backbone, prepared *via* a zirconium tandem cyclisation reaction, which were designed to target certain orphan nuclear receptors. Chapter three looks at the insertion of benzyl carbenoids into unsaturated zirconacycles, to increase the scope of benzyl carbenoids previously inserted by S. Fillery[1] and L. Norman[2] and to investigate the use of zirconocene traps in the reaction. The work described in chapter four investigates the unprecedented reactivity of benzyl chlorides with zirconocene, first observed when conducting the work of chapter three. Correspondingly the first half of the introduction provides a brief description of the biological background for the bicyclic compounds, whilst the second half describes organozirconium reactions which are of relevance to the work in this thesis.

1.2 – Agonists for Orphan Nuclear Receptors LRH-1 and SF-1

1.2.1 – Nuclear Receptors

Nuclear receptors (NRs) are a class of protein receptors which belong to a large superfamily of mammalian transcription factors composed of 48 members in the human genome, subdivided into seven families (NR0-NR6).[3, 4] NR signalling can either be ligand-dependent or ligand-independent, genomic or non-genomic and can result in gene repression and gene activation.[5] In contrast to many other receptors, NRs are able to directly bind to specific DNA sequences known as hormone response elements (HREs) and thereby regulate transcriptional events.[6] The two modes of action for NRs are dependent on their intracellular localisation. NRs confined to the cytoplasm are found within a multi-protein complex which, as a consequence of ligand binding, enter the nucleus *via* active transport and bind to HREs. NRs located in the nucleus are often complexed with corepressor proteins whilst bound to HREs, ligand binding results in the dissociation of the corepressor complex and recruitment of a coactivator complex.[6, 7] Both modes result in activation of gene transcription. NRs associated to corepressors mediate the active repression of NRs, thus NRs can either inhibit or facilitate the initiation of transcription.[8, 9]

NRs with no known natural ligands are termed 'orphan nuclear receptors' (ONRs), these may be capable of regulating transcription independent of ligands.[6, 10] However, when endogenous ligands are later identified for NRs originally classified as orphans, these become termed 'adopted' nuclear receptors. Examples of these are; hepatocyte nuclear factor-4 (HNFα/NR2A1) which has been found to bind to linoleic acid[11] and farnesoid X receptor (FXR/ NR1H4) which has been found to bind to bile acids such as chenodeoxycholic acid.[12] Certain ONRs lack a binding cavity and so function ligand independent however, there are ONRs that possess ligand-binding cavities and therefore have potential as pharmaceutical targets.[6] Due to the influence of NRs on mammalian development, metabolism, physiology and human disease (including cell proliferation, differentiation, cellular homeostasis and cancer), they are of great therapeutic interest as their activity could be modulated by the binding of natural or synthetic molecules.[6, 9]

1.2.2 – Structural Features of Nuclear Receptors

NRs have conserved modular structures consisting of four domains.[8] The structural and functional domains that define the NR superfamily are; an activation function domain (AF-1), a DNA-binding domain (DBD), a hinge region, a ligand-binding domain (LBD) and a second activation function domain (AF-2) (Figure 1).[9, 13-15] The LBD is composed of 12 α-helices with a short β-turn which creates a hydrophobic pocket for the binding of a hydrophobic ligand.[13, 14, 16] The LBD mediates nuclear localisation and contains sites for coactivator and corepressor interactions.[9] DBD, in contrast, binds to specific DNA sequences and so is composed of two cysteine-rich zinc finger binding motifs which are required for DNA binding.[13-15] Both the LBD and the DBD are highly conserved across NRs.[9, 14-17] AF-1 is located in the amino terminal, this domain facilitates transcriptional activation of NRs independently of ligand binding[17]; conversely, AF-2 mediates ligand-dependent transactivation by NRs.[9] NRs have a flexible and large hinge domain which allows for targeting by post-translational modifications.[14, 17] Structural studies have suggested that ligand-mediated activation is not required for all NRs due to the structure of the LBD regions.[17]

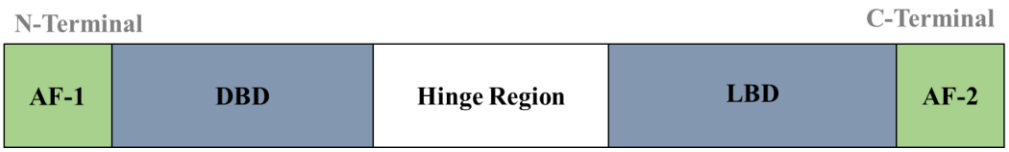


Figure 1 - Illustration of nuclear receptor structure.

1.2.3 – Biological Function of Orphan Nuclear Receptors LRH-1 and SF-1 (NR5)

Liver receptor homolog-1 (LRH-1, NR5A2) is known as an ONR that is mainly expressed in tissues of endodermal origin, such as the intestine, exocrine pancreas, liver and the ovary.[8, 18] The receptor plays vital roles in cell differentiation during embryonic development.[19] LRH-1 is critical in regulating factors required to maintain pluripotency[10, 19] and has been shown to regulate multiple stages of liver and pancreas development.[20] In adulthood it modulates cholesterol transport,[21, 22] bile acid biosynthesis,[23, 24] lipogenesis,[25] steroidogenesis[14] and is involved in the resolution of hepatic endoplasmic reticulum stress.[26] Furthermore, increasing evidence is prevailing of LRH-1 involvement in cancer[8], particularly cell proliferation and tumour pathogenesis of pancreatic,[27] breast,[28-31] gastric[32-34] and colon cancers.[35, 36] However, further studies are required in order to determine LRH-1 functional relationship to cancer as well as its modulation of pathological and physiological activities.[17] There are a variety of benefits for targeting LRH-1, activation can be beneficial for metabolic diseases such as diabetes however, suppression of LRH-1 activity in tumour cells has the potential to result in an anti-proliferative effect.[10]

Steroidogenic factor-1 (SF-1, NR5A1) is a key regulator of endocrine function and an essential factor in sex determination; particularly for the function and development of the gonad and adrenal glands.[4, 37, 38] Maintenance of SF-1 levels is essential, mutations resulting in underexpression can lead to congenital adrenal and gonadal defects, while overexpression is suggested to lead to hyperplasia and adrenal tumours.[39] Mutations are also associated with disorders of sexual development.[39] Targeting of this receptor would allow for further elucidation of its function in mammalian physiology. [40, 41]

1.2.4 – Natural LRH-1 and SF-1 Ligands

LRH-1 and SF-1 were classified as ONRs due to their constitutive activity and lack of known endogenous ligands. However, crystal structure analysis along with mass spectrometry studies revealed large and hydrophobic pockets in the LBD of both SF-1 and LRH-1. The LBD of human LRH-1 and for both mouse and human SF-1 was occupied by different bacterial phospholipids, such as phosphatidylglycerol **01** and phosphatidylethanolamine **02** (Figure 2).[42-45] A variety of phospholipids were found in in the LBD of purified proteins, showing the receptor pocket is able to accommodate phospholipids with different head groups and acyl chains.[42] Phospholipid binding is not constitutive as bacterial phospholipids have been shown to exchange for exogenously added phosphatidylcholine.[46] The polar headgroup of bound phospholipids is positioned outside of the receptor pocket with the

hydrophobic tails inside the pocket, leading to both polar and hydrophobic interactions with the receptor.[43] This high affinity binding is demonstrated by the retention of the bound phospholipid after protein purification.

The transcriptional activity of these receptors has been shown to be modulated by phospholipids with maximal activity achieved with ligand binding.[42-44] Furthermore, mutations in the binding pocket to reduce phospholipid binding affected the recruitment of coactivators causing inhibition of transcriptional activity of LRH-1 and SF-1.[10, 43, 44] Conversely, crystal structures of mouse LRH-1 showed the binding pocket to be in an active conformation but in the absence of phospholipids. Furthermore, mutations to mouse LRH-1 residues within the pocket did not affect the transcriptional activity, rendering ligands dispensable for activity of mouse LRH-1.[47] More recently, the binding of PIP_3 **03** (Figure 2) in both SF-1 and LRH-1 has shown stabilisation of the LBD, the binding also identified an interaction site on the receptor surface that facilitates recruitment of coregulatory factors for SF-1.[48, 49]

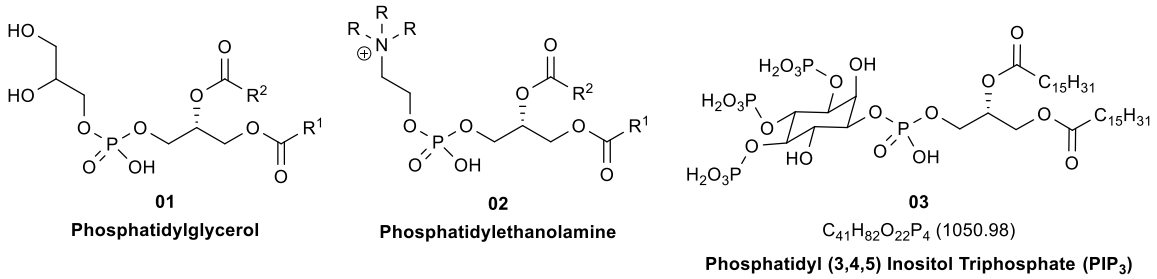


Figure 2 – Structures of phospholipids.

Correspondingly, sphingosine-1-phosphate **04** has been shown to regulate the transcription of Cytochrome P450 17 (CYP17) on binding to SF-1 (Figure 3).[50] Furthermore, phosphatidycholines dilauroyl phosphatidylcholine (DLPC **05**) and diundecanoyl phosphatidylcholine (DUPC **06**) have been proposed as LRH-1 agonists as both have shown equivalent dose dependent responses on human and mouse LRH-1 (Figure 3).[25, 51] Treatment with DLPC **05** induced bile production in mouse liver, lowered hepatic triglycerides and serum glucose and improved insulin sensitivity as well as glucose homeostasis. Interestingly, the mode of binding of DLPC **05** leaves the hydrophobic pocket deep inside the receptor unoccupied. The binding of phospholipid ligands increases the pocket volume and width by displacing one of the helices (helix 6) which in turn modulates the activity of the receptor by promoting allosteric signalling of the LBD.[52] However, high concentrations of DLPC are required for LRH-1 activation ($EC_{50} > 100$ μM).[25]

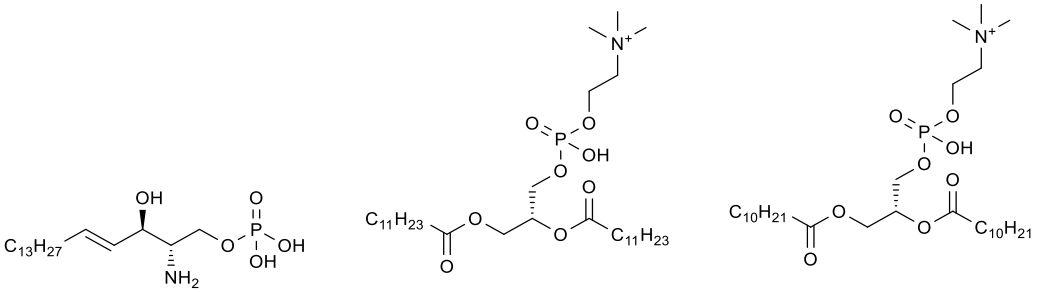


Figure 3 - Structure of sphingosine-1-phosphate **04**, DLPC (phospholipid dilauroylphosphatidylcholine **05**) and DUPC (diundecanoyl phosphatidylcholine **06**).

1.2.5 – Synthetic LRH-1 and SF-1 Ligands

The first successful small molecule agonist targeting orphan nuclear receptors LRH-1 and SF-1 reported was GSK8470 **08** (EC_{50} 0.43 µM for LRH-1 and EC_{50} 0.05 µM for SF-1). GSK8470 was identified as a potential ligand for both receptors by a high-throughput-screen (HTS) using a fluorescence resonance energy transfer (FRET) biochemical assay (Figure 4).[40, 53] The compound was prepared within the group using a zirconocene cyclisation of a 1,6-enyne. From a structure-activity relationship (SAR) study of generation of compounds **07**, compound **09** was identified as a more active analogue for both receptors (EC_{50} 0.03 µM for LRH-1 and EC_{50} 0.04 µM for SF-1) but a less efficacious one for LRH-1.[53] GSK8470 was found to increase the expression of LRH-1 in liver cells.[40]

The development of a second generation of compounds (**10**) within the group found RJW100 **12-*exo*** (Figure 4) as an alternative to GSK8470 with similar activity (EC_{50} 1.1 µM for LRH-1) but with much improved acid stability.[41, 53] RJW100 was designed according to the crystal structure of GSK8470 bound inside the LRH-1 receptor (Figure 5). Crystal structure analysis identified the aniline made no polar interactions with the protein residues but the phenyl group of the aniline made a hydrophobic interaction (π-π stacking) with residue His-390.[41] Furthermore, RJW100 was also designed to introduce a polar functional group (OH) to carbon 4 of the bicyclic ring as the crystal structure also showed residues with polar functional groups (Arg-393, His-390 and Gln-432) to be within close proximity to carbon 4 of GSK8470 (Figure 5). An interaction between a hydroxyl on C4 and these polar residues could potentially further increase the activity. The theory was supported by RJW100 analogue compound **13** (without the hydroxyl group) having a reduced efficacy compared to RJW100 (Figure 4). Another compound of importance from the SAR work carried out on

the second generation of compounds was RJW101 **11** which was the only compound found to be LRH-1 selective (Figure 4).

Due to the hydroxyl functionality at carbon 4 of RJW100, two racemic diastereoisomers (**12-*exo*** and **12-*endo***) are formed from the zirconocene cyclisation reaction for the synthesis of RJW100 (reaction described in Section 1.2.6). Both diastereomers were found to have similar binding (EC_{50}) but the *exo* diastereomer (RJW100) had a higher relative efficacy, most likely due to better interaction with polar residues as a result of the conformation. Both enantiomers of RJW100 showed similar binding (EC_{50} values) but with different efficacies.

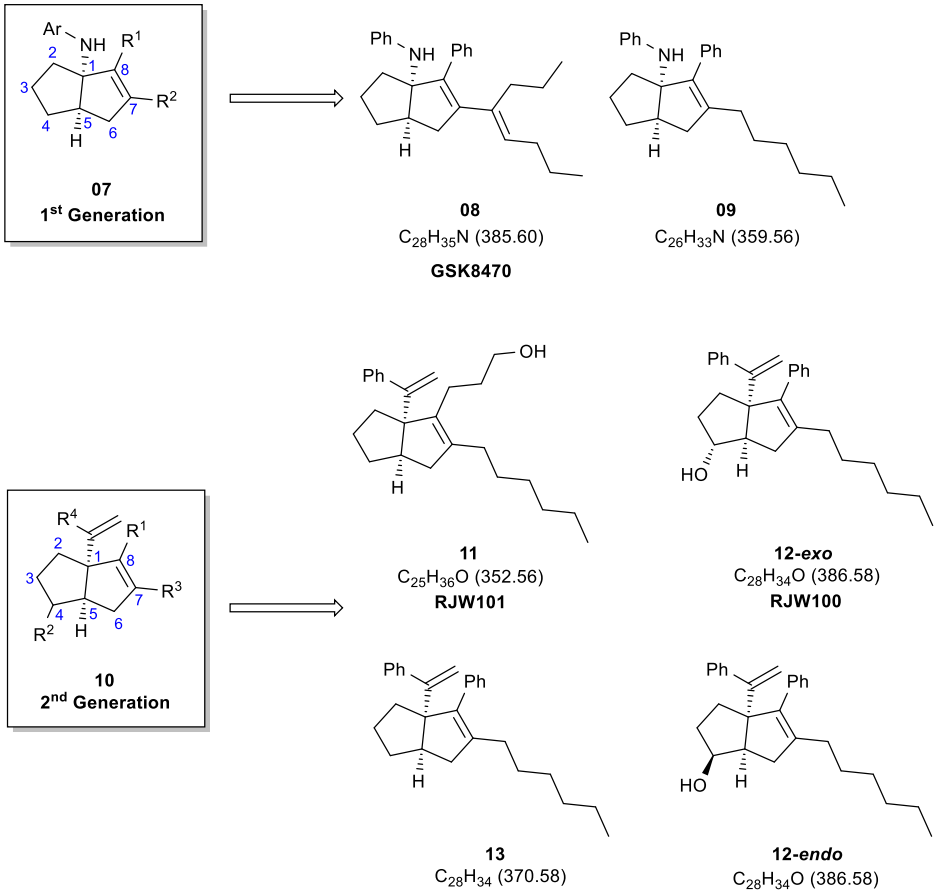


Figure 4 – Structure of synthetic LRH-1 and SF-1 ligands with a *cis*-bicyclo[3.3.0]-oct-2-ene backbone.

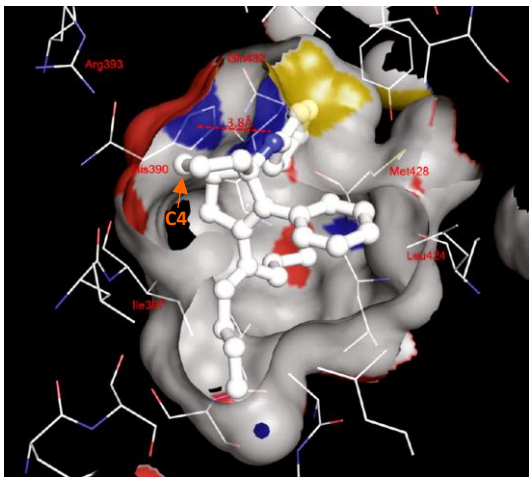


Figure 5 – GSK8470 **08** bound inside LRH-1 receptor.[41]

Crystal structure analysis of RJW100 and GSK8470 bound inside LRH-1 showed how both synthetic agonists had different binding modes.[52] Compared to GSK8470, RJW100 was rotated 180 ° and thus the bicyclic rings were in a perpendicular position with the alkyl chain pointing in the opposite direction (Figure 6). As a result, the hydroxyl group of RJW100 was not interacting in the predicted manner with the residues forming a polar pocket near helix 5 (Arg-393, His-390, Gln-432).[52] Despite the different conformations, both compounds share similar hydrophobic interactions, particularly the π-π-stacking with His-390 residue. However, two key differences were the aryl group involved in the interaction and the mode of interaction with His-390; GSK8470 was a face-to-face interaction using the aniline phenyl attached to the bridgehead of bicyclic backbone (C1) whereas RJW100 used the phenyl ring coming from the alkene of the bicyclic backbone (C8).[52] The positioning of RJW100 appeared to be driven by an indirect hydrogen-bonding interaction of the hydroxyl group with Thr-352 on helix 3, *via* a bridging water molecule. Interestingly, GSK8470 and RJW100 bound deep inside the receptor and neither interacted with helix 6 in a similar manner to the phospholipid ligands suggesting the synthetic ligands activate the receptor *via* a different mode.[52]

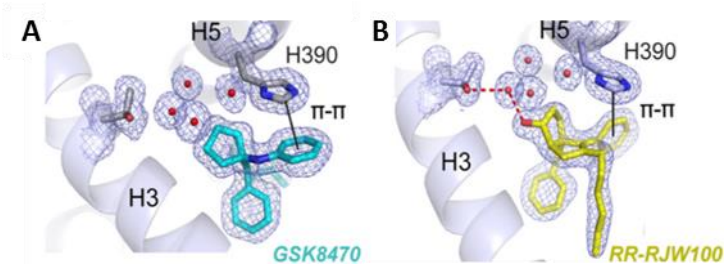


Figure 6 – Crystal structures of GSK8470 **08** (A) and RJW100 **12** (*R*,*R*-enantiomer) (B) bound inside LRH-1.[52]

Diastereomers **12-*endo*** and **12-*exo*** (RJW100) both interacted with Thr-352 through the same water molecule despite the hydroxyl group pointing in a different direction. However,

the positioning of the **12-*endo*** also permitted a second water-mediated hydrogen-bonding interaction with Val-406 residue.[52] Molecular simulations of this hydrogen bonding showed these water molecules near the ligand binding site were important for activation of the receptor for both diastereoisomers (**12-*endo*** and **12-*exo***).[52] Furthermore, simulations in which His-390 was mutated showed the activity of RJW100 to be unaffected but made GSK8470 inactive. Mutating Thr352 reduced activity of both GSK8470 and RJW100 despite the former not interacting with this residue however, it appeared the mutation affected GSK8470's activity-dependent binding to His-390.[52]

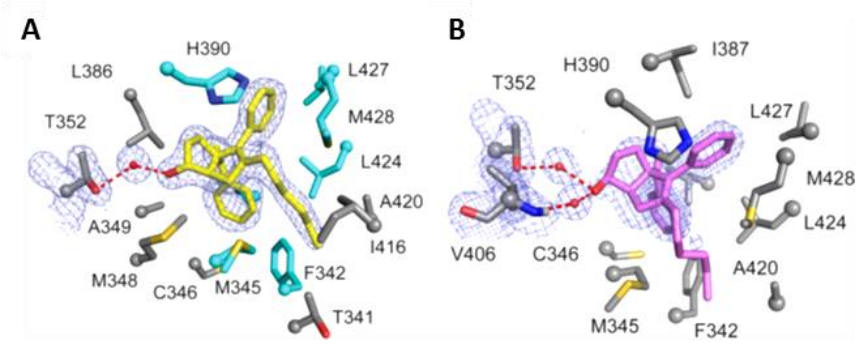
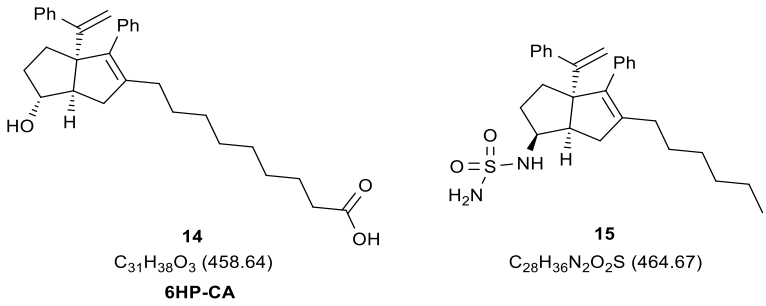


Figure 7 - Crystal structures of **12-*exo*** (RJW100, *R*,*R*-enantiomer) (A) and **12-*endo*** (*R*,*S*-enantiomer) (B) bound inside LRH-1.[52]

Recent publications have shown modifications to RJW100 in which the R^3 group was modified to a carboxylic acid with a long alkyl chain to mimic a phospholipid (compound **14**, Figure 8).[54] The compound was aimed at combining the binding features of the *cis*-bicyclo[3.3.0]oct-2-ene backbone deep inside the receptor and the phospholipid interaction with the surface residues in order to achieve greater binding. The compound displayed greater activation and efficacy for LRH-1 than RJW100 (EC_{50} 0.4 μM).[54] As the crystal structure of RJW100 showed the indirect interaction of the hydroxyl group with Thr-352, the introduction of larger polar functional groups at carbon 4, such as a sulfonamide as shown by compound **15** (Figure 8), has also been reported which has been quoted as the most active agonist with nanomolar potency (EC_{50} 0.02 μM). For this compound, the *endo* diastereomer was found to be more active and efficacious than its equivalent *exo* diastereomer.[55] This new agonist has been shown to increase expression of LRH-1 and promote anti-inflammatory gene expression changes.[55]

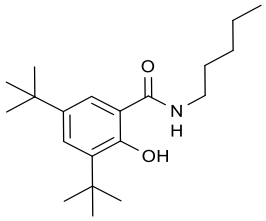


14
$C_{31}H_{38}O_3$ (458.64)
6HP-CA

15
$C_{28}H_{36}N_2O_2S$ (464.67)

Figure 8 – Structure of recently published LRH-1 agonists.

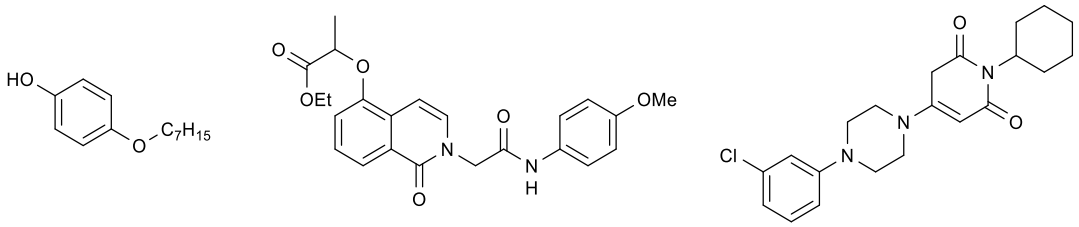
Activation of LRH-1 has also been reported by a synthetic ligand which did not have the *cis*-bicyclo[3.3.0]oct-2-ene backbone, named PME9 **16** (Figure 9).[56] This substituted aryl amide has been shown to reversibly bind with high efficiency to a cysteine residue lining the hydrophobic cavity of LRH-1 LBD (Cys-346) resulting in an increase of LRH-1 activity in cells, demonstrated by the increased expression of CYP24A1 transcripts in HepG2 cells. PME9 showed greater relative activity than RJW100 in HepG2 cells. SAR work on this series of compounds showed that larger and bulkier alkyl substituents increased the activity of the compounds.[56]



16
$C_{20}H_{33}NO_2$ (319.49)
PME9

Figure 9 – Structure of PME9 **16** agonist.

Inverse agonists have also been reported for SF-1[57-59] and more recently for LRH-1 (Figure 10).[60] Phenol **17** (named AC-45594) was identified by a HTS as an SF-1 inverse agonist and has been shown to inhibit SF-1 in cell based assays with an IC_{50} of 7.2 µM.[57] In addition to this, an isoquinoline series has also been identified as potent SF-1 inverse agonists with compound **18** having an IC_{50} of 0.2 µM.[58, 59] Compound **19** (named SR1848) has been identified as an LRH-1 repressor with IC_{50} 2.8 µM in Huh-7 cells in which it showed inhibition of cell proliferation through the repression of cyclin-D1 and cyclin-E1 expression, without inducing cell death.[60]



17
$C_{13}H_{20}O_2$ (208.30)
AC-45594

18
$C_{23}H_{24}N_2O_6$ (424.45)

19
$C_{21}H_{26}ClN_3O_2$ (387.91)
SR1848

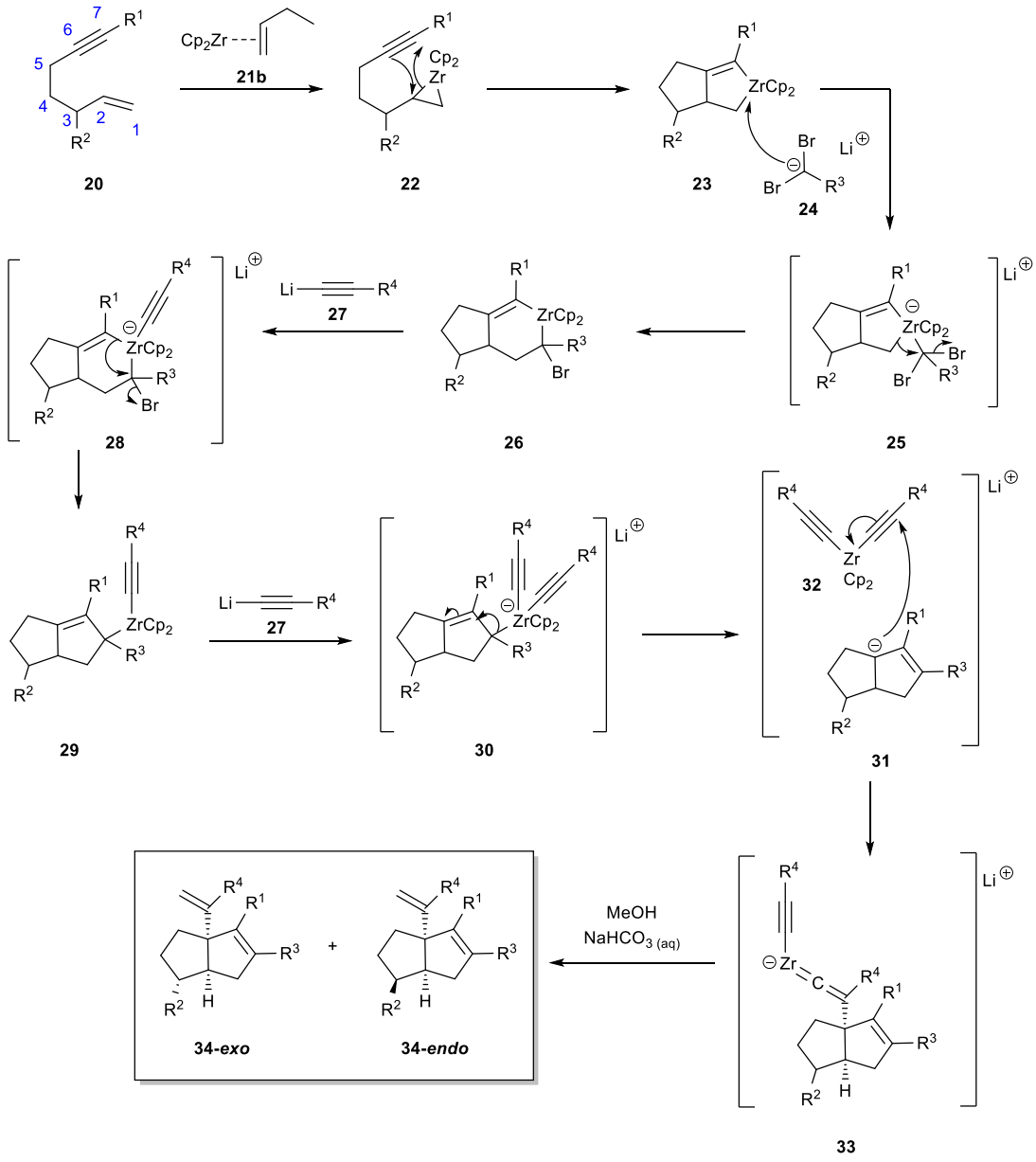
Figure 10 – Structure of SF-1 and LRH-1 inverse agonists.

1.2.6 – Preparation of *Cis*-Bicyclo[3.3.0]oct-2-ene Backbone of Synthetic Ligands

Synthetic agonists for LRH-1 and SF-1 receptors (discussed in Section 1.2.5) are prepared from a three-component one-pot zirconocene tandem cyclisation reaction developed within the group, as shown in Scheme 1 (detailed introduction to organozirconium chemistry in Section 1.3).[61, 62] Firstly zirconacycle **23** is formed from the cyclisation of an enyne **20** using zirconocene(1-butene), prepared *in situ* from zirconocene dichloride and two equivalents of *n*-BuLi to form dibutylzirconocene which then undergoes cyclometallation when warmed to room temperature to form the reactive zirconocene species (**21b**). Subsequently, 1,1-dibromo-1-lithium species **24**, a carbenoid prepared *in situ* from the deprotonation of a 1,1-dibromo compound using LDA or LiTMP, inserts into the empty orbital of the zirconocene from zirconacycle **23** forming the 'zirconate' 18-electron species **25**.[61, 62] Ring expansion, as a result of a 1,2-metallate rearrangement, affords zirconacycle **26** in which the zirconocene centre returns to its preferred 16- electron configuration. With the addition of lithium acetylide **27**, zirconate species **28** is formed which undergoes a ring closure by a 1,2-bond migration to give the neutral 16-electron zirconocene intermediate **29**.[61, 62] Insertion of the second lithium acetylide results in fragmentation of the species into allyl anion **31** and bis(alkynyl)zirconium **32**. Re-addition of **31** to the β-carbon atom of the bis(alkynyl)zirconocene **32** affords intermediate **33** which, on protic quench, cleaves the C-Zr bond to furnish the desired racemic diastereomers **34-*endo*** and **34-*exo***.[61, 62]

Derivatisation of R^1 and R^2 is achieved from the synthesis of a different enyne for the reaction whereas alterations to R^3 and R^4 is achieved within the reaction by introducing different alkynes or 1,1-dihalo compounds. The two diastereomers, **34-*exo*** and **34-*endo***, are formed when R^2 does not correspond to hydrogen. This is the case for previously mentioned RJW100 as R^2 was a hydroxyl group, once it was deprotected after the zirconium cyclisation reaction. For RJW100, a 1:1.6 ratio between *endo* and *exo* was reported when the alcohol was protected with a TBDMS group.[41] However, it has been recently reported that with the

use of a MOM protecting group, a 7.2:1 diastereomeric ratio favouring the *exo* isomer is achieved.[54]



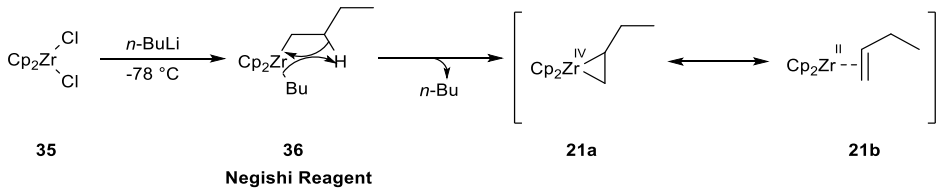
Scheme 1 – Zirconocene tandem cyclisation to construct compounds with a *cis*-bicyclo[3.3.0]oct-2-ene backbone.

1.3 – Organozirconium Chemistry

1.3.1 – Formation of Carbon-Zirconium Bonds

Zirconium is one of the least expensive transition metals and it is not associated with acute or severe toxicity.[63] Zirconocene dichloride (Cp_2ZrCl_2) was first prepared by Wilkinson and Birmingham in 1954.[64] Subsequently, Wailes and Weigold reported both the synthesis of zirconocene hydrochloride ($Cp_2Zr(H)Cl$) and its application in the reduction of alkenes and alkynes in the 1970s.[65, 66] However, it was Schwartz who further developed and investigated the reaction demonstrating its synthetic utility and terming it hydrozirconation (Section 1.3.1.1), thus the reagent was named after him.[67-70] Zirconocene complexes are most commonly in the +4 oxidation state and, unlike other transition metal complexes, prefer a 16-electron configuration over 18-electrons. Consequently, zirconocene has a vacant low energy orbital which can accept electrons giving zirconocene its unique reactivity.

Reacting zirconocene dichloride **35** with two equivalents of *n*-BuLi at -78 °C gives dibutylzirconocene, also known as the Negishi reagent **36** (Scheme 2).[71] Upon warming the Negishi reagent to room temperature, C-H activation occurs resulting in the loss of butane to form zirconocene(1-butene) **21b** which is used for the reductive coupling of alkenes and alkynes (Section 1.2.3). It was work from Buchwald[72] that indicated the reactive species must be zirconocene(1-butene) **21b** rather than dibutylzirconocene **36**, which was later confirmed by Negishi.[73] Zirconocene(1-butene) **21b** can either be considered as $Cp_2Zr(II)$ **21b** or $Cp_2Zr(IV)$ **21a**, '$ZrCp_2$' is believed to be too unstable to be the true intermediate. The butene ligand is weakly bound and, therefore, is readily displaced in the presence of alkene and alkyne substrates resulting in the reductive coupling of unsaturated compounds. The use of *n*-BuLi for preparing the "$ZrCp_2(II)$" species *in situ* replaced treating Cp_2ZrCl_2 with Mg (10 equivalents) and $HgCl_2$ (1 equivalent).[74, 75]

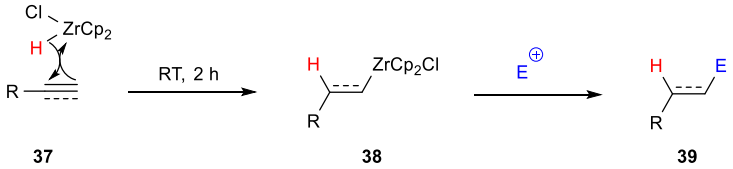


Scheme 2 – Formation of zirconocene(1-butene) from zirconocene dichloride.

The reactions herein will discuss organozirconocene chemistry with the use of zirconocene dichloride, Schwartz reagent and zirconocene(1-butene).

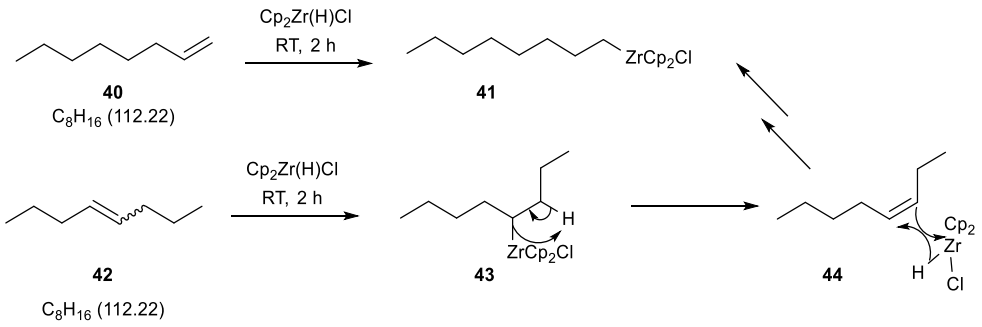
1.3.1.1 – Hydrozirconation

The Schwartz reagent is prepared by reacting Cp_2ZrCl_2 with aluminium hydrides (such as $LiAlH_4$).[65] The Schwartz reagent adds across alkene and alkyne π-bonds to afford alkyl- and alkenylzirconocene chlorides respectively.[67-70] The addition occurs in a *syn*-manner presumably *via* a concerted 4-centered process in which zirconocene is placed at the least substituted carbon atom resulting in *E*-configuration only of the alkenylzirconocene **38** when alkynes are the starting material. The reaction is analogous to hydroboration.[76] Organozirconocenes can be converted to organic compounds by addition of electrophiles, such as HCl $_{(aq)}$ (discussed in detail in Section 1.3.3.1).



Scheme 3 – Hydrozirconation of alkenes/alkynes using the Schwartz reagent.

Hydrozirconation of internal alkenes, such as **42**, results in the migration of the zirconocene along the hydrocarbon chain to yield a terminal organozirconocene **41** (Scheme 4). The isomerisation involves reversible hydrozirconation and β-hydrogen elimination. Thus, alkenes **40** and **42** yield the same organozirconocene intermediate **41** after hydrozirconation.[67]

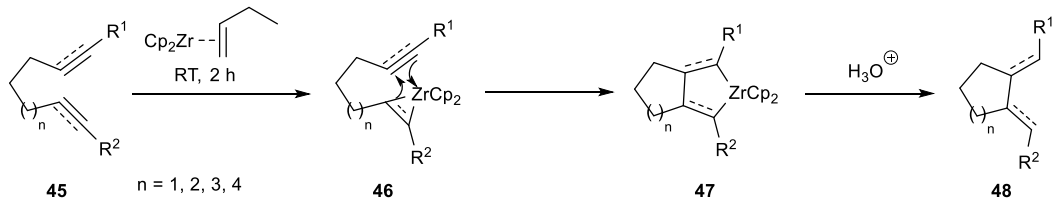


Scheme 4 – Hydrozirconation of alkene regioisomers.

1.3.1.2 – Zirconocene Mediated Cyclisation

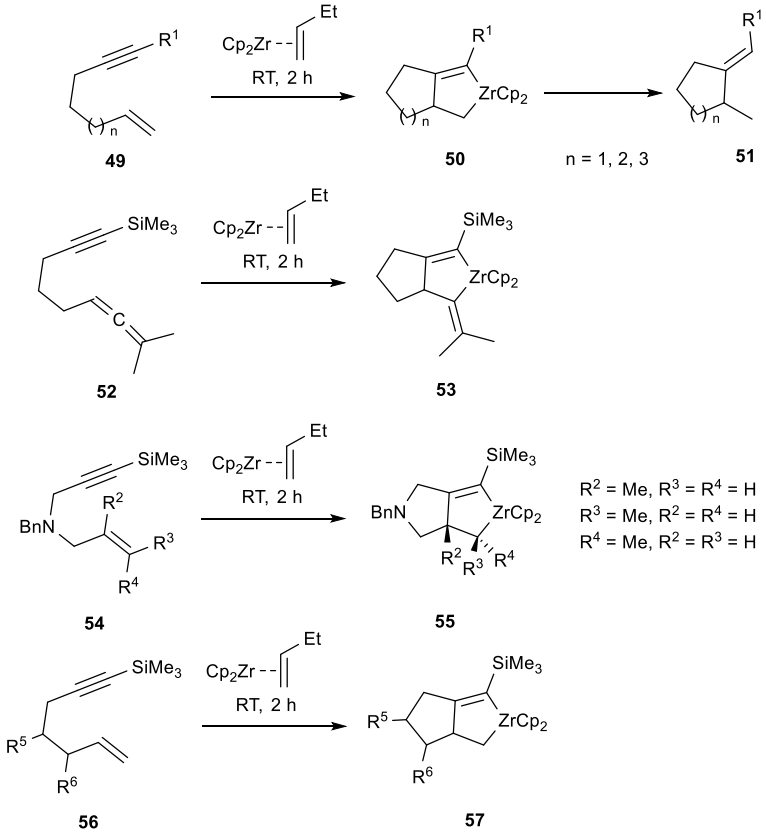
The Negishi reagent is most often used in organic synthesis for intramolecular cyclisation of dienes[77], enynes[71, 75] or diynes[71, 73], resulting in the reductive coupling of the unsaturated molecule to form a zirconacycle intermediate **47** (Scheme 5).[63] The weakly bound butene ligand is readily exchanged for one of the π-bonds of the unsaturated molecule **45** forming organozirconocene **46**, which then adds across the second π-bond to form zirconacycle **47**.

The co-cyclisation is generally not compatible with terminal alkynes due to the acidity of the sp-bound hydrogen. Aryl, SiR_3 and alkyl chains are examples of R^1/R^2 for alkynes.[73]



Scheme 5 - Cyclisation of dienes/enynes/diynes with zirconocene(1-butene).

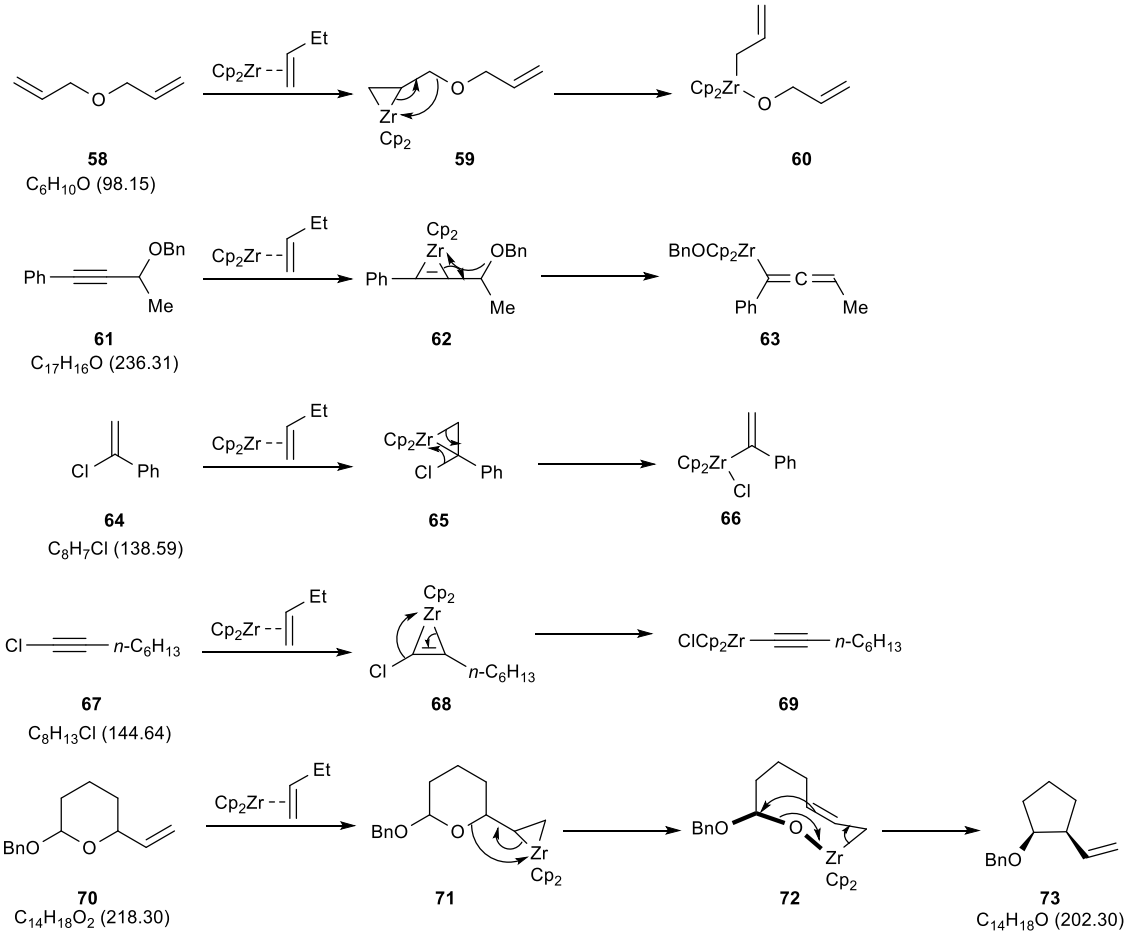
Focusing on enynes (**49**), both 1,6- and 1,7-enynes are efficiently cyclised to bicyclic zirconacyclopentadienes, the formation of the zirconacycle configures the alkene configuration as shown (structures **50** and **51**, Scheme 6).[78] Generally enyne cyclisation is conducted on unsubstituted alkenes however, the cyclisation of nitrogen-containing enynes with methyl substituted alkenes has been reported (**54**).[73] Furthermore, the cyclisation has also been conducted between an alkyne and an allene, such as with compound **52**.[73, 79] There are several successful examples of the cyclisation with substitution on the ring fused by zirconocene at R^5 or R^6, such as alkyl[73], protected alcohol[78, 80], amines[80] and amides[80] (**57**). Cyclisation of enynes with substituents on the α-position (R^6) to the alkene show diastereoselectivity.[80]



Scheme 6 – Examples zirconocene co-cyclisation of enynes.

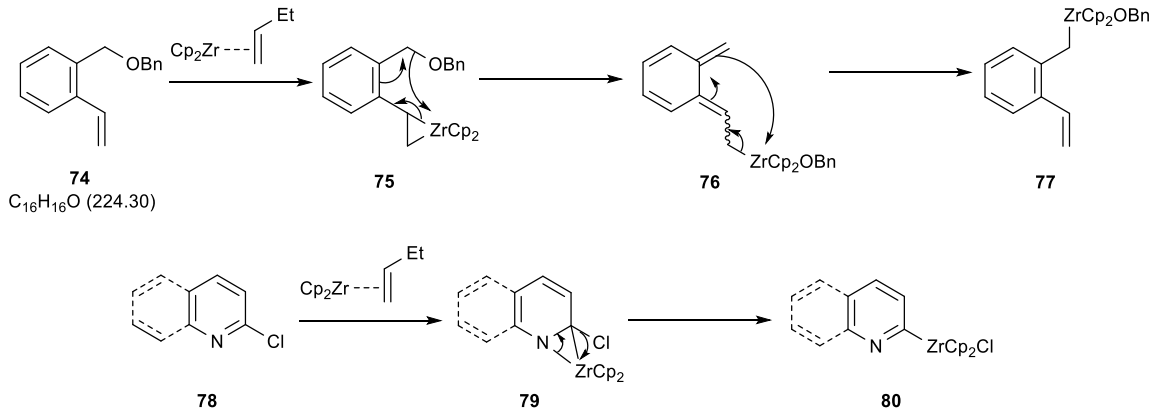
1.3.1.3 – Oxidative Addition

Oxidative addition of allyl ethers was first unexpectedly observed when attempting to cyclise diallyl ether **58**, which resulted in the formation of allyl(allyloxy)zirconocene **60** (Scheme 7).[77] The reaction proceeds first by ligand exchange of zirconocene(1-butene) with the allyl ether **58**, followed by a β-elimination of the alkoxy group to ultimately yield the allylzirconocene **60**, thus exploiting the oxophilicity of zirconium.[81-84] Oxidative addition has been further developed for preparation of allenyl **63**[82], alkenyl **66**[85] and alkynyl **69**[86] zirconocene derivatives. Furthermore, the reaction has been applied in the ring contraction of 2-vinylheterocycles (such as **70**).[87] Oxidative addition has also been used for the synthesis of natural products.[88, 89]



Scheme 7 – First example of oxidative addition of an allyl ether **58** into zirconocene(1-butene), examples of oxidative addition preparing allenyl **63**, alkenyl **66** and alkynyl **69** zirconocenes, and for use in ring contraction of 2-vinylheterocycles **70**.

The reaction was later extended to *ortho*-vinyl- and alkynylbenzyl ethers (such as **74**) by Taguchi (Scheme 8) and has been applied in the synthesis of steroid derivatives.[90-96] More recently, oxidative addition of zirconocene(1-butene) into heteroaromatic halides **78** has been reported in Et_2O-THF solvent but the reaction does not proceed with phenyl halides (Scheme 8).[97]

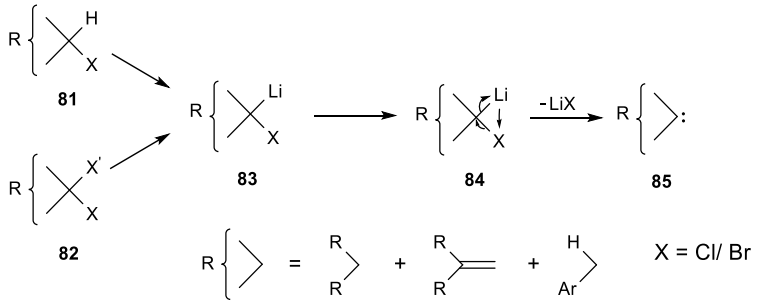


Scheme 8 – Oxidative addition of *ortho*-vinylbenzyl ethersand *ortho*-heteroaromatic halides with zirconocene(1-butene).

1.3.2 – Carbenoids

A carbenoid is a species which has a bond to a metal atom (such as lithium) and a leaving group (such as a halide) on the same carbon atom and thus has electron-donating and electron-accepting properties similar to carbenes.[98, 99]

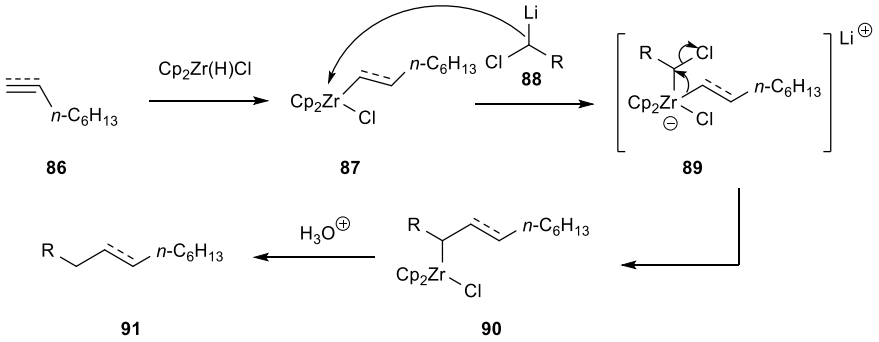
Lithium halocarbenoids **83** are prepared either by deprotonation of a halogenated hydrocarbon **81** with a lithium base or by halogen-lithium exchange of a *gem*-dihalide **82** with an alkyl lithium at temperatures between -120 °C and -70 °C (Scheme 9).[100-102] These carbenoids are thermally unstable and undergo decomposition at temperatures higher than -70 °C. Decomposition most commonly occurs by α-elimination which yields the highly reactive carbene **85** and an LiX salt.[100] Therefore, the reaction is limited by the rate of formation and the rate of decomposition.[98] Carbenoids show amphiphilic reactivity as they react as both nucleophiles (in alkylation, acylation and halogenations) and electrophiles (with alkyl metals). The combined properties allow carbenoids to insert into single and double bonds.[98, 100-103]



Scheme 9 – Formation and decomposition of lithium carbenoids.

1.3.2.1 – Carbenoid Insertion into Acyclic Organozirconocenes

Negishi was the first to demonstrate the insertion of α-haloorganolithium carbenoids **88** into an acyclic zirconocene intermediate **87** from hydrozirconation (Scheme 10).[104] The carbenoid **88** inserts into the empty orbital of the zirconocene intermediate generating an 18-electron zirconate species **89** which undergoes a 1,2-metallate rearrangement to form the 16-electron organozirconocene **90**. The reaction results in the formation of a new C-C bond and regenerates the C-Zr bond, which has the potential for further elaboration. The reaction is analogous to carbenoid insertions into organoboron species and other main group elements.[105]



Scheme 10 – Generic mechanism of carbenoid insertion into acyclic organozirconocene followed by 1,2-metallate rearrangement with protic quench.

This methodology was later expanded by the Whitby group with the insertion of other carbenoids, such as alkenyl (**92**-**95**), α-substituted alkyl (**96**-**99**) and epoxide (**100** and **101**) (Figure 11).[106-113] Insertion of γ-haloorganolithium carbenoids, such as allenyl **102**, has also been reported by Negishi.[104] Insertion of 2-monosubstituted 1-halo-1-lithio-1-alkenes (**93**-**95**) results in the inversion of the alkene configuration at the sp^2 centre from 1,2-metallate rearrangement.[106, 107] For the epoxide carbenoids **100** and **101**, the identity of 'A' (**105**) affected the outcome of the 1,2-metallate rearrangement; nitriles resulted in the cleavage of the oxirane ring whereas phenylsulfonyl resulted in the loss of phenylsulphinate, presumably due to greater stability of this anion compared to cyanide (Scheme 11).[109, 110]

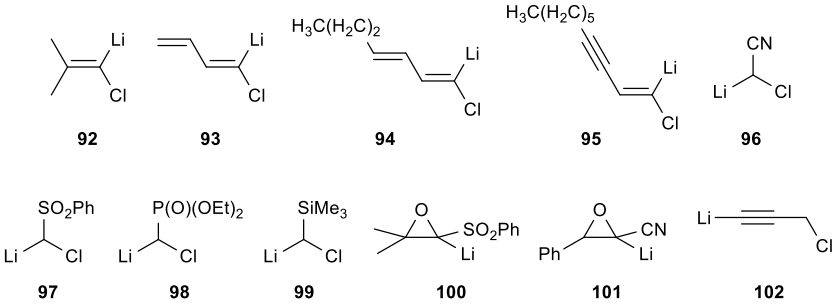
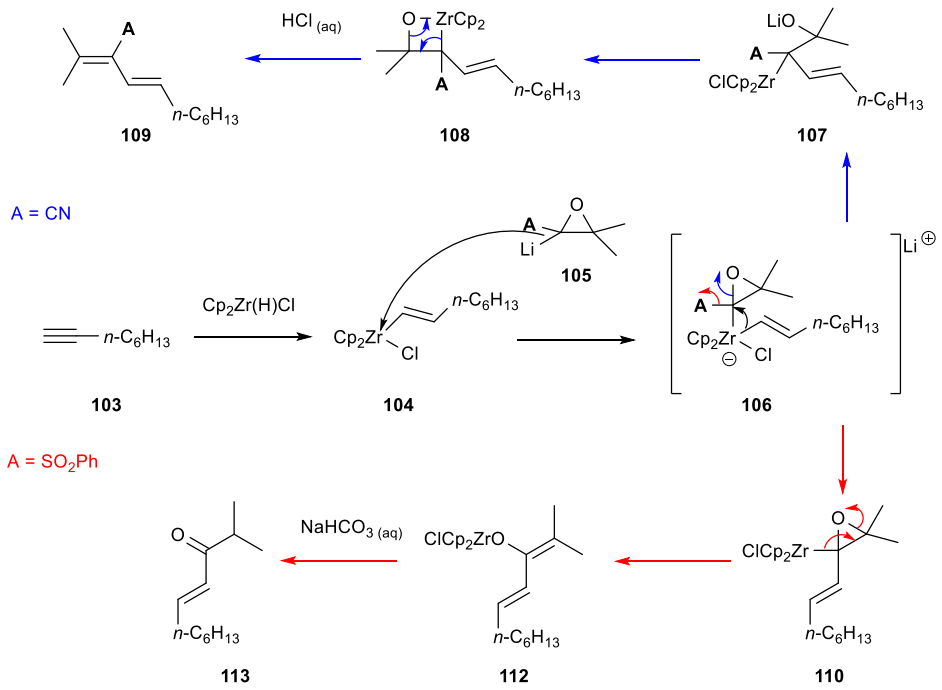
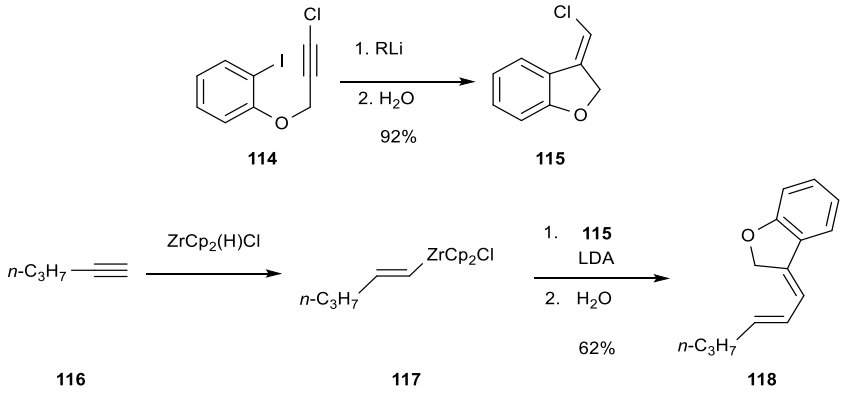


Figure 11 – Examples of carbenoids inserted into acyclic zirconocene chlorides.



Scheme 11 – Different 1,2-metallate rearrangement from epoxide carbenoid insertion.

More recently the preparation of bicyclic alkenes (such as **115**) and their insertion, through *in situ* carbenoid formation, into alkenylzirconocene chlorides **117** has been reported (Scheme 12).[114]

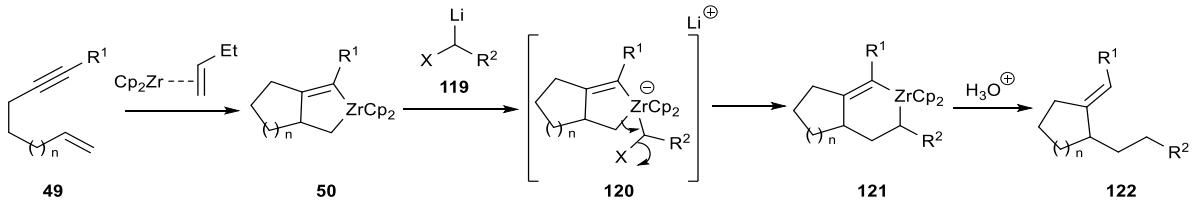


Scheme 12 – Example of a preparation and insertion of alkenyl cyclic carbenoids into acyclic organozirconocenes.

1.3.2.2 – Carbenoid Insertion into Zirconacycles

The insertion of carbenoids into unsaturated zirconacycles **50** (prepared from zirconocene mediated cyclisation of enynes) was extensively investigated by the Whitby group. After *in situ* preparation of the desired carbenoid using LDA, nucleophilic attack of the carbenoid **119** on the zirconium atom (inserting into the empty orbital) forms an 18-electron 'ate' complex **120** (Scheme 13). The insertion induces a 1,2-metallate rearrangement resulting in

the expansion of the zirconacycle from a 5-membered ring to a 6 membered ring. Zirconacycle **121** can be further elaborated or alternatively quenched with water to afford product **122**. The insertion of the carbenoid for unsymmetrical zirconacycles (such as **50**) is regioselective towards the alkyl-zirconium bond, thus affording one regioisomer as shown. A range of carbenoids have been successfully inserted into unsaturated zirconacycles, such as allyl[115], epoxide[116], alkenyl[117, 118], allenyl[119] and substituted alkyl[117] carbenoids. In addition to this, the insertion of *gem*-dibromo alkyl carbenoid has also been shown which was described in Section 1.2.6 for the synthesis of *cis*-bicyclo[3.3.0]oct-2-enes. This carbenoid insertion methodology has also been applied to saturated zirconacycles.[116-118, 120, 121]

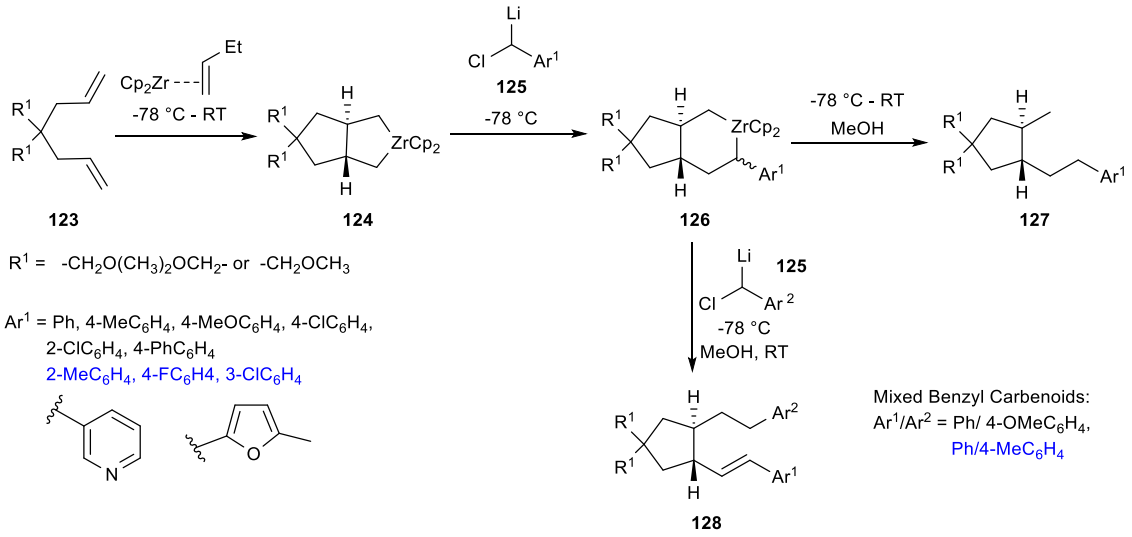


Scheme 13 – Generic mechanism of carbenoid insertion into zirconacycles followed by 1,2-metallate rearrangement and protic quench.

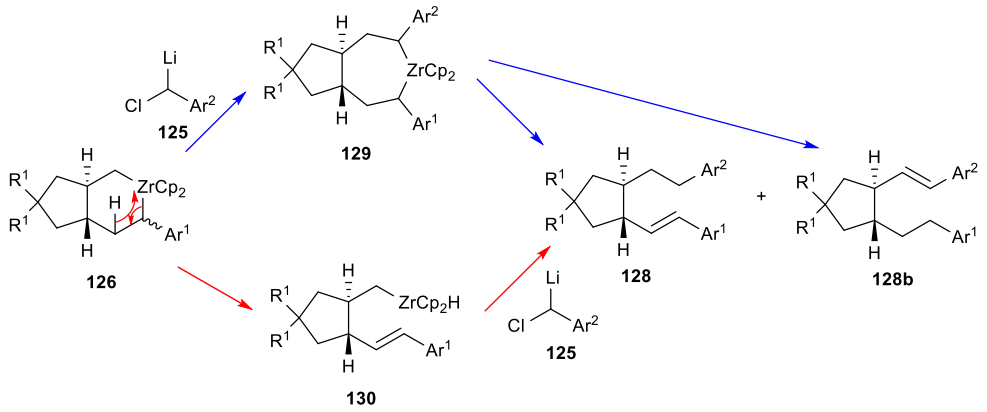
1.3.2.3 – Benzyl Carbenoid Insertion into Zirconacycles

S. Fillery demonstrated the successful insertion of a range of benzyl carbenoids **125** into saturated zirconacycles **124** to give product **127** after protic quench in yields ranging from 76-89% (Scheme 14).[1] These benzyl carbenoids **125** were prepared *in situ* from the corresponding commercially available benzyl chlorides and LDA at -78 °C. The range of benzyl carbenoids was further extended by L.Norman with 2-methyl, 4-fluoro and 3-chlorobenzyl carbenoids in 46-61% yield.[2] Furthermore, the insertion of heteroaromatic carbenoids, such as 3-pyridylmethyl and 2-methylfuran, conducted by S. Fillery was also successful and gave 87% and 75% yields respectively.[1] A small proportion of bis-inserted product **128** was observed (approximately 5% yield) from the reactions, full conversion to the bis-inserted product **128** was achieved by the addition of 5.0 equivalents of benzyl carbenoid instead of 1.1 equivalents, giving yields of 76-81% (where Ar^1=Ar^2).[1] Attempts by S. Fillery and L. Norman to elucidate the mechanism for the formation of the bis-inserted product **128** through the insertion of two different benzyl carbenoids (where $Ar^1 \neq Ar^2$) showed alkene formation occurred preferentially next to the aryl group inserted first (Ar^1), forming compound **128**. The result appeared to support the mechanism involving a β-hydride intermediate **130** as both compounds **128** and **128b** would be expected from the

zirconacycloheptane **129** (Scheme 15).[1, 2] Investigations by L.Norman into the formation of the product from a zirconacycloheptane **129** intermediate were inconclusive.[2]

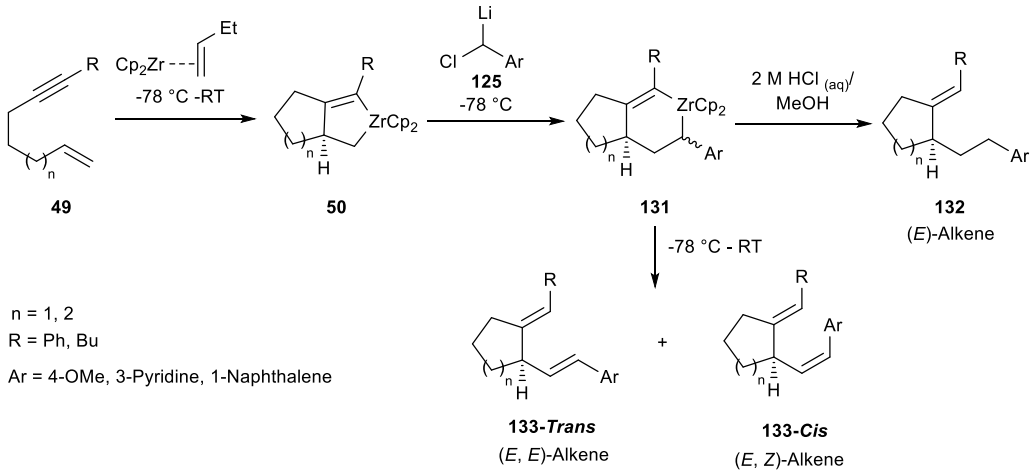


Scheme 14 – Benzyl Carbenoid insertion into saturated zirconacycles. (Carbenoids shown in black were conducted by S. Fillery and those in blue by L. Norman).



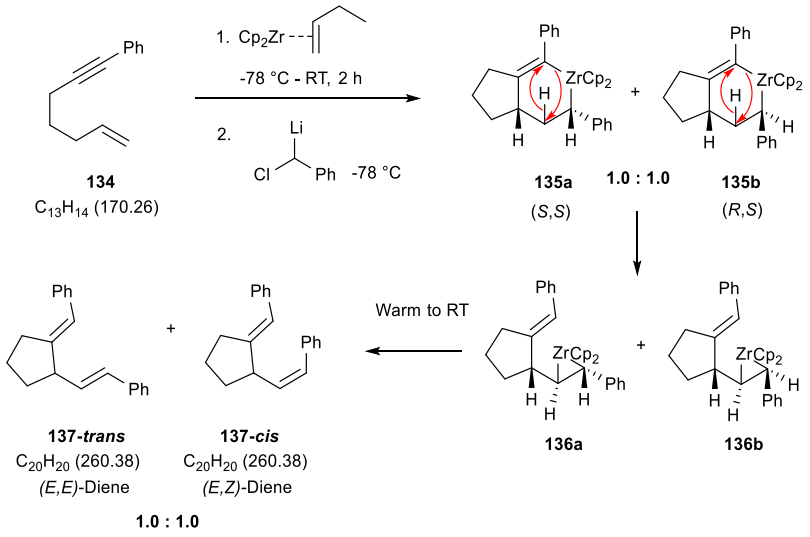
Scheme 15 – Two proposed mechanisms for the formation of alkene **128**, via a zirconacycloheptane (blue) or a zirconium hydride intermediate (red).

S. Fillery inserted benzyl carbenoids into an unsaturated zirconacycle **50** (n = 1, R = Ph) using 4-methoxybenzyl carbenoid and the 3-pyridylmethyl carbenoid to afford product **132** in 82% and 85% with no double carbenoid addition (Scheme 16). However, repeating the reaction on a different unsaturated zirconacycle **50** (n = 2, R = Bu) with 1-naphthalene carbenoid, S. Fillery isolated the diene **133-*trans*** as the major product in 93% yield.[1] L. Norman identified that for the isolation of alkene **132** compounds, the reaction must be quenched at -78 °C as warming to room temperature results in the formation of dienes **133** which was not observed for the saturated zirconacycles.[2] S. Fillery speculated the formation of the dienes **133** was from a β-hydride elimination generating a zirconocene-hydride intermediate[1] however, L. Norman later showed it was most likely *via* an unprecedented endocyclic cyclometallation.[2]

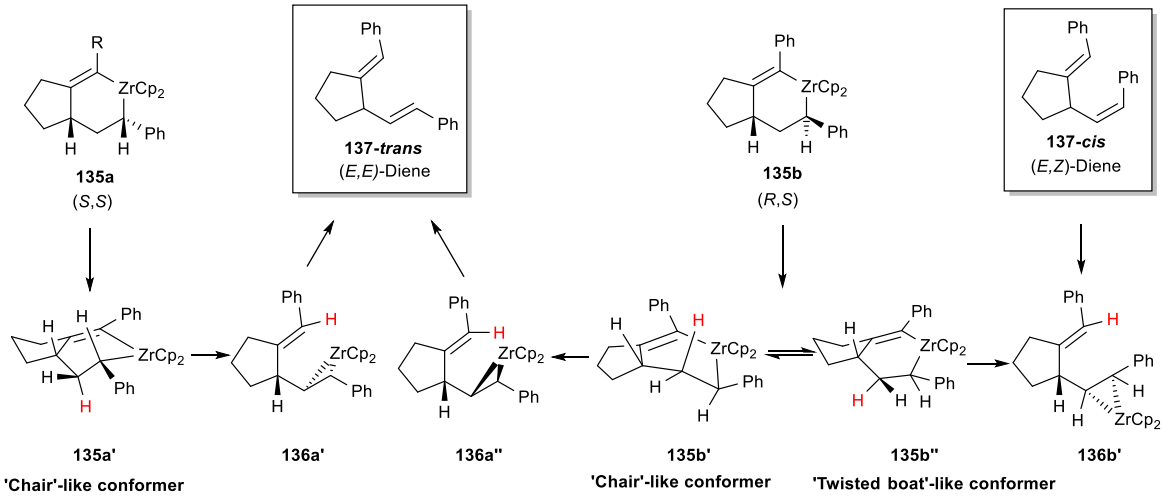


Scheme 16 – Benzyl carbenoid insertion into unsaturated zirconacycles.

Endocyclic cyclometallation is demonstrated in Scheme 17 for the synthesis of **137-*trans*** and **137-*cis*** dienes (obtained in a 1:1 ratio by L. Norman).[2] Upon warming above -78 °C, zirconacycles **135a** and **135b** (1:1 ratio) undergo endocyclic cyclometallation to form zirconocene η^2-alkene complexes **136a** and **136b**. Decomplexation of **135** yields the corresponding dienes **137-*trans*** and **137-*cis*** (in a 1:1 ratio) [2] The decomplexation was assumed by L. Norman to be aided by diisopropylamine present in the reaction mixture from the *in situ* formation of the benzyl carbenoid.[2] DFT calculations identified two low energy conformations zirconacycle **135b** could adopt (**135b'** and **135b"**), in which **135b'** would lead to the formation of the diene **137-*trans*** and **135b"** to the diene **137-*cis*** after endocyclic cyclometallation (Scheme 18). Only one low energy conformation was identified for zirconacycle **135a** (**135a'**) which would lead to the formation of the diene **137-*trans*** only. Thus, calculations appeared to show two pathways for the formation of diene **137-*trans*** and only one pathway for the diene **137-*cis***.[2]



Scheme 17 – Benzyl carbenoid insertion into an unsaturated zirconacycle followed by endocyclic cyclometallation to form dienes **137-*cis*** and **137-*trans*** conducted by L. Norman.



Scheme 18 – Low energy conformations for **135a** and **135b** identified by DFT calculations showing the formation of dienes **137-*trans*** and **137-*cis*** reported by L. Norman.

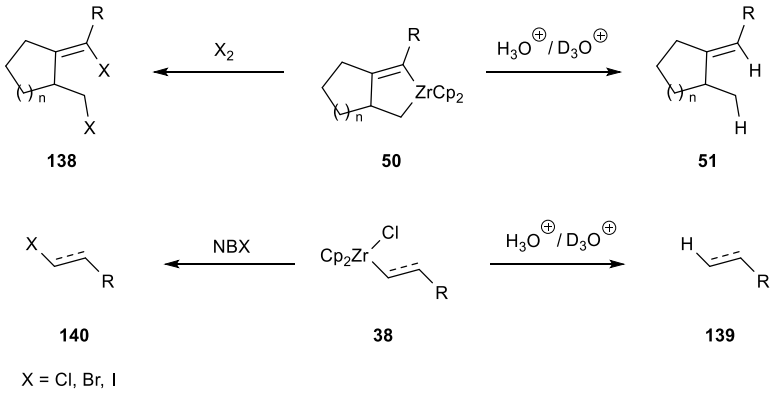
L. Norman showed the formation of diene **133-*trans*** was significantly faster than the formation of the diene **133-*cis*** in all examples (Scheme 16). Increasing the ring fused by the zirconocene from 5-membered to 6-membered (from n = 1 to 2) also increased the reaction rate.[2] Furthermore, the alkyne substituent (R) group was also influential as changing from phenyl to butyl increased the reaction rate. In addition to rate differences, these latter two changes also influenced the ratio of the dienes **133-*trans*** and **133-*cis*** in favour of the **133-*trans*** product.[2] The greater amount of diene **133-*trans*** was rationalised by DFT calculations showing a decrease in energy of the equivalent chair-like conformer of (*R*,*S*) zirconacycle **131** (equivalent to **135b'**, Scheme 18**)** which resulted in more (*R*,*S*) zirconacycle **131** converting to diene **133-*trans*** instead of **133-*cis***. Conversely, insertion of *para*-substituted carbenoids with electron-donating and electron-withdrawing groups (methoxy and chloride) appeared to not affect the reaction, both in the kinetics and ratio of alkene products isolated.[2]

1.3.3 – Final Organozirconocene Elaborations

The utility of organozirconium chemistry is increased by the ability to further functionalise the C-Zr bond, such as by protonation, halogenation, transmetallation or carbonylation, particularly after carbenoid insertion. This section will focus only on the elaborations utilised in reactions described in this thesis.

1.3.3.1 – Protonation, Deuteration and Hydrogenolysis

The cleavage of C-Zr bonds can be readily achieved using water, methanol, dilute acids (such as aqueous 2 M HCl) or in basic conditions (such as with aqueous $NaHCO_3$). This quench replaces the C-Zr bond with a C-H bond, thus giving the corresponding hydrocarbon **51** and **139** from the organozirconocene **50** and **38** respectively (Scheme 19). Similarly, quenching with D_2O or DCl in D_2O provides the equivalent **51** and **139** compounds (where H = D) but with deuterium incorporated in the positions of the C-Zr bond(s) of compounds **50** and **38**. Deuteration has great utility in establishing C-Zr bond presence and can be useful is elucidating reaction mechanisms. Alternatively, cleavage of C-Zr bonds can be achieved by halogenation using I_2, Br_2 and $PhICl_2$ for alkylzirconocenes and NBS or NCS for alkenylzirconocenes, replacing the C-Zr bond for a C-X bond such as in structures **138** and **140** (Scheme 19).[67, 68] For the zirconacycles, methodology has been developed for selective mono-halogenation by Takahashi.[122] Protonation, deuteration and halogenation are thought to proceed by a concerted σ-bond metathesis resulting in the retention of configuration from the organozirconocene to the quenched product.[68, 123]

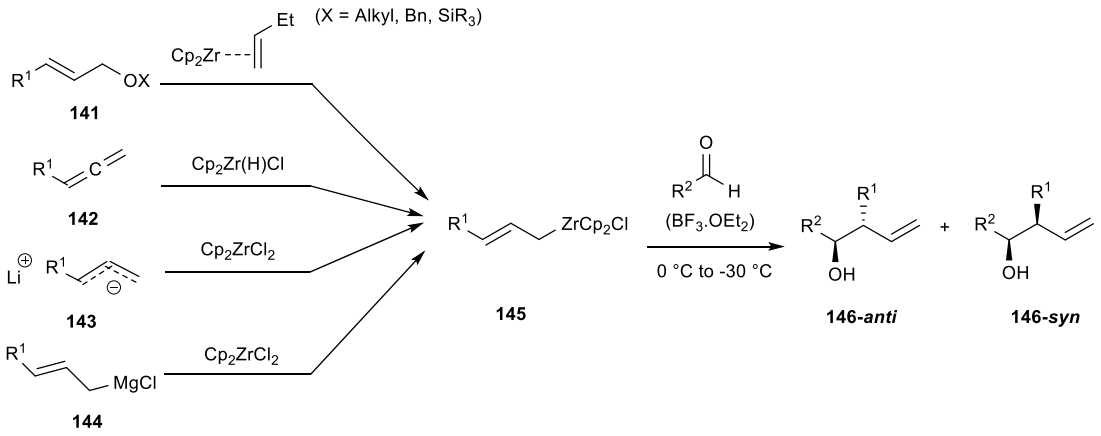


Scheme 19 – Protonolysis and halogenolysis of organozirconocenes.

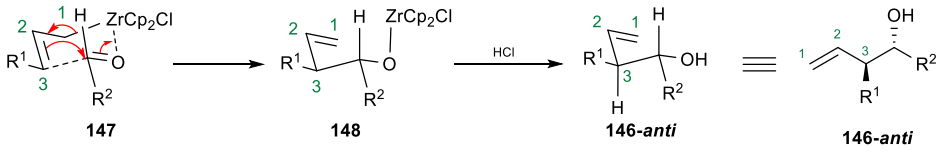
1.3.3.2 – Carbonyl Addition into Allylzirconocenes

Organozirconocenes are generally unreactive to carbonyls, excluding allylzirconocenes**.** The addition of aldehydes to allylzirconocenes **145** was first reported by Yamamoto who showed a range of aldehydes (such as benzaldehyde and alkyl aldehydes) inserted well into allylzirconocenes in an average of 90% yield with and without the presence Lewis acid $BF_3.OEt_2$ (Scheme 20).[124] Upon addition of the aldehyde, two chiral centres are created in which **146-*anti*** is generally favoured with ratios as high as 99:1 and as low as 64:1. On addition of an α-chiral aldehyde, the Cram product is favoured over *anti*-Cram.[124]

Allylzirconocenes can be prepared *via* various means, such as by oxidative addition of allyl ethers (Section 1.3.1.3)[81, 82], reduction of allenes by hydrozirconation (1.3.1.1)[125] and insertion of allyl lithiums or Grignard reagents into zirconocene dichloride[124] (Scheme 20). Their reactivity for aldehydes is thought to be due to the 6-membered chair-like transition state **147** adopted which results in addition of the carbonyl to the γ-carbon (carbon 3). Diastereoisomer **146-*anti*** is favoured over the **146-*syn*** due to the positioning of the R^1 group in an equatorial position (Scheme 21).

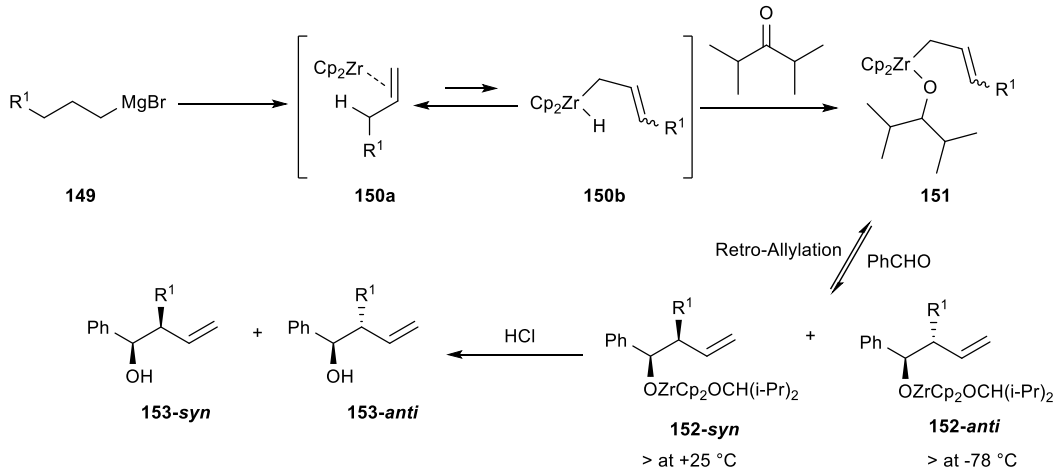


Scheme 20 – Carbonyl addition into allylzirconocenes synthesising homoallylic alcohols.



Scheme 21 – Chair-like transition state showing γ-carbon and anti-selectivity for allylzirconocene carbonyl insertion.

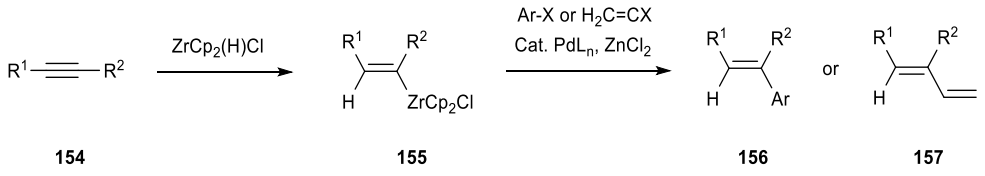
However, it has been reported the ratio between *syn* and *anti* diastereomers can be skewed in favour of the *syn* by a process termed retro-allylation when the allylzirconocene has a bulky alkoxy group.[126] This reaction showed that the temperature at which the reaction was quenched after benzaldehyde addition affected the diastereoselectivity (Scheme 22). Quenching at -78 °C favoured **153-*anti*** (kinetic product) and at 25 °C **153-*syn*** was favoured (thermodynamic product).[126] This was attributed to the benzaldehyde addition being a reversible step which was confirmed by a cross-over experiment. The bulky alkoxy group is reported to be indispensable as it is thought to destabilise intermediate **152-*anti***, facilitating the retro-allylation. No other aldehyde additions to allylzirconocenes warmed to room temperature report *syn* as the major diastereomer product.[127]



Scheme 22 - Retro-allylation of allylzirconocenes after benzaldehyde addition.

1.3.3.3 – Transmetallation of Alkenylzirconocenes

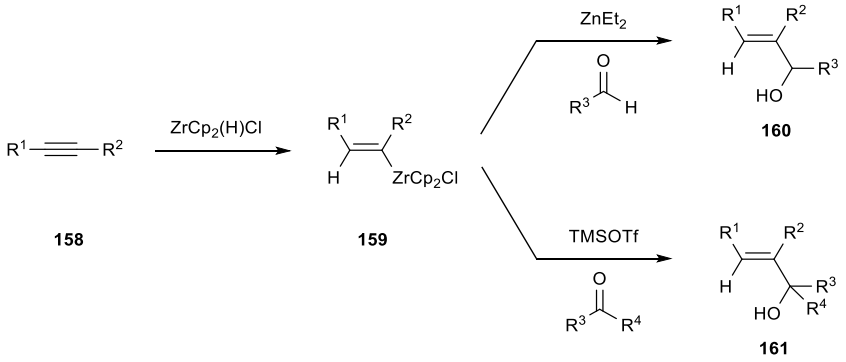
The coupling of alkenylzirconocene chlorides with aryl and alkenyl halides was first successfully achieved using nickel and palladium catalysis respectively however, the reaction was very slow for di-substituted alkenylzirconocenes.[128, 129] The use of $ZnCl_2$ for the coupling was later reported by Negishi, a reagent which significantly accelerated the reaction of di-substituted alkenylzirconocenes **155** with aryl and alkenyl halides (Scheme 23).[130] The reaction is thought to proceed by a double transmetallation, zirconium to zinc followed by zinc to palladium, which ultimately results in the coupling of the organozinc and the organohalide *via* a standard Pd(0) catalysed cross-coupling pathway. This cross-coupling reaction (termed Negishi coupling) allows for the stereo-, regio- and chemoselective synthesis of a wide variety of alkene-containing compounds (**156** and **157**). Examples of the reaction's use in the synthesis of natural products can be found in the literature.[131]



Scheme 23 – Negishi Cross-Coupling of Alkenylzirconocenes with alkenyl or aryl halides with transmetallation to zinc using palladium catalysis.

Transmetallation of alkenylzircocene to zinc using commercial alkyl zinc reagents (dimethyl or diethyl zinc) allows for addition of aldehydes and activated ketones (such as α-keto esters), resulting in the synthesis of secondary allylic alcohol products **160** and **161** as shown (Scheme 24).[132, 133] The reaction is only successful in dichloromethane and is thought to proceed *via* a rapid 1,2-addition of the alkenylzinc to the carbonyl accelerated by

zirconocene. Enantioselectivity of the new chiral centre can be controlled using amino thiols as chiral inducers affording chiral allylic alcohols in >95% enantiomeric excess.[134, 135] The addition of aldehydes can also be achieved with additives such as $ZnBr_2$,[136] $BF_3.OEt_2$,[137] and TMSOTf[137] with the highest yields in dichloromethane instead of coordinating solvent (THF). Addition of non-activated ketones has most recently been shown to be possible using Lewis acid TMSOTf which affords tertiary allylic alcohols **161** (Scheme 24).[137] Transmetallation to zinc for carbonyl addition has also been employed in natural product synthesis.[63, 138]



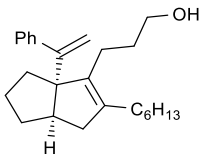
Scheme 24 – Generic carbonyl addition to alkenylzirconocenes.

Chapter 2 – Synthesis of LRH-1 & SF-1 Orphan Nuclear Receptor Agonists

The work discussed in this chapter describes the synthesis of four different LRH-1 and SF-1 targets with a *cis*-bicyclo[3.3.0]oct-2-ene backbone, prepared using a zirconocene tandem cyclisation reaction (Section 1.2.6). These compounds were designed on the basis of pharmacological data obtained for the compounds synthesised by J. Stec[41] and according to crystallographic data obtained of RJW100 bound inside LRH-1.[52]

2.1 – Target A Synthesis

Target A **11** (also known as RJW101) was originally synthesised by former group member J. Stec.[41, 53] This target is of particular interest as it shows selectivity for LRH-1 over SF-1 whereas other agonists synthesised targeted both receptors or were SF-1 selective. This subsection will discuss the optimisation of steps for the resynthesis of Target A.

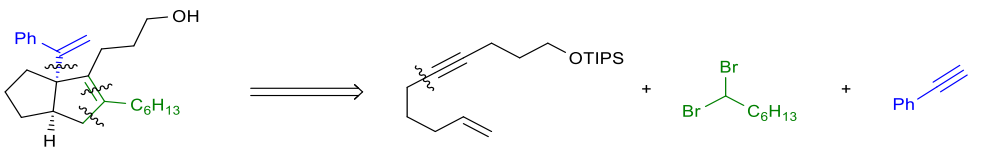


11
$C_{25}H_{36}O$ (352.56)
Target A

Figure 12 - Structure of Target A.

2.1.1 – Enyne Synthesis

For the synthesis of Target A, preparation of enyne **162** along with 1,1-dibromoheptane **163** was required for the zirconocene tandem cyclisation step, as shown through the retrosynthetic analysis in Scheme 25.



11, Target A
$C_{25}H_{36}O$ (352.56)

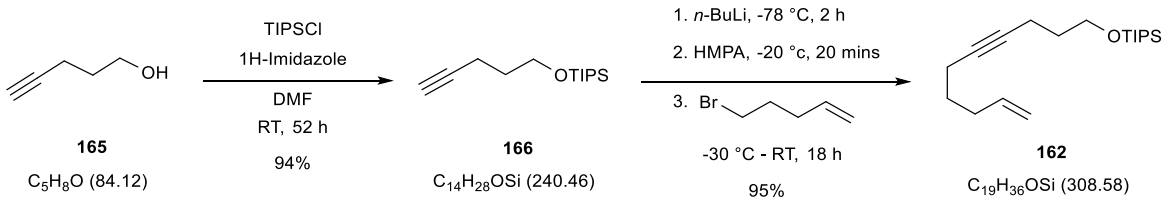
162
$C_{19}H_{36}OSi$ (308.58)

163
$C_7H_{14}Br_2$ (258.00)

164
C_8H_6 (102.14)

Scheme 25 – Retrosynthesis of Target A **11** (RJW101).

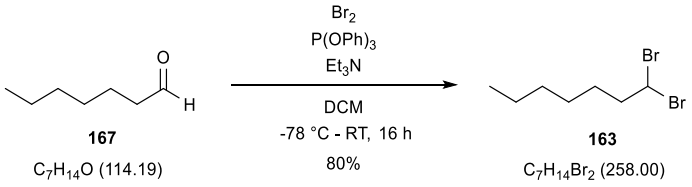
Enyne **162** was synthesised by protecting 4-pentyn-1-ol **165** with TIPS (94%) followed by an S_N2 of alkyne **166** with 5-bromopent-1-ene (95%), as shown in Scheme 26. For the protection, increasing the reaction concentration from 0.4 M to 1.0 M resulted in the highest yields. A greater conversion from alkyne **166** to enyne **162** (and thus highest yields) was realised by increasing the time gaps between reagent additions. The TIPS protecting group was used instead of TBDMS to avoid nucleophilic attack from the lithiated alkyne onto the TBDMS group of another alkyne, as encountered by J. Stec.[53]



Scheme 26 – Synthesis of enyne **162** from 4-pentyn-1-ol **165**.

2.1.2 – Synthesis of 1,1-Dibromoheptane

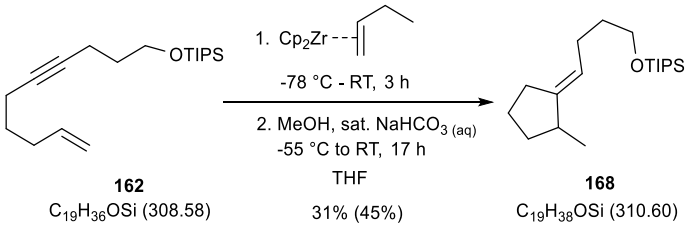
As shown from the retrosynthesis of Target A (Scheme 25), 1,1-dibromohepatane **163** was required for the zirconocene tandem cyclisation reaction. Bromination of heptanal **167** was conducted using bromine, triphenylphosphite and Et_3N to yield dibromide **163** (80%), as shown in Scheme 27. The reaction conditions used were from the bromination of alkyl aldehydes to alkyl *gem*-dibromides of varying alkyl chain lengths, in yields of 88% and 92%.[139, 140] Using literature conditions specific for the synthesis of 1,1-dibromoheptane **163**, which did not use Et_3N, resulted in no isolation of product.[141]



Scheme 27 – Synthesis of 1,1-dibromoheptane from the bromination of heptanal.

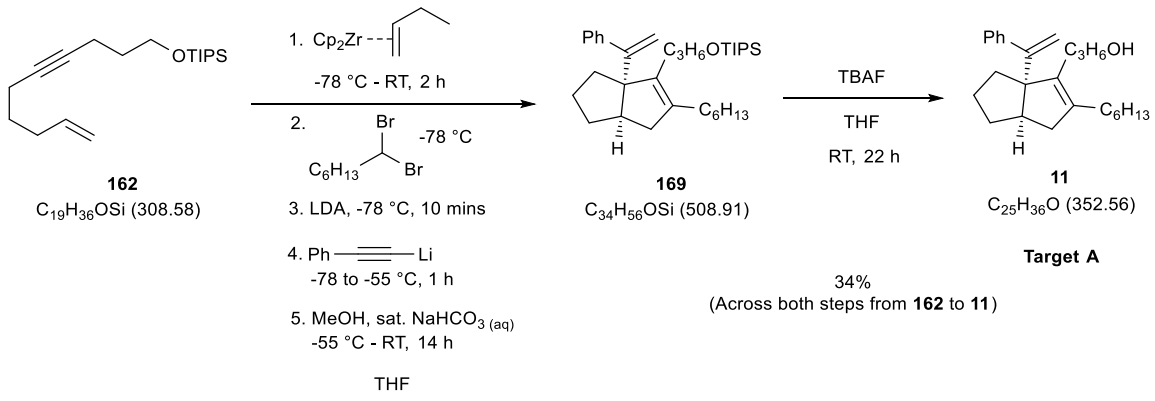
2.1.3 - Zirconocene Tandem Cyclisation and TIPS Removal

The zirconocene co-cyclisation of enyne **162** yielded cyclised product **168** in 31% isolated yield (Scheme 28). Some mixed fractions of starting material and product were obtained due to incomplete conversion of enyne **162** to cyclised product **168**, resulting in an estimated total yield of 45% and an isolated yield of 31%.



Scheme 28 – Reaction of enyne **162** to cyclised product **168** *via* a zirconocene cyclisation reaction.

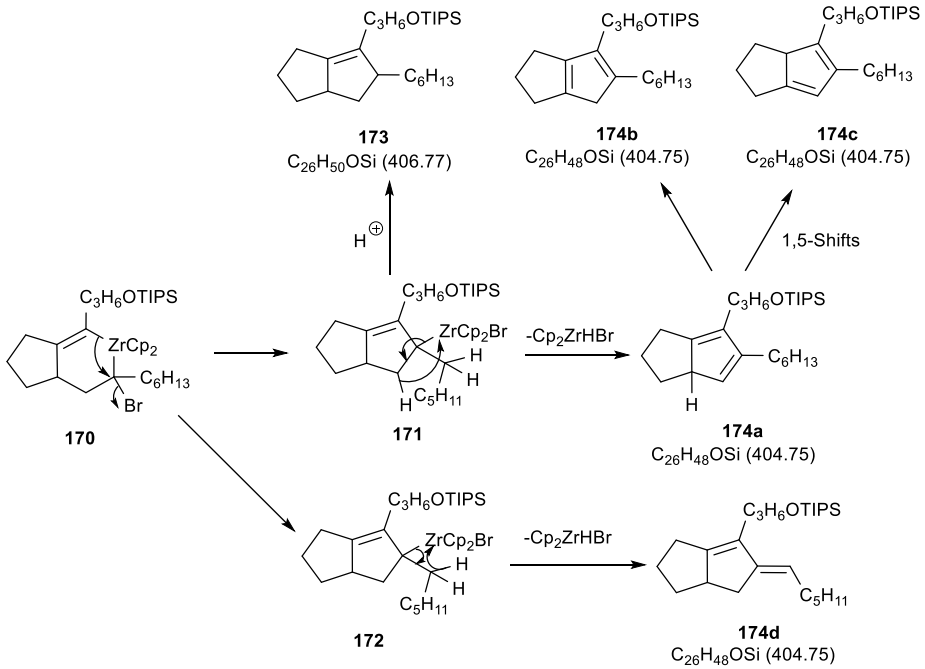
Zirconocene tandem cyclisation of enyne **162** synthesised bicyclic compound **169**, TIPS removal using TBAF then yielded bicyclic alcohol **11** in 34% yield across both steps (Scheme 29). Successful removal of TIPS-F from the deprotection reaction (identified by ^{1}H-NMR)[142] was achieved by column chromatography using an ISOLUTE®SI pre-packed column. Although standard column chromatography resulted in some separation between the product **11** and TIPS-F, the pre-packed silica column resulted in separate elution of both compounds.



Scheme 29 – Enyne **162** tandem cyclisation on zirconocene followed by TBAF deprotections to yield **11**, Target A.

The zirconocene tandem cyclisation reaction was conducted three times, the first two of which did not result in clean formation of product **169**. Alternatively, GC monitoring showed various peaks at a similar retention time which GCMS (CI) confirmed to be of *m/z* 407 and 405 ($[M+H]^{+}$). These peaks are believed to correspond to structures resulting from decomposition of the zirconacycle **170** before lithium phenyl acetylide addition. Decomposition can occur if the time interval between the addition the carbenoid of 1,1-dibromoheptane **163** and the lithium phenyl acetylide exceeds 25 minutes (Scheme 30). As

a result, this time interval was rigorously maintained to 10 minutes for the final attempt to successfully yield the desired product **169**.



Scheme 30 - Decomposition mechanism of zirconacycle **170** forming various isomers of the similar mass.

2.2 – Target B Synthesis

Target B **175** is a derivative of RJW100[41] with a *meta*-bromophenyl at the vinylbenzene position of the compound instead of a non-substituted phenyl (Figure 13). Rationale for the synthesis of this compound was to attain a good crystal structure of the compound bound in the receptor. The presence of bromine, which possesses high electron density, would be expected to facilitate this. Furthermore, the compound would allow us to observe what effect this substituent would have on the biological activity of the compound compared to RJW100. *Meta*-substitution was preferred to *para*-substitution as it was deemed less likely to hinder the binding within the receptor compared to RJW100. Furthermore, *meta*-substitution was less likely to cause steric hindrance compared to *ortho*-substitution in its insertion into the organozirconocene intermediate as a lithium acetylide.

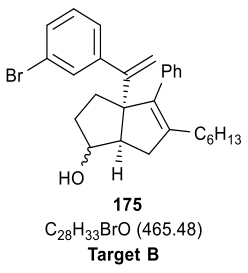
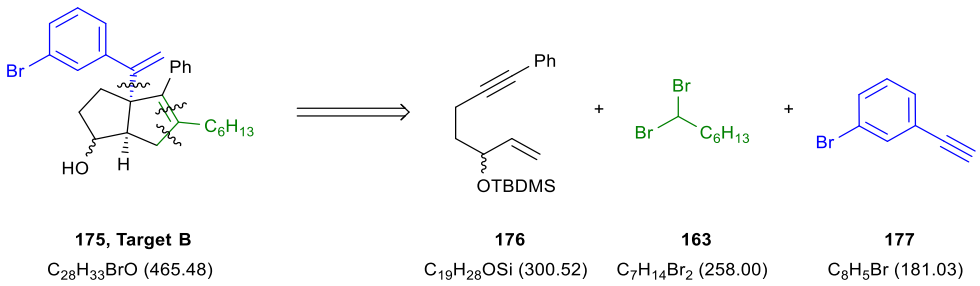


Figure 13 - Structure of Target B.

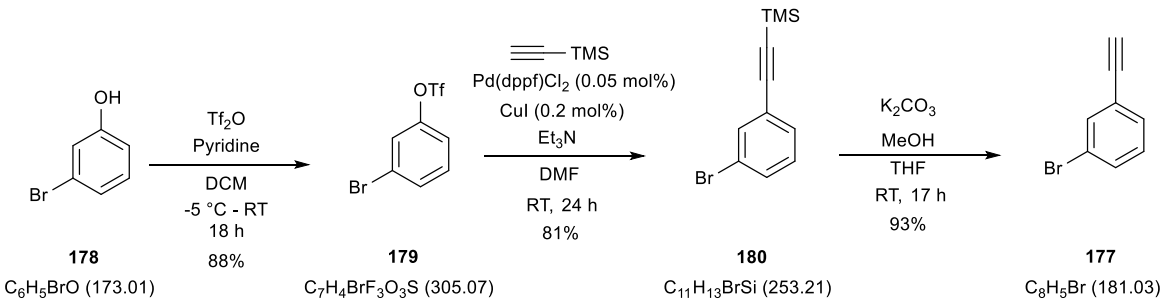
2.2.1 – 3-Bromophenyl Acetylene Synthesis

Enyne **176**, 1,1-dibromoheptane **163** and 3-bromophenyl acetylene **177** were required for the synthesis of Target B (Scheme 31). Synthesis of the dibromide **163** was discussed in Section 2.1.2 and enyne **176** was provided by a group member due to being the same enyne necessary for the synthesis of RJW100.[41, 53] 3-Bromophenyl acetylene **177** was not viable to purchase commercially so was synthesised *via* a three-step route (Scheme 32).



Scheme 31 – Retrosynthesis of Target B for the zirconocene tandem cyclisation reaction.

3-Bromophenyl acetylene **177** was synthesised by triflating 3-bromophenol **178** (88%) followed by a Sonogashira reaction (81%) with trimethylsilyl acetylene using optimised conditions developed within the group. Good chemoselectivity was achieved between sp^2 triflate and sp^2 bromide. Removal of the TMS group from alkyne **180** using potassium carbonate in methanol gave alkyne **177** (93%). Care was needed when concentrating *in vacuo* to avoid loss of product – minimal concentration followed by Kugelrohr distillation (55 °C at 103 Torr)[143] was used (Scheme 32).

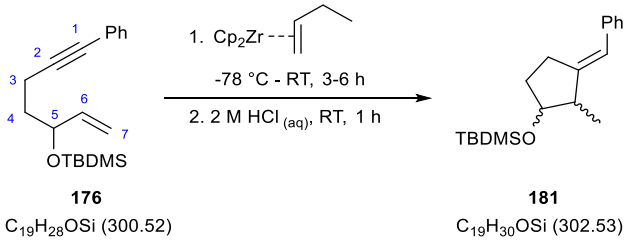


Scheme 32 - Synthesis of acetylene **177** *via* triflation, Sonogashira and TMS removal reactions.

2.2.2 – Zirconocene Tandem Cyclisation and Protecting Group Removal

For the zirconocene cyclisation of enyne **176**, it had been reported within the group that incomplete cyclisation occurs within the standard 3 hour reaction time normally followed. This was likely due to the steric hindrance introduced by the TBDMS-protected alcohol on C5 (Scheme 33). In an attempt to achieve the highest conversion from enyne **176** to cyclised product **181**, cyclisation of enyne **176** using zirconocene(1-butene) was conducted with an

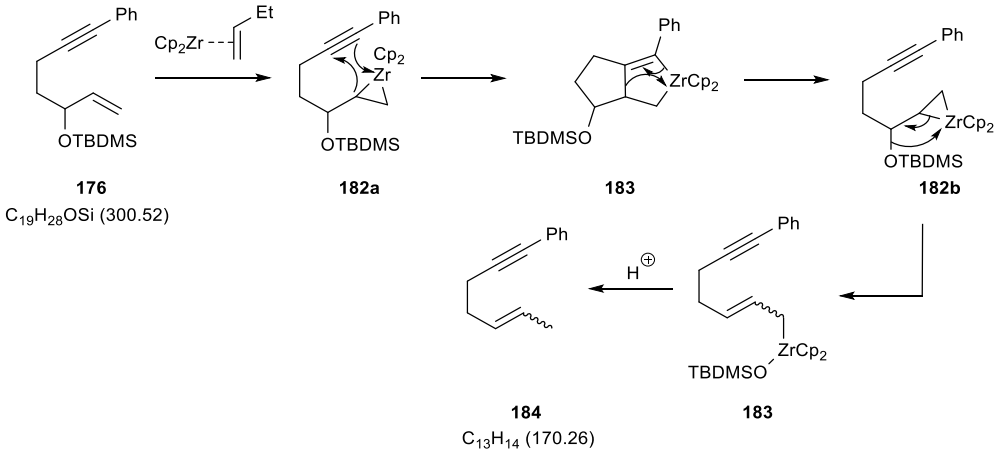
internal standard for GC monitoring over a 3 to 5 hour period (Table 1). During the monitoring, the conversion of enyne **176** to product **181** increased from 3 to 4 hours however, the amount of product was shown to decrease when monitored at 5 hours. It was proposed that decomposition of the zirconacycle begins to occur beyond 4 hours (Scheme 34) therefore, it was suggested that the cyclisation reaction should not be allowed to proceed for longer than 4 hours.



Scheme 33 - Zirconocene cyclisation of enyne **176** to form the corresponding cyclised product **181**.

	GC Peak Ratios in Reference to Decane Standard	
Reaction Time (h)	Enyne **176** Normalised to 1	Product **181** Diastereoisomers Normalised to 1
3	1.00	0.98
4	0.90	1.00
5	0.80	0.90

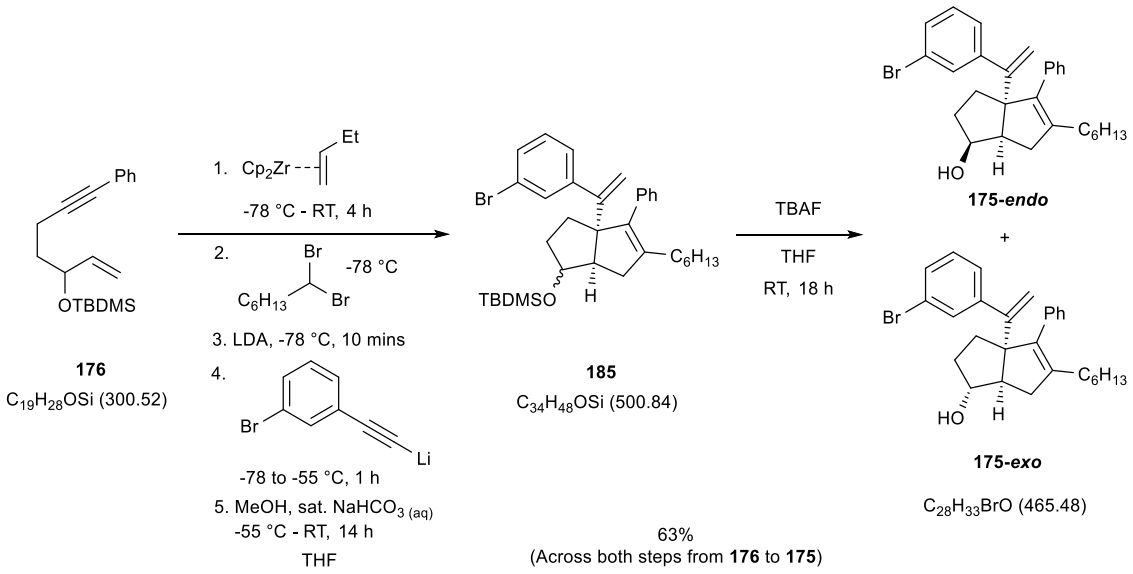
Table 1 – Ratios between enyne **176** and product **181** from GC monitoring of the zirconocene cyclisation (Scheme 33).



Scheme 34 – Proposed decomposition mechanism during zirconacyclisation of enyne **176**.

For the synthesis of Target B, 3-bromophenyl lithium acetylide was prepared using LDA as some lithium-halogen exchange was observed when using *n*-BuLi (Scheme 35). ^{1}H-NMR of the crude compound after TBAF deprotection showed a 1:1.3 ratio between the racemic **175-*endo*** and **175-*exo*** diastereomers. Ratios were determined from the diagnostic peaks of the CHOSi proton observed at 4.18 ppm (ddd, *J* 14.2, 9.2, 5.3 Hz) for the **175-*endo*** and 3.97

ppm (br s) for the **175-*exo***, as determined by J. Stec.[41, 53] The reaction was successful and the desired compound was synthesised in 63% yield for both diastereomers across both steps.



Scheme 35 - Zirconocene reaction for the synthesis of bicyclic alcohol **175**.

Separation of the two diastereoisomers of **175** was only achieved using an ISOLUTE®SI pre-packed column for the chromatography. Diastereomer **175-*endo*** eluted first from the column and **175-*exo*** second. As RJW100 (which was the *exo* diastereomer) was the most active, biological testing of the separate **175-*exo*** enantiomers was of interest. Thus, chiral separation of racemic **175-*exo*** was realised by HPLC on a Daicel OD-H column. The separation between the enantiomers was large, with a seven minute retention time difference using 1.5% IPA in hexane and with the levorotary enantiomer eluting first.

2.3 – Target C Synthesis

Target C **186** combines features of RJW100 and RJW101 (Figure 14).[41] The compound has two hydroxyl functionalities, one at carbon 6 on the bicyclic backbone and one on the propyl substituent at carbon 2. The rationale for the synthesis of this compound was to combine the selectivity for LRH-1 of RJW101 with the potency of RJW100.[41]

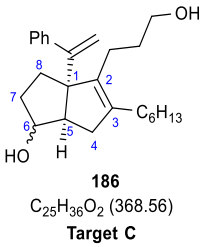
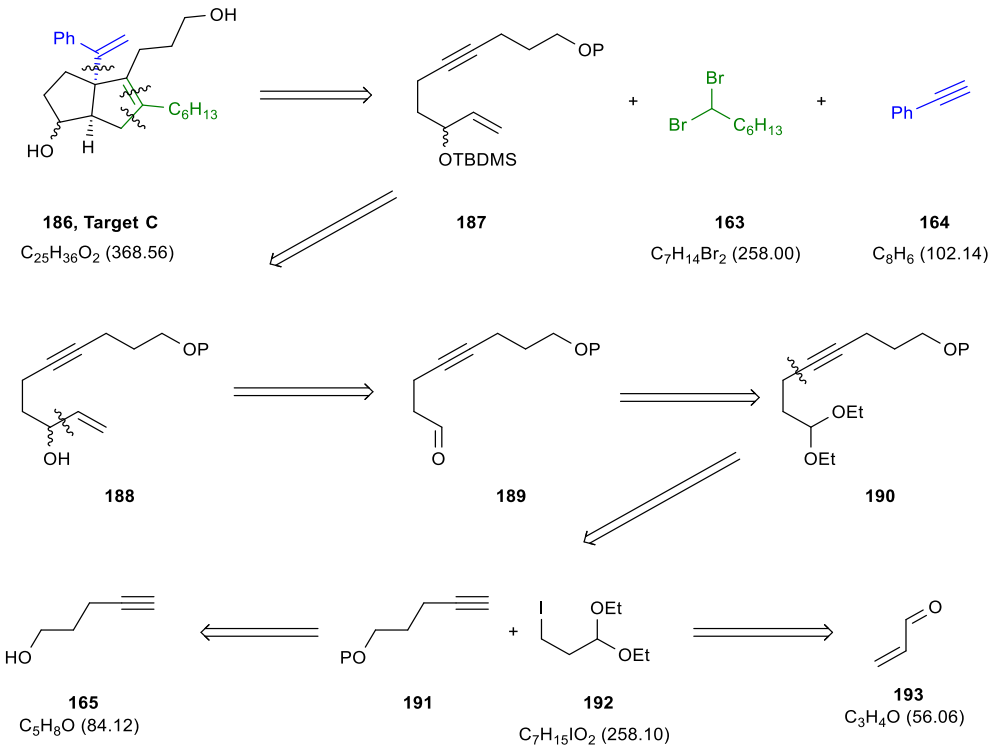


Figure 14 - Structure of Target C.

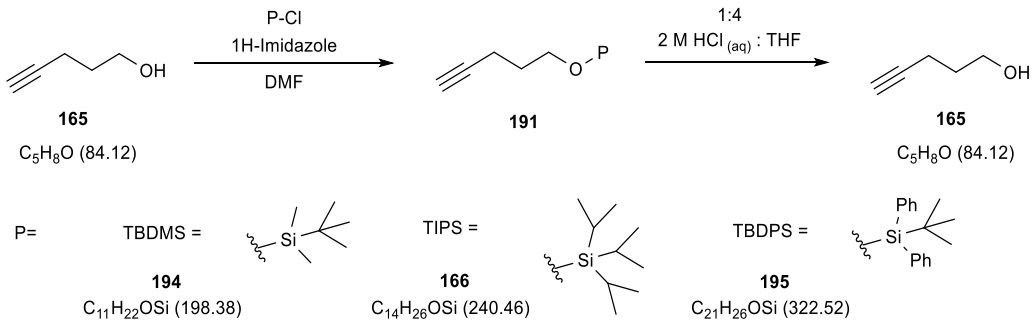
2.3.1 – Devising the Synthetic Route

The synthetic route devised for the synthesis of Target C was one adapted from the synthesis of RJW100 [41, 53], the retrosynthetic analysis of which is shown in Scheme 36. For this route, a reasonably acid-stable protecting group was required (denoted as 'P') to withstand the hydrolysis of acetal **214**. A silyl ether protecting would be the most favourable as 'P' as this would allow for its removal along with the TBDMS protecting group in one step with the use of TBAF.



Scheme 36 – Retrosynthesis of Target C adapted from RJW100. ('P' is an acid stable protecting group).

Literature on acid stability testing of silyl ether protecting groups on linear primary alcohols identified TBDPS as a relatively acid stable group.[144] Therefore, 4-pentyn-1-ol **165** was protected with TBDPS, TIPS and TBDMS and then exposed to the acidic conditions of the acetal hydrolysis (Scheme 37 and Table 2).[41, 53] The loss of protected alcohol **191** was monitored by GC using an internal standard. The reaction confirmed TBDMS to be very unstable in acidic conditions, TIPS showed a gradual decrease in protected alcohol **191** and TBDPS remained fairly consistent across the 4 hour period (Figure 15). It was concluded from these results that TBDPS was sufficiently stable to allow for the acetal hydrolysis to occur before removal of the protecting group, which J. Stec showed occurred within 3 hours.[41, 53]



Scheme 37 – Silyl ether alcohol protections followed by followed by acid stability monitoring.

Entry	Protecting Group	Compound No.	Alcohol Protection Scale (mmol)	Alcohol Protection Yield (%)
1	TBDMS	**194**	4.0	88
2	TIPS	**166**	20.0	94*
3	TBDPS	**195**	4.0	93

Table 2 - Summary of the 4-pentyn-1-ol **165** silyl ether protecting group reactions (Scheme 37). (*Section 2.1.1).

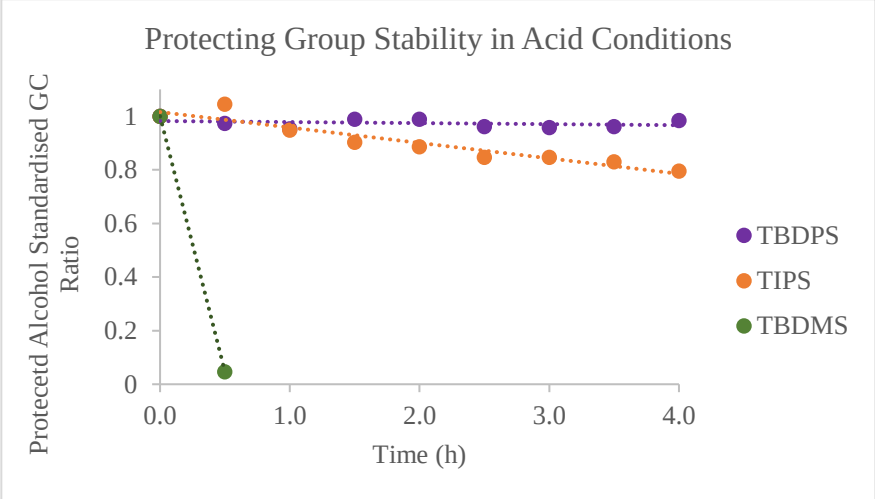
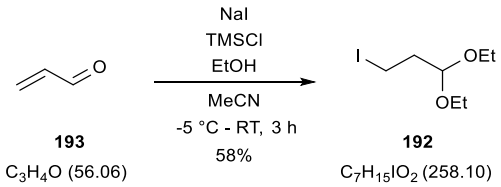


Figure 15 - Scatter graph showing loss of protected alkyne **191** in acidic conditions (Scheme 37).

2.3.2 – Enyne Synthesis

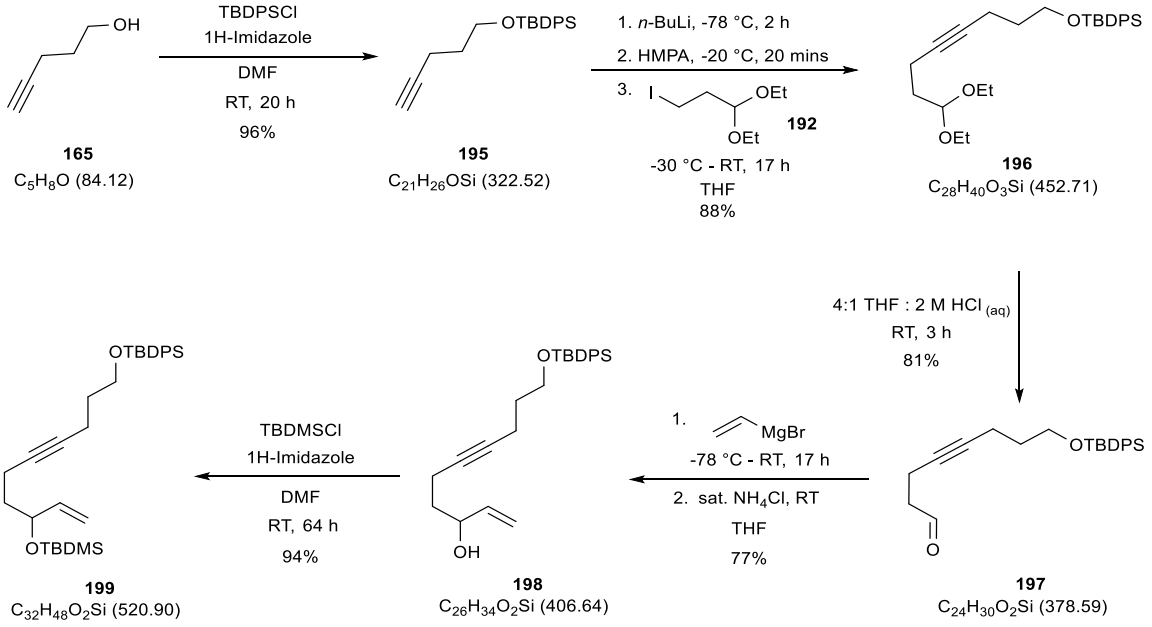
The enyne required for the synthesis of Target C was prepared *via* a six-step route as proposed in Section 2.3.1, a route adapted from the synthesis of RJW100.[41, 53]

Firstly 1,1-diethyoxy-3-iodopropane **192** was prepared on a 120 mmol scale, achieving a yield of 58% (Scheme 38).[41] For the synthesis of this compound, acrolein **193**, ethanol and acetonitrile were freshly distilled on the day of the reaction; work up and purification was also conducted immediately to avoid risk of degradation.



Scheme 38 – Synthesis of 1,1-diethoxy-3-iodopropane **192** from acrolein.

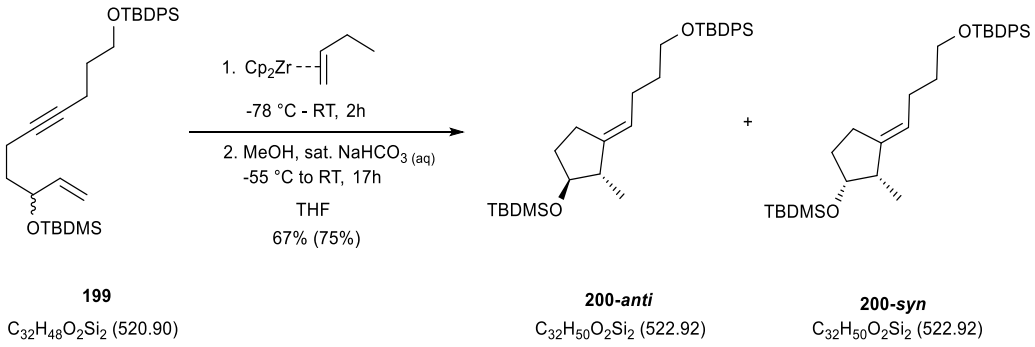
The subsequent five steps involved the protection of 4-pentyn-1-ol **165** with the chosen TBDPS group on a 60.0 mmol scale (96%) followed by an S_N2 reaction between alkyne **195** and acetal **192** to afford alkyne acetal **196** in 88% (Scheme 39). To achieve separation between alkyne acetal **196** and unreacted 1,1-diethoxy-3-iodopropane **192**, slow elution of the product was required by column chromatography using 10% Et_2O in hexane. Acetal **196** was hydrolysed to aldehyde **197** in 81% yield, a ratio of 1:4 between aqueous 2 M HCl to THF was identified as optimal for acetal hydrolysis in less than 4 hours. Despite frequent GC monitoring to determine reaction completion, ^{1}H-NMR of the crude aldehyde **197** showed a minor amount of TBDPS-OH (1:16.9 TBDPSOH to product respectively) suggesting some protecting group loss occurred in the reaction. Alkyne aldehyde **197** was next subjected to a Grignard reaction to form the corresponding enyne alcohol **198** (77%)[41, 53] which was then protected with TBDMS to yield the desired enyne **199** (94%). The choice of TBDMS as the protecting group (instead of TIPS or TBDPS) was due to steric considerations for the zirconocene tandem cyclisation reaction as discussed in Section 2.2.2, but also to allow for potential selective deprotection of one hydroxyl group after the zirconocene tandem cyclisation.



Scheme 39 – Synthesis of enyne **199**.

2.3.3 - Zirconocene Cyclisation and Silyl Ether Removals

The zirconocene induced co-cyclisation of enyne **199** yielded cyclised racemic diastereomers **200-*anti*** and **200-*syn*** in 67% combined isolated yield, 75% estimated total yield due some mixed fractions with unreacted enyne **199** (Scheme 40). Separation of **200-*anti*** and **200-*syn*** diastereoisomers, as well as unreacted enyne **199**, was best achieved using 20-30% DCM in hexane eluent over silica for the column chromatography. ^{1}H-NMR of the crude compound showed a 1.6:1 ratio between **200-*anti*** and **200-*syn*** diastereoisomers respectively. Characteristic peaks were 3.51 ppm (1 H, td, *J* 8.6, 6.1 Hz) for **200-*anti*** and 4.10 ppm (1 H, q, *J* 4.1 Hz) for **200-*syn***. The relative stereochemistry of the diastereoisomers was assigned according to molecular modelling calculations conducted by R. J. Whitby which predicted the lowest energy conformers for the 5-membered ring of the diastereomers (**200'**) and thus the corresponding dihedral angles between the bonds (Figure 16 and Table 3).[145] The predicted coupling patterns were calculated using the Altona modification[146] of the Karplus relationship[147] between the dihedral angle and ^{3}J ^{1}H-NMR coupling.[148] In general, predicted and observed coupling patterns were consistent; **200-*anti*** with two large coupling constants and **200-*syn*** with predominantly small coupling constants.



Scheme 40 – Enyne **199** zirconocene cyclisation to form cyclised diastereoisomers **200**.

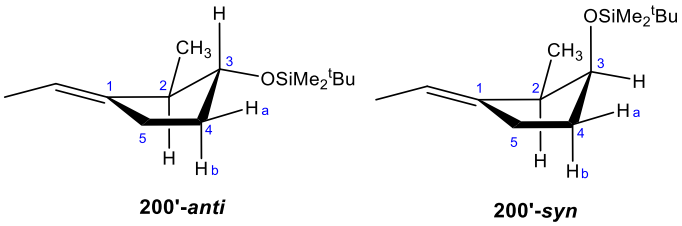
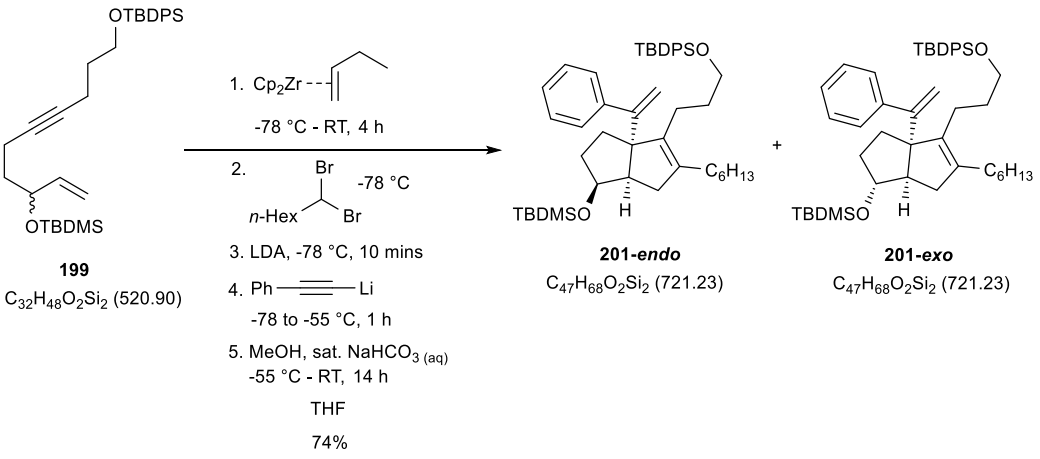


Figure 16 – Calculated lowest energy conformation for 5-membered ring of compound **200**.[145]

	200-*anti*			**200-*syn***		
	H3-H2	H3-H4$_b$	H3-H4$_a$	H3-H2	H3-H4$_b$	H3-H4$_a$
Dihedral Angle (°)	169.8	166.8	48.1	47	43.7	75.9
Calculated ^3J (Hz)	9.3	11.4	3.4	3.1	6.6	2.0
Observed ^3J (Hz)	8.6	8.6	6.1	4.1	4.1	4.1

Table 3 – Correlation between predicted (**200'**) and observed (**200**) coupling constants for the diastereomers (Scheme 40 and Figure 16).[145-148]

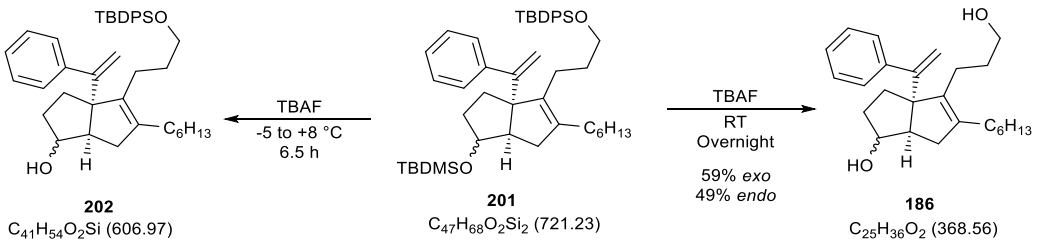
For the synthesis of Target C, a zirconocene tandem cyclisation reaction was undertaken on enyne **199** to yield **201-*exo*** and **201-*endo*** diastereoisomers (Scheme 41). ^{1}H-NMR of the crude compound showed a ratio of 1:1.4 between **201-*endo*** and **201-*exo*** respectively. The ratio between the two diastereoisomers was determined from the two diagnostic peaks corresponding to the CHOSi proton in which *exo* was observed at 3.77 ppm (1 H, br s) and *endo* at 4.04 ppm (1 H, ddd, 10.3, 8.7, 5.4 Hz), as assigned by J. Stec.[41, 53] The reaction afforded bicyclic compound **201** (both diastereoisomers) in 74% yield.



Scheme 41 - Zirconocene tandem cyclisation of enyne **199**.

Before separation of the **201-*endo*** and **201-*exo*** diastereoisomers was attempted, test reactions were conducted on **201** *endo*-*exo* mixtures to identify whether separation was best realised at the fully protected **201**, partly deprotected **202** or fully deprotected stages **186** (Scheme 42). For selective deprotection of a secondary TBDMS group over a primary TBDPS group, TBAF was used at 0 °C to yield compound **202**. For a global deprotection of both silyl ethers, TBAF was used at room temperature to afford **186**.[149] TLC analysis of **201**, **202** and **186** showed no separation between the diastereomers at the partially or fully deprotected stages and minimal separation for the fully protected stage. Therefore **201-*endo*** and **201-*exo*** were poorly separated by chromatography using 5% DCM in hexane over an ISOLUTE®SiII pre-packed column. The column chromatography resulted in the isolation pure **201-*endo*** and **201-*exo*** samples but with the majority of the material eluting mixed and

201-*endo* eluting first. Despite difficult separation between the diastereoisomers, sufficient material was isolated allowing for separate deprotections of **201-*endo*** and **201-*exo*** compounds.

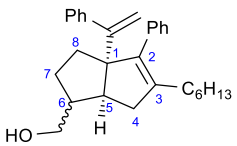


Scheme 42 - Deprotection of the silyl ether groups of bicyclic compound **201**, selectively and non-selectively.

Diastereomers **201-*endo*** and **201-*exo*** were globally deprotected separately with TBAF to yield bicyclic diols **186-*endo*** (49%) and **186-*exo*** (59%) (Scheme 42). Removal of the TBDPS-F after deprotection was achieved using a pre-packed column (as described in Section 2.1.3). Both **186-*exo*** and **186-*endo*** diols subsequently underwent chiral purification, realised using an OD-H HPLC column. Similarly to Target B, the levorotary enantiomer eluted first from the column for both **186-*endo*** and **186-*exo***. The $[\alpha]_D$ values determined for the diastereoisomers were opposite but not equal (-83.9 ° and +85.2 ° for **186-*exo*** and -82.0 ° and +95.5 ° for **186-*endo***). The difference is likely due to error, such as error of mass value and volume of solvent.

2.4 – Target D Synthesis

Target D **203** is a derivative of RJW100[41], possessing a CH_2OH functionality at C6 instead of the OH of Target C (Figure 17). The crystal structure of RJW100 bound in LRH-1 has shown the hydroxyl group was too far from a positively charged pocket of the receptor, specifically residue Thr-352, for direct interaction. Instead, interaction was achieved with a bridging water molecule.[52] Therefore, the target rationale for synthesising this compound was to increase the potency of RJW100 by potentially allowing for direct interaction between the compound hydroxyl with the receptor residue Thr-352 by increasing the distance of the hydroxyl group from the bicyclic backbone.

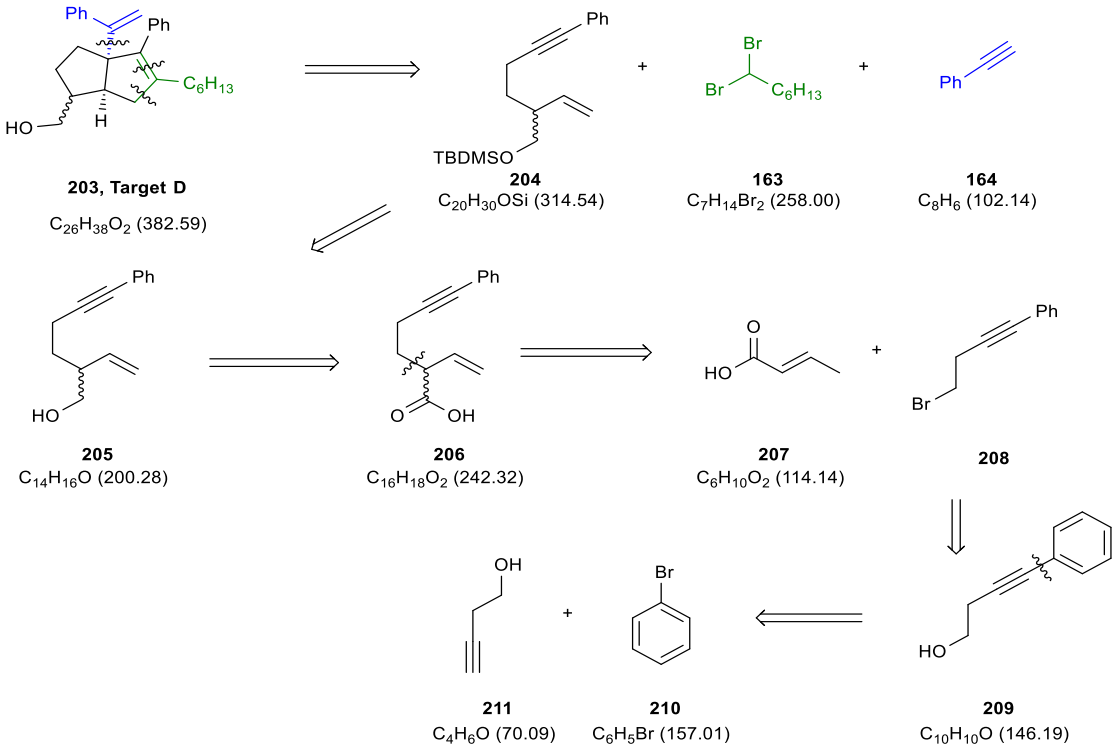


203
$C_{29}H_{36}O$ (400.61)
Target D

Figure 17 - Target D Structure.

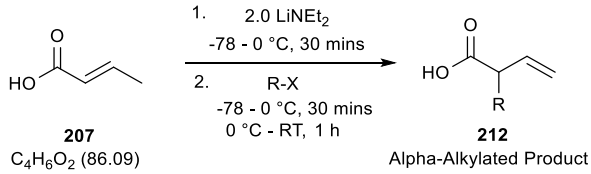
2.4.1 – Synthetic Route and Reaction Testing

Retrosynthetic analysis identified a viable synthetic route for the synthesis of Target D (Scheme 43). For this proposed route, literature precedence was found for almost all steps. A potential issue was thought to be the α-alkylation of a crotonic acid **207** which requires the selective alkylation at the α-carbon of the ester, rather than the γ-carbon. However, literature precedent exists for this type of alkylation, for both crotonic esters[150-153] and crotonic acid.[150, 151, 154, 155] Both the crotonic ester and crotonic acid can be reduced to the corresponding alcohol *via* $LiAlH_4$ and precedent is also found in the literature for reduction of similar compounds.[155-159] In terms of the alkyl halide utilised for the alkylation reaction, no literature precedence was found for alkylation using halides or triflates of similar structure to **209** (Scheme 43), excluding alkylation of malonic esters.[160]



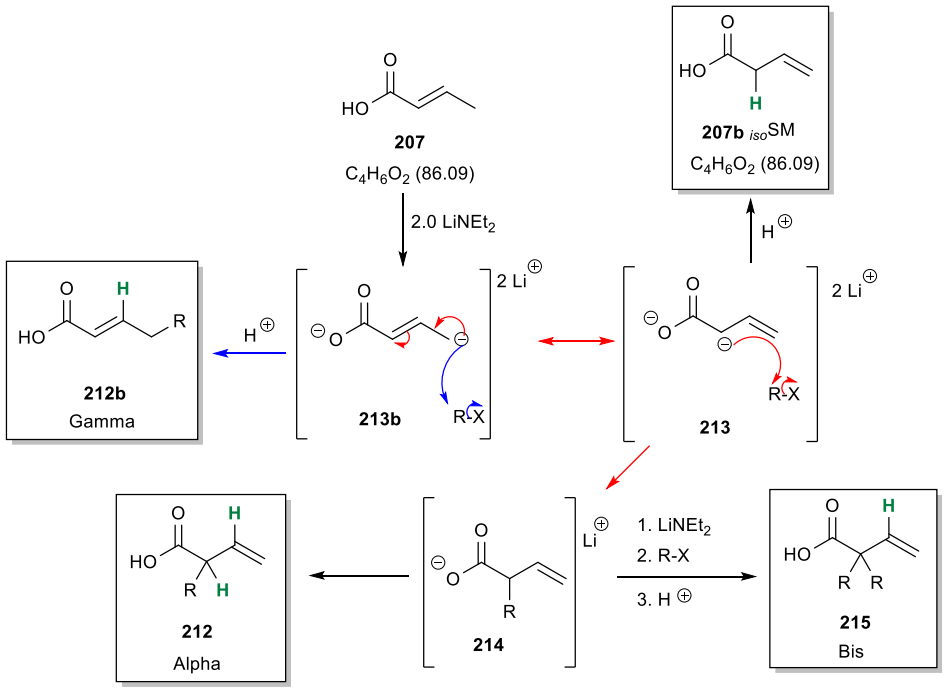
Scheme 43 - Proposed synthetic route for Target D.

Initial trials of the alkylation step were conducted using ethyl crotonic ester and 1-bromobutane[150, 152, 153, 161] however, despite various reaction attempts, no formation of desired product was identified. Instead, GCMS monitoring suggested a mixture of self-addition products of the crotonic ester and/or double alkylations had occurred. Thus, in order to avoid self-additions, test reactions were subsequently conducted on crotonic acid **207** using simple alkyl halides following a literature procedure (Scheme 44).[150]



Scheme 44 - Alpha-alkylation of crotonic acid with alkyl bromides.

Due to the nature of the allylic anion formed from the double deprotonation of crotonic acid **213b**, two regioisomeric products, α- and γ-alkylated carboxylic acids (**212** and **212b**), can be formed from the reaction (Scheme 45). Furthermore, double alkylation can also occur yielding the bis-alkylated product **215**. If alkylation does not occur after dianion formation, the isomerised form of the starting material **207b** (*iso*SM) could also be observed.



Scheme 45 - Reaction mechanism showing the formation of the different products from the alkylation of crotonic acid. ('R' denotes butyl or hexyl and protons coloured in green denote the most diagnostic peaks by ^{1}H-NMR).

Literature conditions were used for the alkylation of crotonic acid **207** with butyl bromide, yielding α-alkylated **212** and bis-alkylated **215** products in a 2:1 ratio respectively by crude ^{1}H-NMR (Table 4). Switching from the literature use of $LiNEt_2$ to LDA afforded only the bis-alkylated **215** (entry 2). Therefore the use of lithium diethylamide was returned to for the remainder of the test reactions. Subsequently, the alkylation was maintained at -50 °C over 6 hours (i.e. the longest period the cooling bath could be controlled manually) as GC monitoring of the first reaction (entry 1) showed the formation of the bis-alkylated product **215** to be more prevalent above -40 °C. Although an improved ratio between α- and bis-alkylated products (**212** and **215**) was obtained, the reaction did not reach completion was

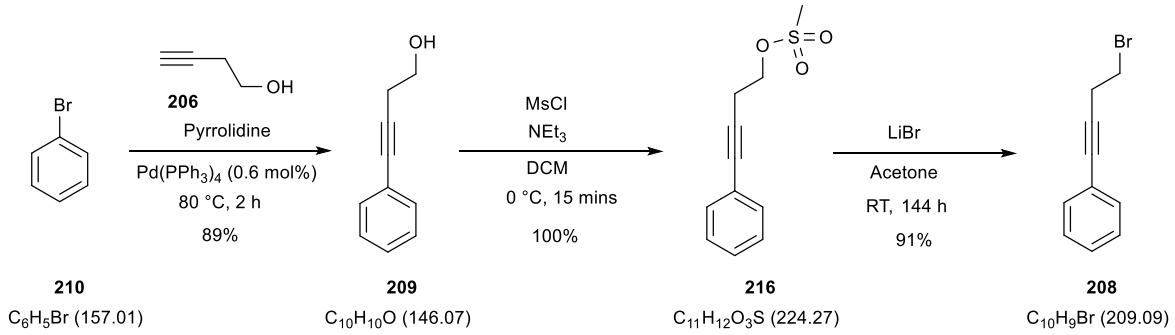
207b was observed in the crude compound (entry 3). Butyl bromide was substituted for butyl iodide to increase the reaction rate at low temperatures (entry 4). However, this lead to the formation of the γ-alkylated product **212b** previously not observed. Repeating the alkyl iodide reaction with the addition of HMPA did not suppress the formation of the γ-product **212b** (entry 5). As a result, the use of alkyl bromide was returned to for the subsequent test reactions. In an attempt to avoid bis-alkylation, an excess of dianionic crotonate **213** to butyl bromide was used in the reaction however, this was did not give improved ratios between the two products (entries 6 and 7). Finally, the ratio of *n*-BuLi to diethylamine was altered from the reaction procedure, which led to an improved ratio between α- and bis-products (**212** and **215**, entry 8). However, similarly to entry 3, the reaction did not reach completion. Reaction completion and the best ratio of α- to bis-products **212** and **215** was realised with the improved *n*-BuLi to diethylamine ratio, maintaining the reaction temperature at -50 °C for the longest period possible and then allowing to warm to +10 °C overnight (entry 9). From these test reactions, entry 9 was identified as the best conditions for the alkylation of crotonic acid **207** required for the synthesis of Target D as 88% of the crude mixture was the desired α-alkylated product **212** by ^{1}H-NMR.

Entry	Temp. (°C)	Halide	Additional Alteration to Literature	Reaction Time (h)	^{1}H-NMR Ratio of Compounds			
					α- **212**	γ- **212b**	Bis- **215**	$_{iso}$SM **207b**
1	-78 to RT	BuBr	---	1.5	2	0	1	0
2	-78 to RT	BuBr	LDA	1.0	0	0	1	0
3	-78 to -50	BuBr	---	6.0	7.7	0	1	1.7
4	-78 to -50	BuI	---	6.0	15	8.3	1	3.3
5	-78 to -50	BuI	HMPA	6.0	3.0	2.8	1.0	0
6	-78 to -50	BuBr	2.0 eq Diionic Crotonate	6.0	1	0	5.9	2.1
7	-78 to -50	HexBr	1.1 eq Diionic Crotonate	6.0	5.8	0	1	2.1
8	-78 to -50	HexBr	2.0 : 2.05 *n*-BuLi : $NHEt_2$	6.0	12	0	1	8.4
9	78 to -50 then +10	HexBr	2.0 : 2.05 *n*-BuLi : $NHEt_2$	6.0 12.5	7.4	0	1	0

Table 4 - Summary of crotonic acid alkylation test reaction associated with Scheme 44 and Scheme 45.

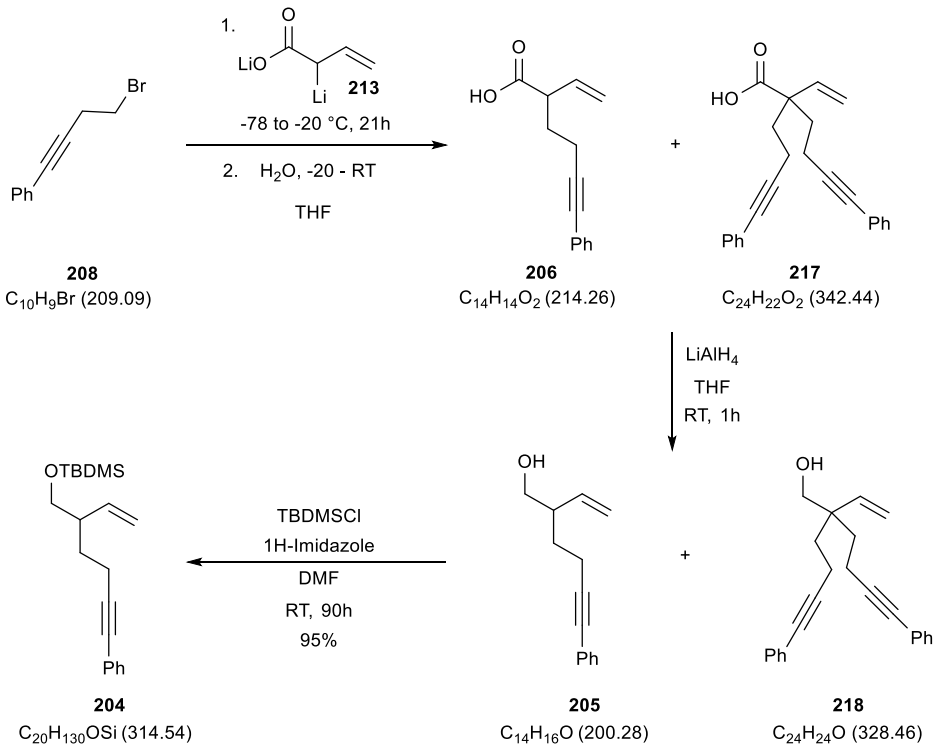
2.4.2 – Enyne Synthesis

1-Bromo-4-phenylbutan-3-yne **208** was prepared *via* a three-step route as depicted in Scheme 46. The Sonogashira reaction was conducted following literature conditions which yielded alcohol **209** in 89% yield.[162] Mesylation of alcohol **209** (100%) followed by bromination (91%) afforded the desired bromide **208**. Despite literature precedence for bromination of alkyl alcohols in one step[163-165], this two-step approach provided a simple high yielding route to the desired bromide.

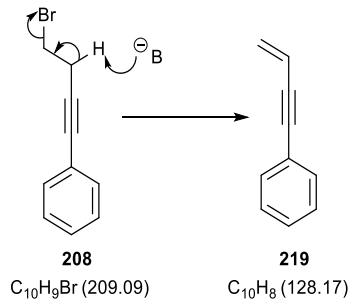


Scheme 46 - Three-step synthesis of (4-bromobut-1-yn-1-yl)benzene **208**.

The alkylation of crotonic acid **207** with alkyl bromide **208** was conducted using the conditions identified during the test reactions discussed in Section 2.4.1 (Scheme 47). Due to the structure of the alkyl bromide **208**, undesired compound **219** was observed by GC and GCMS. Compound **219** was likely formed from an E2-type mechanism in the presence of a base, presumably the dianionic crotonate **213** (Scheme 48). In addition, double alkylation was also observed by GC and ^{1}H-NMR forming carboxylic acid **217** (as expected from the test reactions). An acid-base extraction in the work-up afforded separation of carboxylic acid products **206** and **217** from other organic compounds. However, carboxylic acid products **206** and **217** were inseparable by chromatography, therefore the compound mixture was taken through to the subsequent $LiAlH_4$ reduction step. The yields across both steps were low and variable, ranging from 9-33% for five reaction repeats. The highest yield was obtained on a 5.0 mmol scale in which the reaction was maintained at -20 °C overnight using a LTC2 Grant refrigerated circulating bath. No bis-alkylated product **217** was observed by ^{1}H-NMR in this reaction, presumably due to the cooler overnight temperature. However, repeating these same conditions on a 12.0 mmol scale gave the lowest yield of 9% with a mono-alkylated **206** to bis-alkylated **217** product ratio of 1:8.3 by ^{1}H-NMR – which allowed for full characterisation of the bis-alkylated product after reduction and upon separation (compound **218**). Subsequently, mono-alkylated alcohol **205** was protected with TBDMS which afforded the desired enyne **204** in 95% yield (Scheme 47).

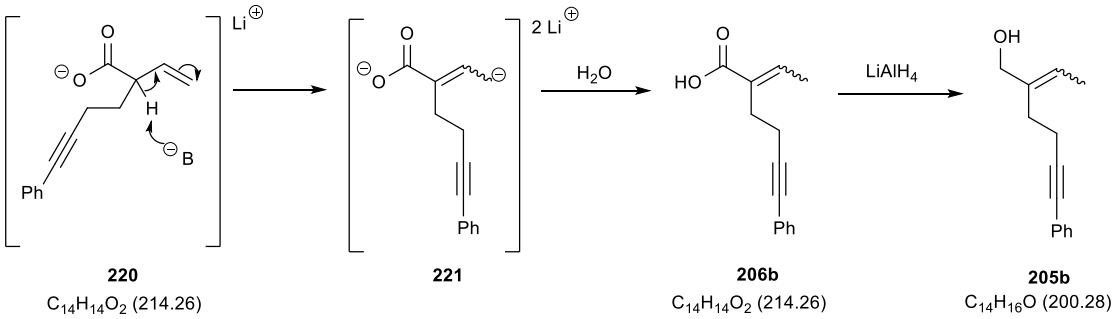


Scheme 47 - Crotonic acid alkylation with (4-bromobut-1-yn-1-yl)benzene **208**.



Scheme 48 – Deprotonation and bromide elimination of alkyl bromide **208** in basic conditions.

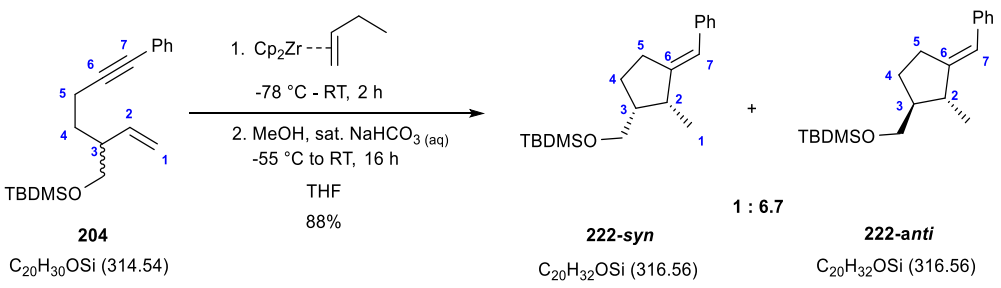
On one occasion an isomer of product **206** was formed from the alkylation, observed as minor unknown peaks by ^{1}H-NMR. Upon reduction of the mixture, GC analysis showed a peak ratio of 11:1 between product **205** and the isomer **205b**. DEPT-135 and ^{13}C-NMR analysis of the mixture after reduction suggested the minor compound to be compound **205b** (alkene configuration unknown), identified by the presence of CH_3 peak at 13.35 ppm and an alkene CH peak at 123.55 ppm. Formation of isomer **205b** was thought to have formed as a consequence of deprotonation and subsequent protonation of compound **220** which isomerised the alkene bond during the alkylation reaction (Scheme 49).



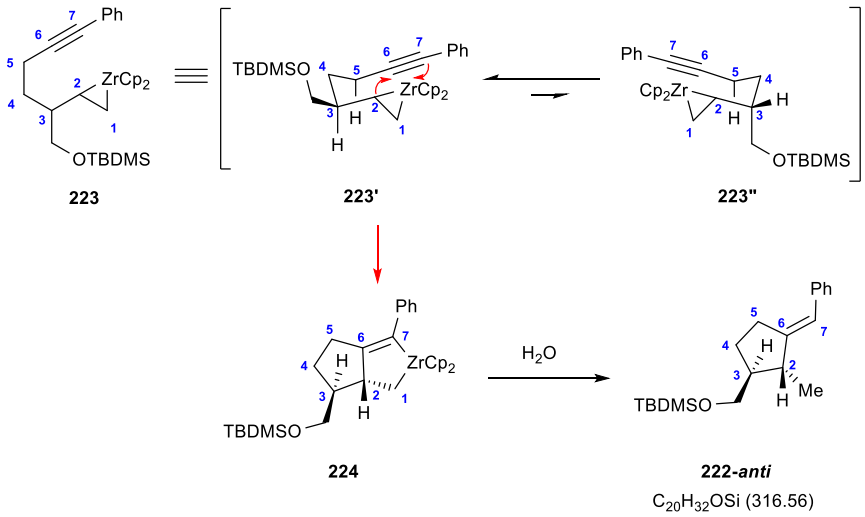
Scheme 49 – Proposed mechanism for the formation of product **205b** isomer.

2.4.3 – Zirconocene Tandem Cyclisation and Protecting Group Removal

The zirconocene induced co-cyclisation of enyne **204** yielded cyclised racemic diastereomeric **222** in 88% combined isolated yield (Scheme 50). ^{1}H-NMR of the crude compound showed a 6.7:1 ratio between *anti* and *syn* diastereomers respectively, the separation of which was not possible by column chromatography. Cyclisation of enyne **204** showed increased selectivity for one diastereoisomer compared to enynes bearing an OTBDMS group at C3 (Targets B and C). Precedent literature has shown that introducing a substituent at C3 of enynes for such cyclisations increases diastereoselectivity for the *anti* diastereoisomer, regardless of the identity of the substituent. The larger the substituent, the greater the proportion of *anti* diastereoisomer.[80] The selectivity can be rationalised by drawing chair-like transition states of organozirconocene **223**, positioning the CH_2OTBDMS substituent in the equatorial position (conformer **223'**) is more energetically favoured than in the axial position (conformer **223"**) prior to cyclisation due to minimisation of quasi 1,3-diaxial interactions and 1,3-allylic strain (Scheme 51). Consequently, the **222-*anti*** cyclised product is the major diastereomeric product as conformer **223'** is favoured.[80] Thus, assignment of **222-*anti*** as the major isomer was based on the reported precedent and the outcome of the molecular modelling for the bicyclo[3.3.0]oct-2-ene **203** product prepared from enyne **204**, the major isomer of which was shown to be the **203-*exo*** (*anti*) compound (discussed below).

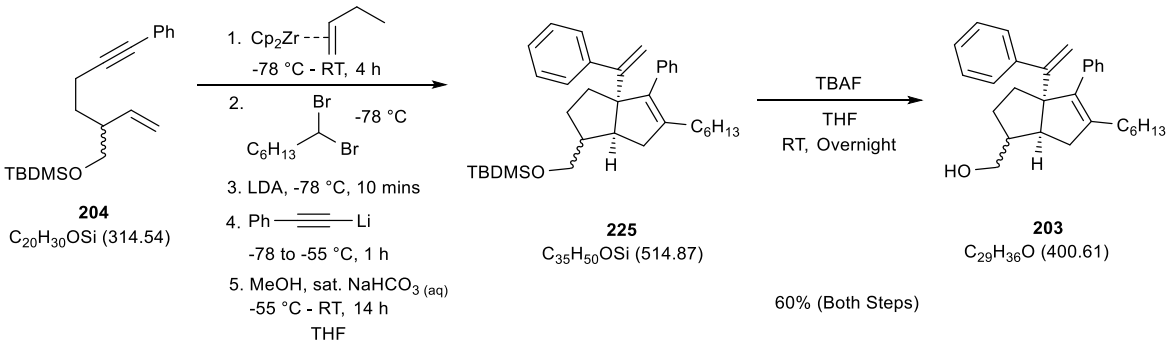


Scheme 50 - Enyne **204** zirconocene cyclisation to form cyclised product **222**.



Scheme 51 – Mechanism for the synthesis of **222** showing organozirconocene chair transition states.

For the synthesis of Target D, a zirconocene tandem cyclisation reaction was undertaken on enyne **204** to yield racemic **225-*exo*** and **225-*endo*** diastereoisomers (Scheme 52). Again, there was increased selectivity for one diastereoisomer observed in the ^{1}H-NMR of the crude compound which showed a 9.1:1 ratio between the diastereoisomers, determined from the integration of the vinyl doublets. A total yield of 60% was obtained for both diastereoisomers across both the zirconocene cyclisation and TBAF deprotection steps. The diastereoisomers were inseparable by normal column chromatography and only partial separation was achieved by normal phase HPLC using 0.5% IPA in hexane. Mixed samples of diastereoisomers were isolated from HPLC purification, with only one pure sample of **203** major diastereomer. Attempted chiral separation of the **203-*major*** diastereoisomer on a Daicel OD-H HPLC column was also poor, enantiomers eluted less than a 1 minute apart using 1% IPA in hexane eluent. As a result, enantiomeric separation was not attempted on compound **203**.



Scheme 52 - Zirconocene tandem cyclisation of enyne **204** and deprotection.

The relative stereochemistries of the diastereoisomers were assigned according to molecular modelling calculations which predicted the lowest energy conformers for the bicyclic ring (**203'**), the corresponding dihedral angles between the bonds and ^{13}C-NMR shifts (Figure 18 and Table 5).[145] For the calculations it was assumed neither the polarity of the solvent nor the length of the alkyl substituent affected the minimum energy conformation of the bicyclic ring. Consistencies in the ^{13}C-NMR were identified between the observed shifts of **203-*major*** and **203-*minor*** to those predicted for **203'-*exo*** and **203'-*endo*** respectively. Similarly, the predicted coupling patterns calculated using the Altona modification[146-148] were also in accord with those observed (Table 6). The coupling patterns for **203-*major*** were best elucidated using benzene-d_6 NMR solvent, full assignment of **203-*minor*** was not possible due to being a mixed sample with **203-*major***. Overall, the predicted and observed data was generally consistent with **203-*major*** being the *exo* diastereomer and **203-*minor*** being the *endo*.

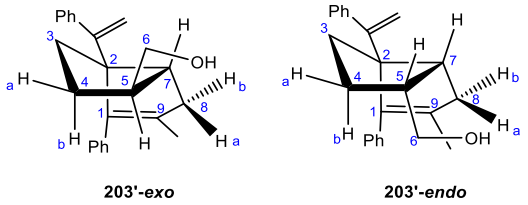


Figure 18 – Lowest energy conformation for bicyclic compounds **203'-*exo*** and **203'-*endo***.[145]

		^{13}C-NMR			
		C5	C6	C7	C8
203'-*exo*	Calculated (ppm)	51.0	67.9	51.0	44.8
203-*major*	Observed (ppm)	51.9	66.4	50.0	42.4
203'-*endo*	Calculated (ppm)	42.3	66.0	48.2	37.6
203-*minor*	Observed (ppm)	46.1	64.7	46.6	-

Table 5 – Correlation between predicted and observed ^{13}C-NMR shifts for **203-*major*** and **203-*minor***.[145]

	203-*major*/ 203'-*exo*			**203-*major*/ 203'-*endo***		
	H7-H5	H7-H8$_a$	H7-H8$_b$	H7-H5	H7-H8$_a$	H7-H8$_b$
Dihedral Angle (°)	116.8	95.6	24.7	11.5	27.0	92.1
Calculated ^3J (Hz)	3.1	1.2	8.8	9.0	8.2	1.0
Observed ^3J (Hz)	4.5	0	7.9	9.0	9.0	2.0

Table 6 - Correlation between predicted and observed coupling constants for **203-*exo*** and **203-*endo***.[145-148]

2.5 – Conclusions for Chapter 2

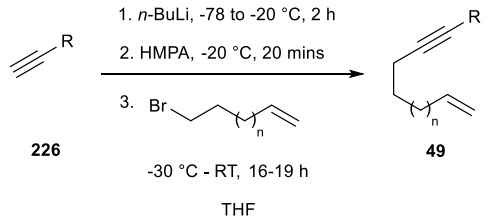
In conclusion, Targets A, B, C and D were synthesised successfully with the use of a one-pot tandem zirconocene cyclisation reaction which constructed the *cis*-bicyclo[3.30]oct-2-ene backbone. To accomplish this, various enynes were prepared, specific for each target, as precursors to the zirconocene cyclisation *via* synthetic routes ranging from 2 to 6 steps long. Many of these steps required optimisation and others followed conditions reported by J. Stec.[41, 53] These targets are currently waiting biological testing to determine their activity and selectivity for LRH-1 and SF-1 orphan nuclear receptor agonists.

Chapter 3 – Insertion of Benzyl Carbenoids into Unsaturated Zirconacycles

This chapter is a continuation of the work done by former group members S. Fillery[1] and L. Norman[2] on the insertion of benzyl carbenoids into unsaturated zirconacycles, introduced in detail in Section 1.3.2.3. This work increases the scope of the benzyl carbenoids inserted into unsaturated zirconacycles and investigates zirconocene traps for the clean formation of (*E*, *E*)-/ (*E*, *Z*)-diene products which are formed from cyclometallation followed by zirconocene decomplexation. Furthermore, the kinetics for the formation of certain (*E*, *E*)-/ (*E*, *Z*)-dienes was studied. A particular aim was to investigate some inconsistencies in previous work on the ratios of (*E*, *E*)-/ (*E*, *Z*)-diene formation in the cyclometallation step.

3.1 – Enyne Synthesis

Unsaturated zirconacyles are prepared from the co-cyclisation of enynes using zirconocene(1-butene) (Section 1.3.1.2). Therefore, the following enynes (shown by generic structure **49**) were prepared using the same conditions as those described in Section 2.1.1 in yields ranging between 72-98% (Scheme 53 and Table 7).[166, 167]



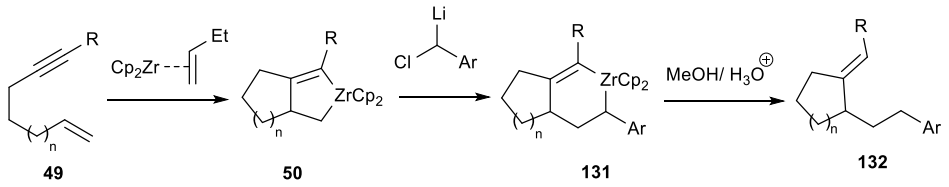
Scheme 53 – Synthesis of enynes from S_N2 reaction between alkynes and alkyl bromides, details in Table 7.

Entry	R	n	Enyne Product No.	Isolated Yield (%)
1	Ph	1	**134**	87
2	Ph	2	**227**	89
3	*n*-Bu	1	**228**	72
4	*n*-Bu	2	**229**	98

Table 7 – Summary of enyne synthesis reactions (Scheme 53).

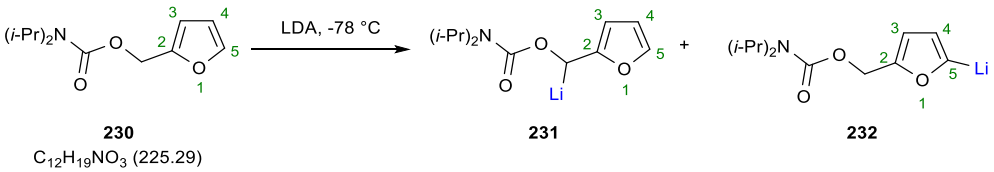
3.2 – Synthesis of (*E*)-Alkenes

(*E*)-alkenes **132** are prepared from the insertion of a benzyl carbenoid (prepared *in situ* from benzyl chloride and freshly prepared LDA -78 °C) into unsaturated zirconacycles **50** (Scheme 54). A 1,2-metallate rearrangement forms zirconacycle **131** which, if quenched at low temperature using either methanol or aqueous hydrochloric acid, yields the corresponding (*E*)-alkene **132**. (The concept of carbenoid insertions into zirconacycles is introduced in Section 1.3.2.2 and 1.3.2.3).



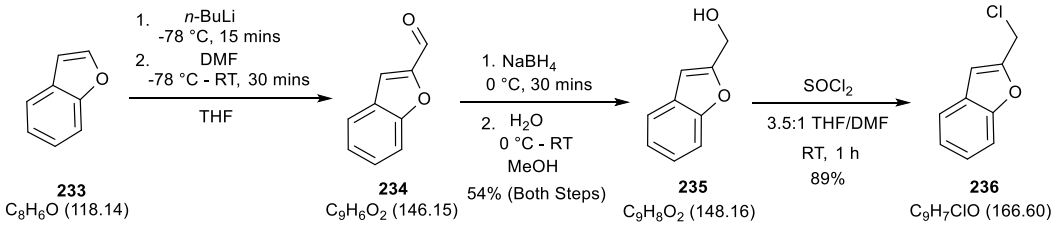
Scheme 54 – Benzyl carbenoid insertion into unsaturated zirconacycles followed by immediate quench.

For unsaturated zirconacycles **50**, the range of benzyl carbenoids used were mainly limited to benzyl, with some examples using 4-methoxybenzyl, 4-chlorobenzyl carbenoids (for R = Ph, n =1 only). To increase the scope of the benzyl carbenoid used, investigation into insertion of heteroaromatic benzyl carbenoids was conducted. As a result, the insertion of carbenoids from 2-(chloromethyl)benzofuran and 3-(chloromethyl)pyridine were explored. Benzofuran was chosen over furan owing to S. Fillery reporting competitive metallation at the 5-position of carbamate furan **230** (Scheme 55), thus leading to poor yields of 9% and 36% for carbenoid insertion into saturated zirconacycles.[1] Blocking the 5-position with a protecting group or fused phenyl ring would prevent the undesired deprotonation.



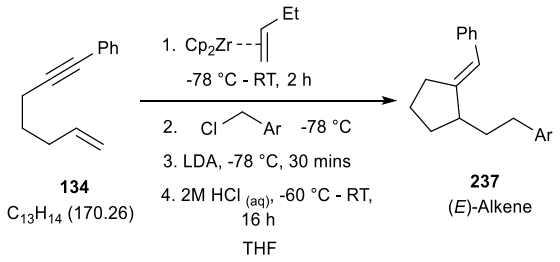
Scheme 55 – Competitive metallation of furan carbamate **230**.

Due to the commercial unavailability of 2-(chloromethyl)benzofuran **236**, this compound was prepared *via* a 3-step route (Scheme 56).[168-170] Firstly, benzofuran **233** was acylated *ortho* to the oxygen using *n*-BuLi and DMF to yield aldehyde **234** which was immediately reduced in its crude form using $NaBH_4$ to alcohol **235** (54% yield across both steps). Immediate reduction was conducted due to concerns over the stability of aldehyde **234**. Despite this, the isolated yields were much lower than expected as GC monitoring showed full conversion of starting material to product for both steps. The subsequent chlorination afforded 2-(chloromethyl)benzofuran **236** in 89% yield.



Scheme 56 – Synthetic route to 2-(chloromethyl)benzofuran **236**.

Insertion of the carbenoid prepared from 2-(chloromethyl)benzofuran **236** into the corresponding zirconacycle of enyne **134** was successful and yielded the desired (*E*)-alkene **239** in 80% yield (Scheme 57 and Table 8). 3-(Chloromethyl)pyridine **238** is commercially available as the hydrochloride salt. Base washing of this salt using sat. $NaHCO_{3\ (aq)}$ and extraction using diethyl ether allows for isolation of the free amine. However, this amine is highly unstable and polymerises within 15 minutes at room temperature forming a pale pink oil only soluble in water. Even preparing the amine directly before use and concentrating *in vacuo* at 0 °C gave a white suspension on dissolution in cold THF. Using the dried and degassed amine solution in diethyl ether from the base treatment of the salt (thus avoiding isolation of the free amine) resulted in failed carbenoid addition, possibly due to more dilute conditions and presence of diethyl ether. Attempts to generate the free amine as a solution in THF by adding 1.0 equivalent of *n*-BuLi to a stirring suspension of 1.0 equivalent of 3-(chloromethyl)pyridine salt was unsuccessful as after addition of the *n*-BuLi, undissolved amine salt remained and the mixture turned black. Finally the original procedure was used but with an excess of 3-(chloromethyl)pyridine (1.7 equivalents) with 1.0 equivalent of LDA to ensure 1.0 equivalent of carbenoid was prepared *in situ*, which gave the desired (*E*)-alkene **240** in 71% yield (Scheme 57 and Table 8).



Scheme 57 – Synthesis of (*E*)-alkenes **237** from heteroaromatic carbenoid insertion into 5-membered unsaturated zirconacyle of enyne **134**.

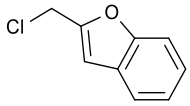
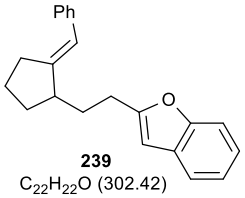
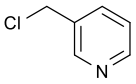
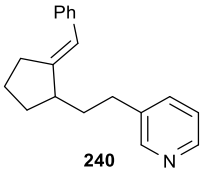
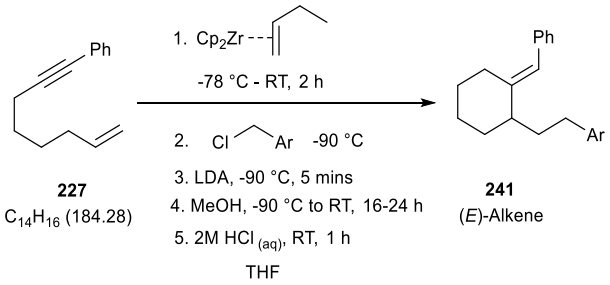
Entry	Benzyl Chloride	Product	Isolated Yield (%)
1	 **236** C_9H_7ClO (166.60)	 **239** $C_{22}H_{22}O$ (302.42)	80
2	 **238** C_6H_6ClN (127.57)	 **240** $C_{19}H_{21}N$ (263.38)	71

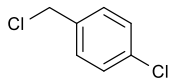
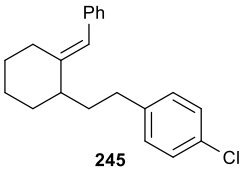
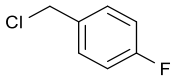
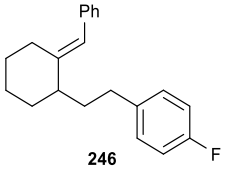
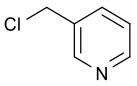
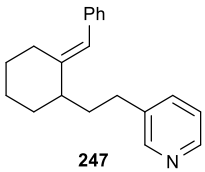
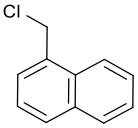
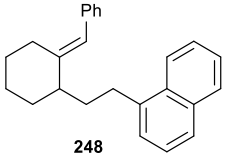
Table 8 – Summary of heteroaromatic benzyl carbenoid insertions into 5-membered unsaturated zirconacycle of enyne **134** (Scheme 57).

Furthermore, the scope of the benzyl carbenoid inserted into the zirconacycle derived from enyne **227** was expanded, resulting in the synthesis of (*E*)-alkenes **241** (Scheme 58 and Table 9). For this system which had a 6-membered ring fused by zirconocene, the use of aqueous HCl as the quench was incompatible for the clean isolation of (*E*)-alkenes **241**. Quenching with aqueous HCl afforded (*E*)-alkene **241**, *cis*-diene **256** and isomerised alkene **241b** in a 11.1:1:9.1 ratio respectively by ^{1}H-NMR (Scheme 59), as observed for the synthesis of (*E*)-alkene **245**. The formation of these products was due to a faster rate for the endocyclic cyclometallation for zirconacycles with 6-membered rings fused by zirconocene compared to 5-membered rings (as identified by L. Norman[2], Section 1.3.2.3). The use of aqueous HCl resulted in slow quenching of zirconacycle **252** as it froze on addition to the reaction at -78 °C which allowed for some cyclometallation to occur. *Cis*-diene **256** and alkene isomer **241b** are likely formed from the respective decomplexation and protic quench of **255b**, formed from cyclometallation of zirconacycle **252** followed by regioisomerisation. (This isomerisation is covered in more detail in Section 3.3). Consequently, the quench was changed to methanol and thus allowed for the synthesis of 4-chloro, 4-fluoro and 3-pyridine products **245-247** in yields ranging from 83-91% (Table 9). A lower yield of 68% for the 1-naphthalene product **248** was a result of balancing the rate of 1,2-metallate rearrangement of the zirconate species **250** after carbenoid insertion and the rate of cyclometallation on **252** (Scheme 59). Addition of MeOH five minutes after carbenoid insertion, as done for examples **245-247**, resulted in a 1:2.9 GC peak ratio between uninserted product **251** and the desired product **241** respectively (for naphthalene as Ar, Scheme 59). Increasing the time interval to 30 minutes, although resulted in full carbenoid insertion, gave the desired compound along with isomer compounds as previously described for the aqueous HCl quench. Therefore to attain the 68% yield reported for compound **248**, a time interval of 10

minutes was provided which resulted in a 1:4.6 GC peak ratio between uninserted product **251** and desired product **241** (where Ar is naphthalene, Scheme 59). The final example was the insertion of the benzofuran carbenoid into the zirconacycle of enyne **227** (Scheme 58). When using this carbenoid with methanol as the quench, two products were isolated from the reaction in a total of 88% yield for both compounds (entry 5, Table 9). Benzofuran **249a** was the expected product whereas benzofuran **249b** was an unexpected regioisomer of **249a**. Identification of this isomer was achieved using GCMS, ^{1}H-^{1}H- COSY and ^{1}H-^{13}C-HSQC NMR. ^{1}H-NMR characteristic peaks for **249b** were; 6.01 ppm (1 H, ddd, *J* 15.7, 7.2, 0.7 Hz) for Ha, 5.76 ppm (1 H, ddd, *J* 15.5, 7.6, 11 Hz) for Hb and 5.25 ppm (qd, *J* 8.01, 0.4 Hz) for Hc (entry 5, Table 9).



Scheme 58 – Benzyl carbenoid insertion into unsaturated zirconacyle of enyne **227**.

Entry	Benzyl Chloride	Product	Isolated Yield (%)
1	 **242** $C_7H_6Cl_2$ (161.03)	 **245** $C_{21}H_{23}Cl$ (310.87)	91
2	 **243** C_7H_6ClF (144.57)	 **246** $C_{21}H_{23}F$ (294.41)	83
3	 **238** C_6H_6ClN (127.57)	 **247** $C_{20}H_{23}N$ (277.41)	85
4	 **244** $C_{11}H_9Cl$ (176.64)	 **248** $C_{25}H_{26}$ (326.48)	68

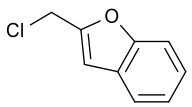
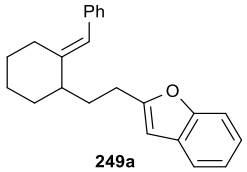
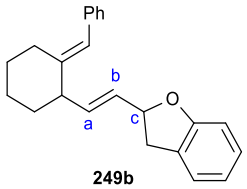
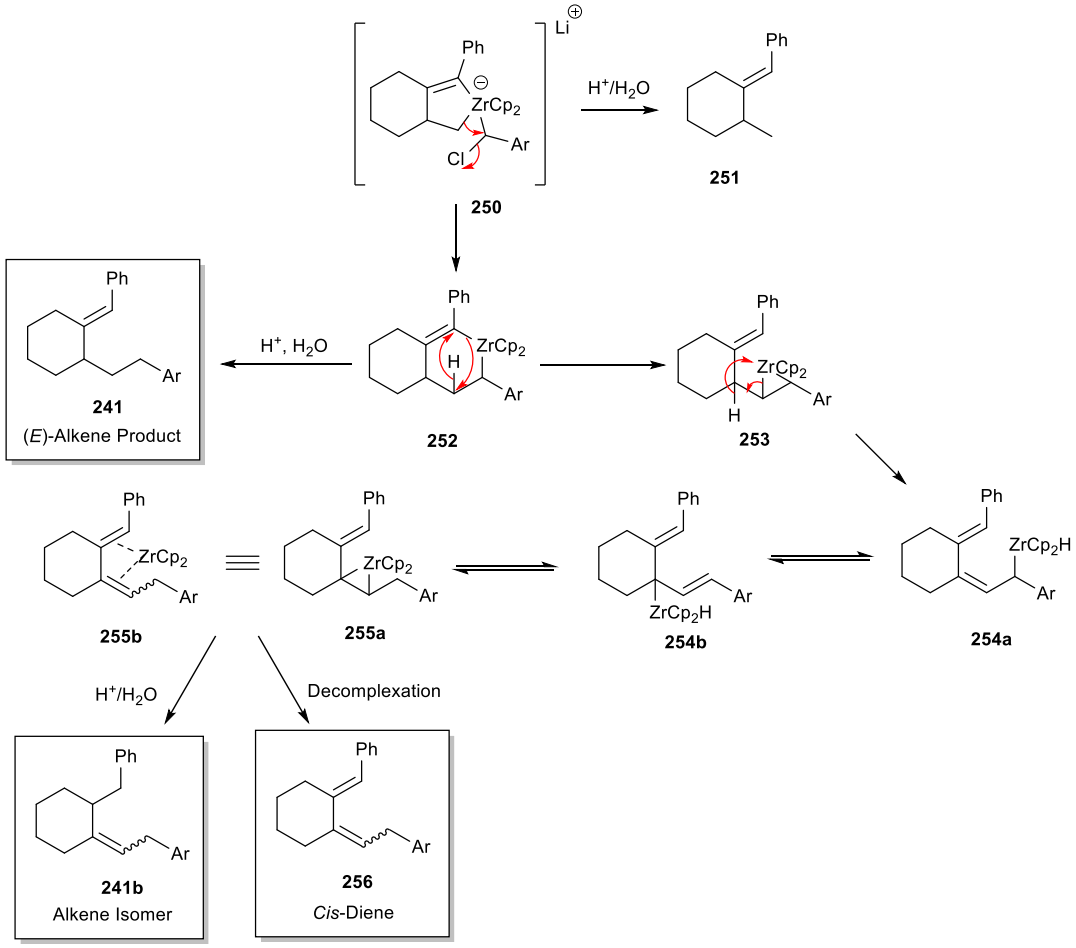
Entry	Benzyl Chloride	Product	Isolated Yield (%)
5	 **236** C_9H_7ClO (166.60)	 **249a** $C_{23}H_{24}O$ (316.44)  **249b** $C_{23}H_{24}O$ (316.44)	88 (59 **249a**) (29 **249b**)

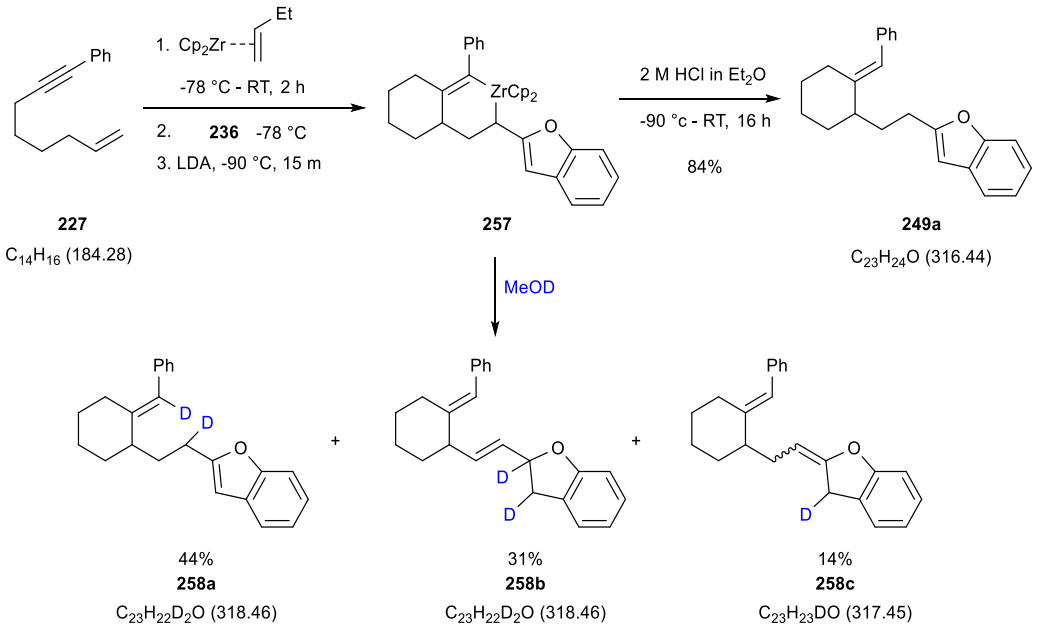
Table 9 – Summary of benzyl carbenoids inserted into zirconacyle of enyne **227** and respective products (Scheme 58).



Scheme 59 – Endocyclic cyclometallation of zirconacycle **252** to afford *cis*-diene **256** and alkene isomer **241b**.

To understand the mechanism behind the formation of unexpected benzofuran product **249b**, the reaction was repeated using deuterated methanol (MeOD-d_4) as the quench, affording three regioisomeric compounds **258a**, **258b** and **258c** in a 2.4:1.4:1 ratio respectively by ^{1}H-NMR of the crude compound (Scheme 60). Mass spectrometry confirmed the presence of two deuterium atoms on compounds **258a** and **258b** but only one deuterium on **258c** (the

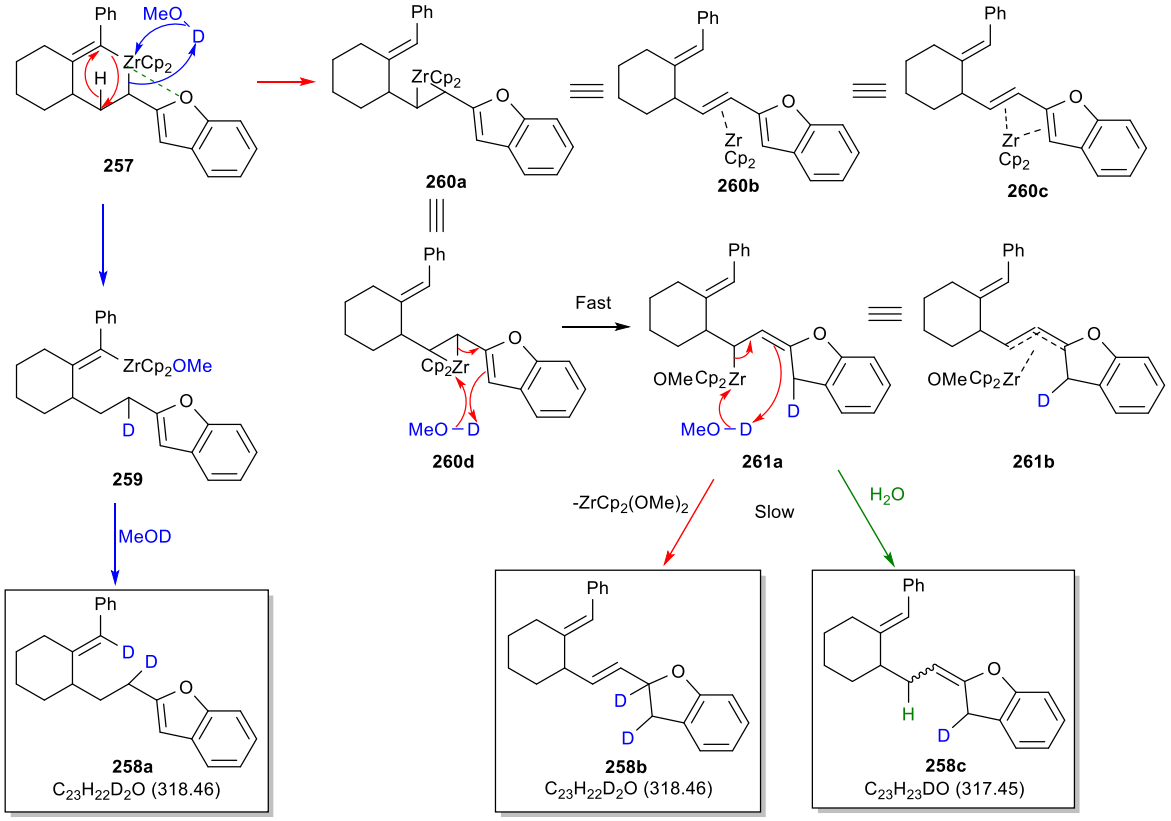
latter compound was obtained as a single isomer but with the stereochemistry undetermined). NMR identified the positioning of these deuterium atoms on the compounds as those shown in Scheme 60.



Scheme 60 – Benzofuran carbenoid insertion into unsaturated zirconacycle of enyne **227** with MeOD quench and HCl in Et_2O quench.

For compound **258a**, this was the expected compound as the quench occurs on the 6-membered zirconacycle **257** (Scheme 61). Products **258b** and **258c** had no deuteration on the benzylidene as observed with **258a**, showing that cyclometallation had occurred despite the use of methanol as the quench. A possible explanation for the formation of **258b** and **258c** was that the furan oxygen may have coordinated to the zirconium of **257**, therefore inhibiting protonlysis/ deuterolysis. The lone pair of the methanol (or water) is likely to coordinate to the zirconium in order to transfer the proton or deuterium and achieve the quench, furan oxygen could compete for this empty orbital involved (Scheme 61). An example of this is shown by certain 18-electron allylzirconocenes having water stability due to the additional coordination.[115, 171] With inhibition of the quench and upon warming from -78 °C, cyclometallation can afford complexes **260a-260d** which allows for zirconocene to coordinate onto the furan alkene forming a conjugated diene complex **260c**, formation of diene complexes are known to be favourable.[172, 173] Quenching of complex **260** with MeOD yields the regioisomer **258b**. The formation of the third regioisomer **258c** was thought to be a result of slow and, thus, incomplete quenching of allylzirconocene **261a** with MeOD and so the quench was completed on exposure to water during the work up.

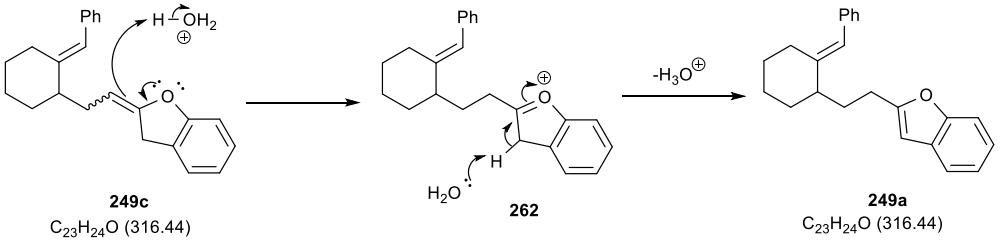
Quenching of allylic organozirconocenes (such as **260d**) tend to occur *via* a 1,3-addition resulting in an allylic rearrangement in which the most hindered end is protonated (or in this case deuterated) as zirconocene is most stable at the least hindered end, as shown in structure **261a** (Scheme 61). However, due to the structure of product **258c**, it was speculated the aqueous quench occurred *via* a 1,2-addition instead of expected 1,3-addiditon for allylic organozirconocenes, consequently yielding compound **258c** with one deuterium incorporated (Scheme 61). The slow quenching of **261a** was not surprising; allylzirconocenes are known for their high stability as Erker[174] and S. Fillery[1] have shown isolation and characterisation of allylzirconocenes. Furthermore, the mode of protonation/ deuteration of allylzirconocenes has been shown to vary, allyl complexes derived from saturated zirconacycles underwent protic quench by a 1,3-addition[171] whereas saturated zirconacycles underwent a 1,2-addition.[115]



Scheme 61 - Mechanism showing formation of regioisomers formed from benzofuran carbenoid inserton into unsaturated zirconacycle and MeOD quench.

The equivalent of **258c** with no deuterium (**249c**) was not initially observed in the MeOH quench reaction as HCl was used before the work up to ensure complete quench of the organozirconocene. Compounds **258c**/**249c** are unstable to acid therefore, in acidic conditions, these would isomerise to compounds **258a** and **249a** respectively (Scheme 62). This acid instability is supported by GC monitoring of the MeOD quenched reaction as two peaks were observed in a 2.6:1 GC peak ratio between **258a** and **258b** (similar to the MeOH

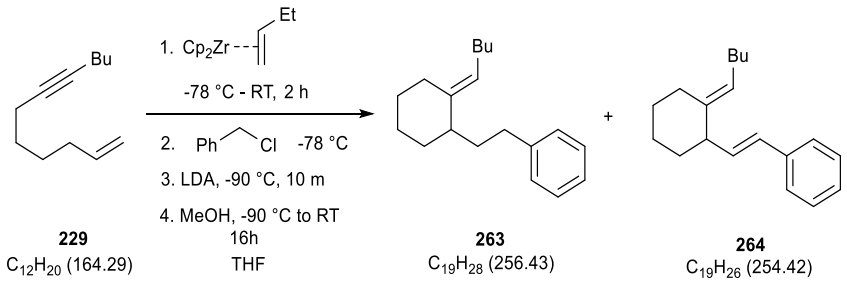
reaction) when HCl was used in the mini-work up of the sample. Due to instability of **258c**, clean isolation of the compound, and therefore full characterisation, was not possible. However, separation of all three regioisomers was relatively facile using a gradient of 5-30% CH_2Cl_2 in hexane, eluting each compound individually.



Scheme 62 – Mechanism showing acid instability of isomer **249c**.

The insertion of the carbenoid from benzofuran **236** was repeated using 2 M HCl in Et_2O as the quench, a fast quench which does not freeze under the reaction conditions. Only one product was isolated from this reaction and this was the expected product **249a** in 84% yield (Scheme 60). Therefore, the formation of the **249** and **258** isomers can be attributed to methanol being a slow quench allowing for some endocyclic cyclometallation to take place, highly favourable for the benzofuran system due to *cis*-diene complexation. Formation of regioisomers was not observed for any of the other examples shown in Table 9 as these would break the aromaticity of benzyl rings. However, the furan portion of benzofuran is less aromatic and so more reactive than substituted benzenes. Further investigation into the formation of the **249** and **258** regioisomers was not possible due to time constraints.

L. Norman reports isolation of compound **263** from benzyl carbenoid insertion into the zirconacycle of enyne **229** as a 9:1 mixture of (*E*)-alkene **263** to (*E*, *E*)-diene **264** in 55% yield (Scheme 63).[2] This was an unprecedented result as none of her other examples showed the presence of diene product(s) when quenched at low temperature. Therefore, the reaction was repeated and led to isolation of pure (*E*)-alkene **263** in 65% yield. It was speculated the presence of diene **264** for L. Norman may be due to inefficient quenching of the organozirconocene post-carbenoid insertion.

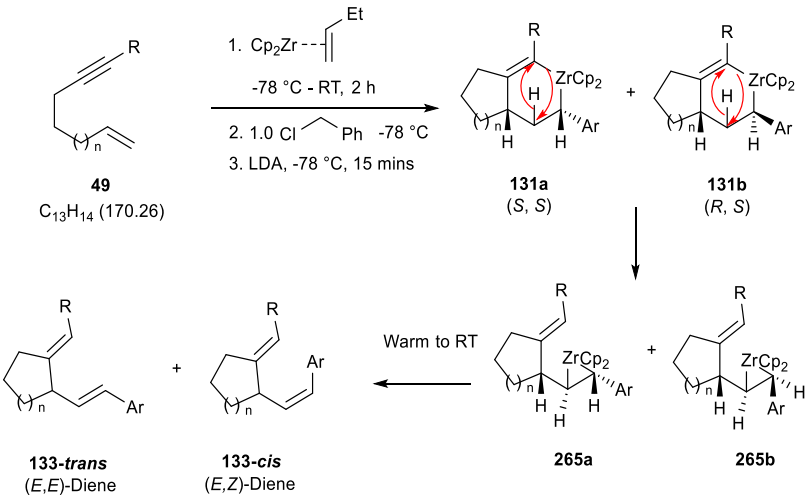


Scheme 63 – Benzyl carbenoid addition into zirconacycle of enyne **229**.

3.3 – Investigation of Conditions for the Synthesis of (*E*, *E*)- and (*E*, *Z*) Dienes

3.3.1 – Screening for a Zirconocene Trap

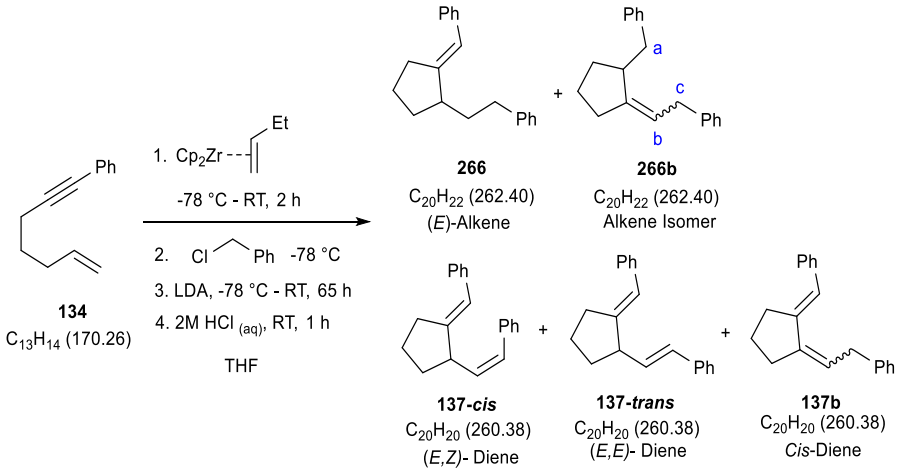
As described in Section 3.2, insertion of benzyl carbenoids into unsaturated zirconacycles yields the corresponding (*E*)-alkenes upon immediate quench of the reaction with HCl or methanol at low temperature. However, S. Fillery and L. Norman report that on warming the reaction to room temperature, the formation of dienes **133-*trans*** and **133-*cis*** were observed after endocyclic cyclometallation of zirconacycles **131a** and **131b** followed by decomplexation of zirconocene from organozirconocene **265a** and **265b** (Scheme 64).[2] However, due to isomerisation as described below, trapping of the zirconocene would be required for the clean formation of dienes **133**. In fact, isomerisation of products was illustrated in Section 3.2 (Scheme 59) for the synthesis of **241** (*E*)-alkenes as a result of slow quenching. However, L. Norman made the presumption that the zirconocene trap was the diisopropylamine present in the reaction from the *in situ* formation of the benzyl carbenoid using LDA and reports successful synthesis of various dienes **133** with these conditions (Scheme 64).[2]



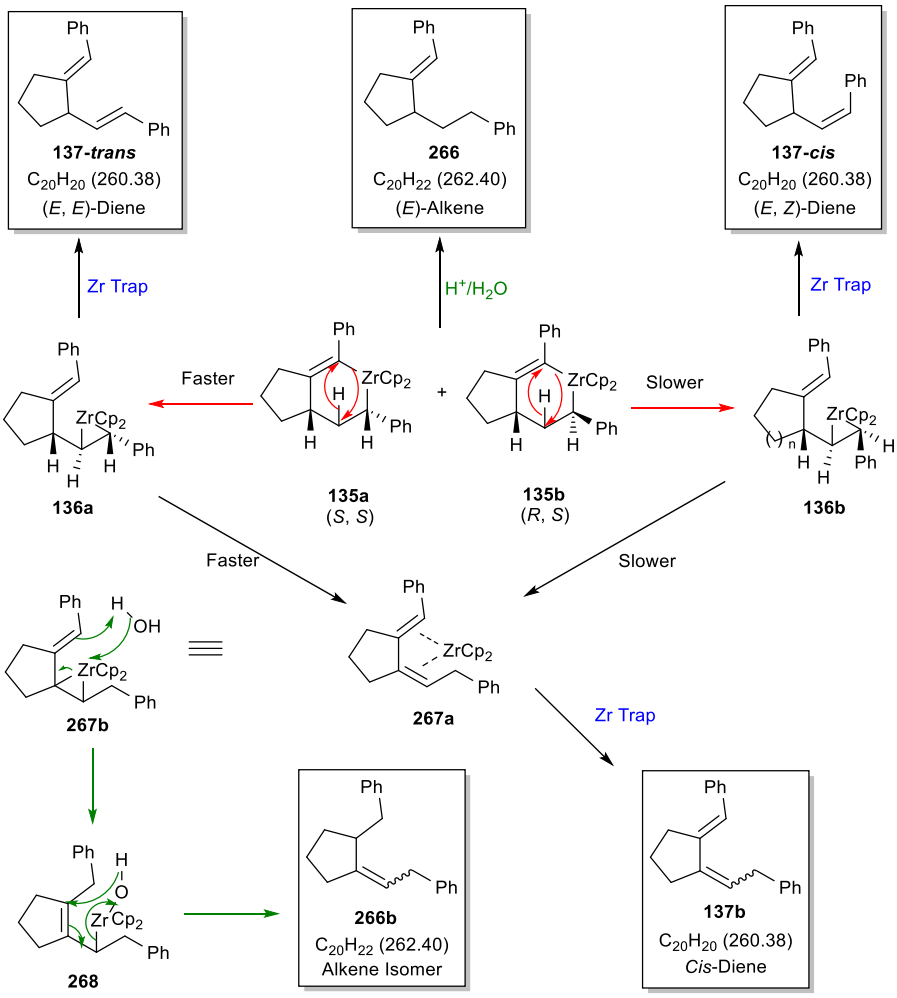
Scheme 64 – Synthesis of (*E*, *E*)- and (*E*, *Z*)-dienes **133** from benzyl carbenoid insertion into the unsaturated zirconacycle of enyne **49** as reported by L. Norman.

Therefore, L. Norman's reaction conditions were repeated in an attempt to reproduce her results for the clean synthesis of dienes **137-*cis*** and **137-*trans*** in a 1:1 ratio as she reported.[2] However, this did not lead to the clean formation of **137** *cis*/*trans* dienes but rather a mixture of three major products (**266b**, **137-*cis*** and **137b**) and several minor ones (Scheme 65). GC peak ratio of the three major isomers was 1:1.2:1.1, the former two were identified by ^{1}H-

NMR and GCMS to be diene **137-*cis*** and the isomerised alkene **266b** respectively. For isomerised alkene **266b**, ^{1}H-NMR showed the following characteristic peaks; 5.44 ppm (ttd, *J* 7.2, 2.4, 2.1 Hz) for Hb, 3.38 ppm (d, *J* 7.2 Hz) for Hc and the CH_2 of Ha was observed as separate peaks 2.96 ppm (dd, *J* 13.4, 5.1 Hz) and 2.45 ppm (dd, *J* 13.4, 9.8 Hz) in $CDCl_3$. A single isomer for **266b** was formed but identification of the alkene configuration was not possible by ^{1}H-NMR. The third major product was assumed to be the *cis*-diene **137b** due to the 260 *m/z* from GCMS however, confirmation by ^{1}H-NMR was not possible due to overlap with other peaks. The minor compounds were unidentified products from isomerisation, GCMS confirmed their masses to be mainly 262 gmol^{-1} with some 260 gmol^{-1} which corresponded to isomers of the alkene and diene products respectively. The formation of alkene isomer **266b** is proposed in Scheme 66 in which hydride abstraction results in isomerisation of zirconocene η^2-alkene complex **136** to give complex **267a** (detailed hydrogen abstraction steps were shown in Section 3.2, Scheme 59). On exposure to water from the quench, a 1,3-addition of water onto complex **267b** results in the alkene rearrangement yielding alkene **266b**. The formation of the *cis*-diene **137b** is formed from decomplexation of organozirconocene **267a** which is an outcome of the isomerisation. If an effective zirconocene trap is present, decomplexation would occur at organozirconocenes **136** to yield dienes **137-*cis*** and **137-*trans***. Slow decomplexation results in the formation of various isomers, the major two of which are shown in Scheme 65 and Scheme 66. Regioisomerisation of alkenes is known, particularly for the formation of η^4-conjugated diene zirconocene complexes (such as structure **267a**, Scheme 66) as reported by Negishi.[172, 173]

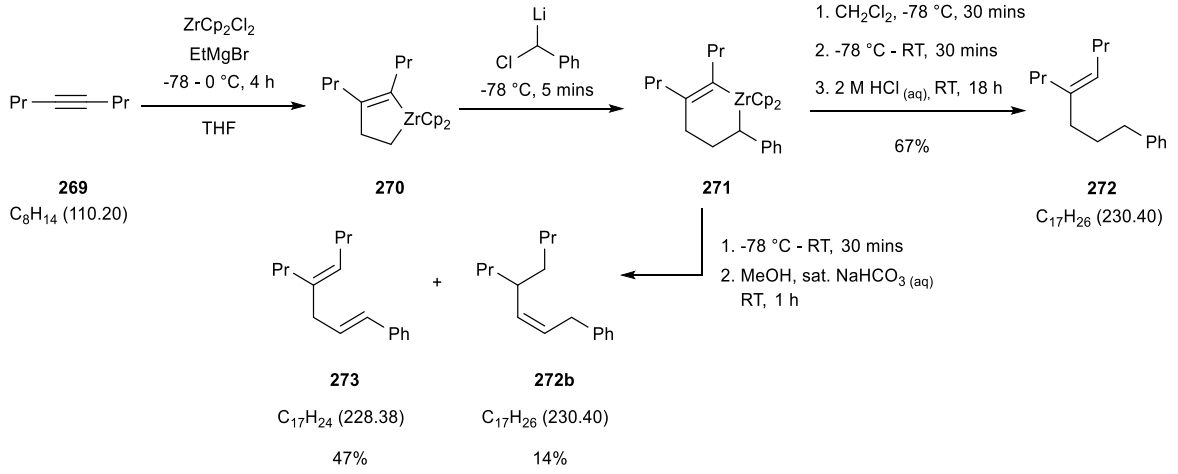


Scheme 65 – Benzyl carbenoid insertion into the unsaturated zirconacycle of enyne **134** followed by decomplexation in the presence of *i*-Pr_2NH.



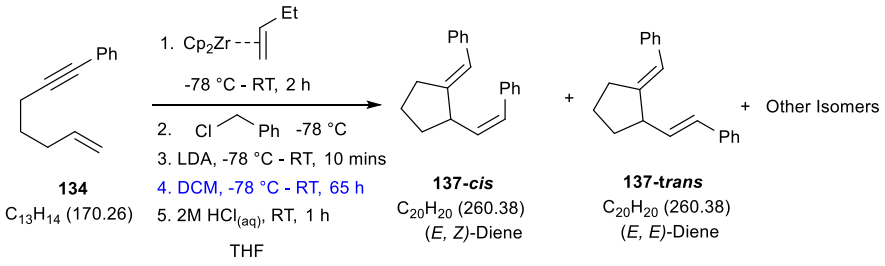
Scheme 66 – Proposed mechanism for the synthesis of products formed from reaction shown in Scheme 65.

Interestingly L. Norman only reports isomerisation of products from for the synthesis of skipped diene **273** which were products formed from benzyl carbenoid insertion into monocyclic zirconacycles followed by zirconocene decomplexation (Scheme 67). In these examples, dichloromethane is used and described as an efficient zirconocene trap for the clean synthesis of skipped diene **273**, thus avoiding alkene isomer **272b** observed in the absence of a trap,[2] which is similar to cyclic alkene isomer **266b** discussed (Scheme 66). L. Norman uses dichloromethane due to work conducted by former group member D. Norton who demonstrated that zirconocene reacted with dichloromethane.[175]



Scheme 67 – Synthesis of skipped diene **273** as reported by L. Norman.

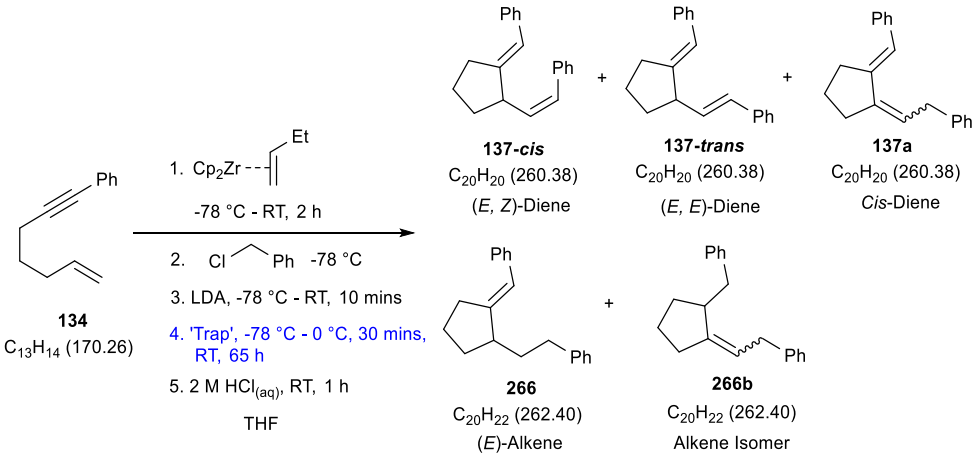
Thus dichloromethane was added to the reaction mixture, after benzyl carbenoid insertion and before warming to room temperature (Scheme 68). GC and ^{1}H-NMR analysis identified no formation of the alkene isomer product **266b** previously observed without the presence of dichloromethane however, a ratio of 2.5:1 between dienes **137-*cis*** and **137-*trans*** was obtained by ^{1}H-NMR, along with small quantities of other isomers. The reaction showed dichloromethane did behave as a zirconocene trap as it prevented the formation of the alkene isomer **266b** however, it did not cleanly yield dienes **137-*cis*** and **137-*trans*** as several small peaks were observed by GC which GCMS (EI) showed to be of *m/z* 260. Despite repeating the reaction with dichloromethane, a similar result was produced. The reaction appeared to show that organozirconocene **136a**, which leads to the formation of **137-*trans***, is more susceptible to isomerisation compared to **136b** if an efficient zirconocene trap is not present (Scheme 66). Therefore, the lower quantity of **137-*trans*** compared to **137-*cis*** is likely due to **136a** isomerising to other products faster than **136b**.



Scheme 68 – Synthesis of dienes **137** from benzyl carbenoid insertion into unsaturated zirconacycle of enyne **134**.

Consequently, in order to attain clean formation of dienes **137-*cis*** and **137-*trans*** in a 1:1 ratio as reported by L. Norman[2], a series of test reactions were conducted to identify a suitable zirconocene trap and the results were analysed by GC and ^{1}H-NMR (Table 10 and Scheme 69). Entries 1-2 investigated the use of *i*-Pr_2NH as a potential trap, as described by

L. Norman, with entry 1 only using *i*-Pr_2NH remaining from the *in situ* preparation of the carbenoid and entry 2 having an additional two equivalents of *i*-Pr_2NH added after carbenoid insertion. As demonstrated in Table 10, little difference in the outcome with different amounts of *i*-Pr_2NH present in the reaction was observed. Entry 3 repeats the use of dichloromethane as a zirconocene trap and a similar result was reproduced, the proportion of diene **137-*cis*** was much greater than that of diene **137-*trans***. Entry 4 explored the use of *n*-butylamine as a potential trap, described by L. Norman as a trap of equal efficacy as dichloromethane.[2] Monitoring of this reaction showed *n*-butylamine did not behave as a trap but rather appeared to protonate the zirconacycle after carbenoid addition yielding predominantly (*E*)-alkene product **266** (the product isolated upon immediate quench of the zirconacycle). This suggests that on coordination of the *n*-butylamine nitrogen lone pair into the empty orbital of the zirconocene, the amine hydrogens were rendered relatively acidic and subsequently quenched the organozirconocene. Finally, entry 5 investigated the use of benzyl chloride as a zirconocene trap. The reaction successfully yielded dienes **137-*cis*** and **137-*trans*** cleanly in a 1.2:1 ratio by ^{1}H-NMR respectively, which appeared as 1.1:1 GC peak ratio (Table 10).



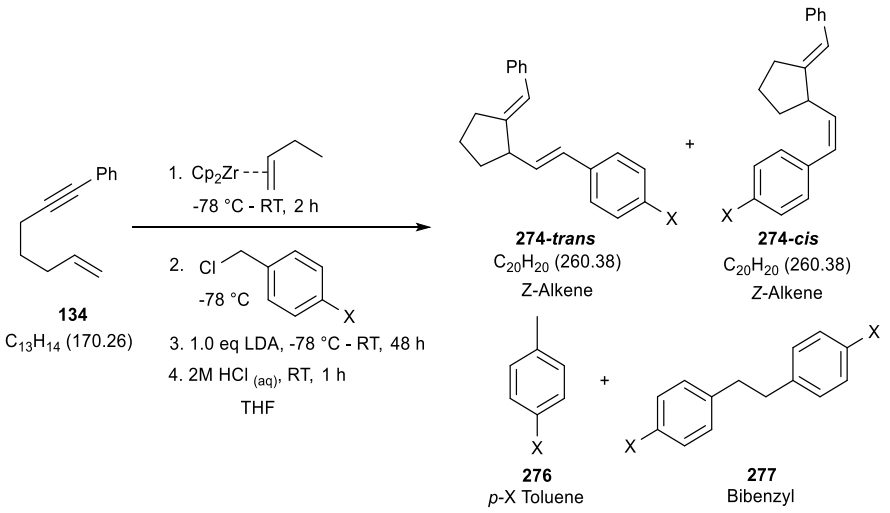
Scheme 69 – Summary of products observed from using different zirconocene traps for the clean formation of dienes **137-*cis*** and **137-*trans***.

Entry	Zirconocene Trap	Trap Molar Eq	Relative GC Peak Ratio of Compounds					Additional GC Peaks
			266	**266b**	**137-*cis***	**137-*trans***	**137 b**	
1	-	-	0.2	2.3	1	-	1.3	Other isomers
2	*i*-Pr_2NH	2.0	0.8	2.3	1	-	1.5	Other isomers
3	CH_2Cl_2	2.0	0.8	-	1	0.2	0.1	Other isomers
4	*n*-$BuNH_2$	2.0	2.5	-	1	1.1	-	Other isomers
5	BnCl	1.1	-	-	1	1.1	-	-

Table 10 – Summary of first zirconocene traps tested on the synthesis of dienes **137-*cis*** and **137-*trans***. (Scheme 69)

The synthesis of dienes **274-*trans*** and **274-*cis*** (X = H/ Cl/ OMe) was conducted on a 1.0 mmol scale using two equivalents of the respective benzyl chlorides to one equivalent of LDA (Scheme 70). As well as the formation of dienes **274-*trans*** and **274-*cis***, GC monitoring of the reaction showed the loss of the second equivalent of benzyl chloride and the appearance of two new peaks. One of these peaks corresponded to bibenzyl **277** (X = H/ Cl/ OMe), identified by GCMS and ^{1}H-NMR. The second peak eluted close to the solvent front for all examples so corresponded to a compound of high volatility. Due to this volatility, analysis of this compound was not possible by ^{1}H-NMR and GCMS. However, compound **276** (X=H) eluted at the same retention time as toluene by GC. Therefore the volatile compounds were believed to be the corresponding *para*-substituted toluene **276** (X = H/ Cl/ OMe). The dienes (**274**) were formed cleanly with the GC peak ratios and ^{1}H-NMR compound ratios generally consistent with each other (Table 11). For all examples, a greater amount of **274-*trans*** was formed than **274-*cis*** which was initially speculated to be due to the quantity of excess benzyl chloride added. With measurement error, at least one equivalent may not remain in the reaction mixture to behave as the zirconocene trap after addition of LDA. Therefore reaction entry 1 (Table 11) was repeated with three equivalents of benzyl chloride (entry 4) which again gave a 1.2:1 ratio between dienes by ^{1}H-NMR.

This reactivity of benzyl chlorides with zirconocene η^2-alkene complexes was explored and discussed further in Chapter 4.



Scheme 70 – Summary of products observed from using benzyl chloride as a zirconocene traps.

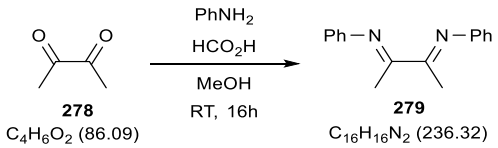
Entry	X	Total *p*-XBnCl Eq	Dienes **274** *trans*:*cis* GC Peak Ratio	Dienes **274** *trans*:*cis* ^{1}H-NMR Ratio
1	H	2.0	1.2 : 1	1.2 : 1
2	Cl	2.0	1.3 : 1	1.3 : 1
3	OMe	2.0	1.1 : 1	1.2 : 1
4	H	3.0	1.2 : 1	1.2 : 1

Table 11 – Summary of dienes **274-*trans*** and **274-*cis*** ratios for decomplexation using benzyl chlorides as zirconocene traps (Scheme 70).

As having an excess of benzyl chloride was the only reagent which successfully behaved as a zirconocene trap for the synthesis of dienes **274-*trans*** and **274-*cis***, it was assumed L. Norman was inadvertently adding an excess of benzyl chloride for the benzyl carbenoid insertion step. Consequently, it was this additional benzyl chloride present in the reaction mixture which behaved as the zirconocene trap allowing for clean formation of dienes **274-*trans*** and **274-*cis***. For her synthesis of the skipped dienes **273** (Scheme 67), the appearance of isomers may have been due to inconsistencies in the quantity of excess benzyl chloride being added, which was solved with the addition of dichloromethane along with the excess benzyl chloride. Furthermore, the inconsistency in the dienes **274-*trans*** and **274-*cis*** ratios obtained compared to the 1:1 ratios reported L. Norman may also be an error. Forming a greater amount of diene **274-*trans*** is more consistent with the DFT calculations reported by L. Norman as it showed *trans* dienes can be formed from both zirconacycles (Scheme 18 and Section 1.3.2.3).

Despite good results with the use of benzyl chloride as the zirconocene trap, further test reactions were carried out to identify a zirconocene trap which would yield either volatile or

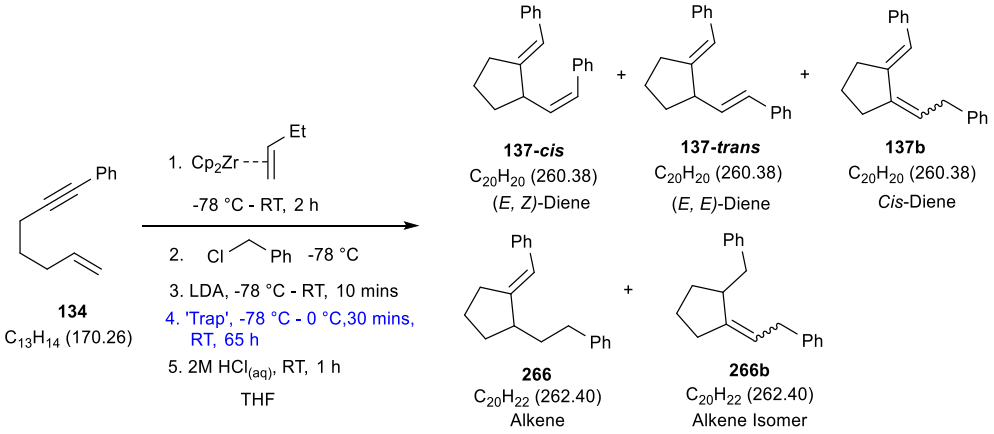
polar products that would allow for easy separation from the dienes (**274**, Scheme 70). Consequently, 1,2-bis(methylamino)ethane (DMEDA), diphenylbutane-2,3-diimine, acetonitrile, nitromethane and chloroform were chosen as potential zirconocene traps to be trialled. All of these compounds were commercial except for diphenylbutane-2,3-diimine **279** which was synthesised using literature precedent from diacetyl **278** and aniline in methanol with catalytic formic acid in 36% yield. Although the yield was low, further crystallisations and filtrations could have isolated more material to achieve the 69% reported in the literature.[176] However, this was deemed unnecessary as sufficient material had been isolated for the purposes of trialling the compound as a zirconocene trap.



Scheme 71 – Synthesis of diphenylbutane-2,3-diimine **279**.

The five compounds (DMEDA), diphenylbutane-2,3-diimine **279**, acetonitrile, nitromethane and chloroform were trialled as zirconocene traps in the same manner discussed previously, the summary of which is shown in Scheme 72 and Table 12. Secondary amine DMEDA was chosen as primary amine (*n*-butylamine) quenched the organozirconocene and *i*-Pr_2NH (a secondary amine) was potentially too bulky to work effectively as a trap. DMEDA was chosen due to being less sterically hindered compared to *i*-Pr_2NH but also due to its potential to coordinate to zirconocene in a bidentate manner allowing for decomplexation. Diimine **279** was also trialled as it could form a 1,4-diazadiene complex with zirconocene. Unfortunately, neither of these compounds worked successfully as zirconocene traps (entries 1 and 2) using either one or two equivalents. Although diimine **279** led to less isomerisation, neither the DMEDA nor diimine **279** resulted in clean formation of dienes **137-*trans*** and **137-*cis***. Subsequently, entries 3 and 4 investigated the use of nitriles and nitro compounds as traps. Nitriles have a long precedence for reacting with metallocenes, most commonly known for their use in synthesising substituted pyridines.[177] A higher equivalent of acetonitrile (20.0 eq) was used for the test reaction due to the slow reactivity of nitriles with zirconocene reported in the literature.[178] Acetonitrile did not behave as a zirconocene trap, instead it showed insertion into the organozirconocene yielding a compound of 304 *m/z*, the structure of which could not be elucidated by ^{1}H-NMR. Nitromethane also did not behave as a trap but instead quenched the reaction to yield predominantly (*E*)-alkene **266**. This was attributed to the acidity of the nitromethane methyl protons which had more of an effect than expected. The reaction was repeated using nitrobenzene to avoid the problem but this was

also not successful and showed the appearance of new compounds of higher mass. Finally, exploring the interesting reactivity of zirconocene with carbon-chloride bonds as shown with the use of dichloromethane and benzyl chloride as a trap, chloroform was trialled (entry 5). This proved to be successful as clean formation of dienes **137-*cis*** and **137-*trans*** was observed. However, the quantity of (*E*)-alkene **266** remaining was attributed to the chloroform not being completely anhydrous therefore on second attempt, the chloroform was extensively dried over calcium chloride overnight before use. This successfully yielded dienes **137-*trans*** and **137-*cis*** in a 1.2:1 ratio respectively (but appeared as a 1:1 GC peak ratio) with no (*E*)-alkene **266** remaining.



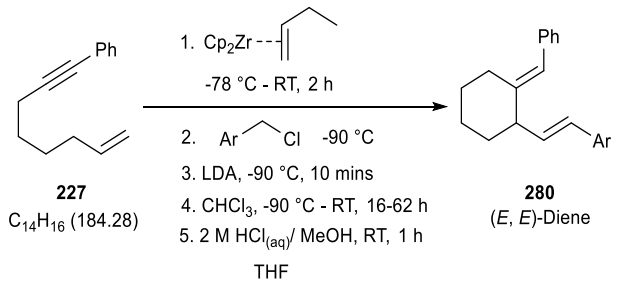
Scheme 72 - Summary of products observed from using different zirconocene traps for the clean formation of dienes **137-*cis*** and **137-*trans***.

Entry	Zirconocene Trap	Trap Eq	Relative GC Peak Ratio of Compounds					Additional GC Peaks
			266	**266b**	**137-*cis***	**137-*trans***	**137b**	
1	Diamine	1.1	0.6	0.1	1	-	0.7	-
		2.0	0.7	0.1	1	-	2.5	
2	Diimine	1.1	-	-	1	0.1	0.7	-
		2.0	-	-	1	0.3	0.3	
3	MeCN	20.0	0.4	-	1	0.1	0.2	Addition product.
4	$MeNO_2$	2.0	3.6	-	1	5.7	-	-
	$PhNO_2$	2.0	-	-	1	29.2	-	Other Compound.
5	$CHCl_3$	1.2	0.1	-	1	1.2	-	-
		2.0	-	-	1	1	-	-

Table 12 - Summary of first zirconocene traps tested on the synthesis of dienes **137-*cis*** and **137-*trans***. (Scheme 72).

3.3.2 – Synthesis of (*E*, *E*)-/ (*E*, *Z*)-Dienes

A series of (*E*, *E*)-dienes (**280**) were prepared from benzyl carbenoid insertion into the unsaturated zirconacycle of enyne **227**, followed by decomplexation with the use of chloroform as a zirconocene trap (Scheme 73). Yields obtained for compounds **281**-**285** were in the range of 40-86% (Table 13).



Scheme 73 - Benzyl carbenoid insertion into unsaturated zirconacyle of enyne **227** followed by decomplexation.

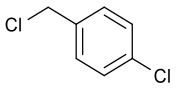
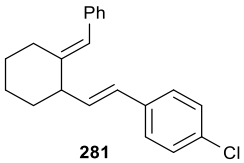
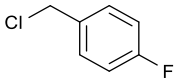
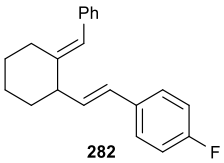
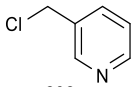
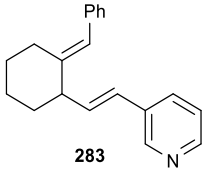
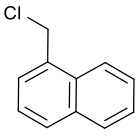
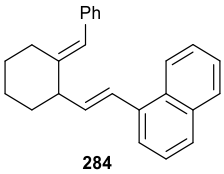
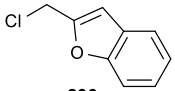
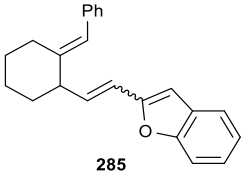
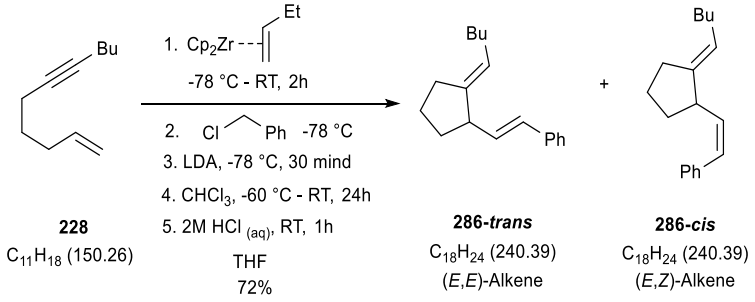
Entry	Benzyl Chloride	Product	Crude GC Peak Ratio of (*E*,*E*)/ (*E*, *Z*)-Dienes	Isolated Yield (%)
1	 **242** $C_7H_6Cl_2$ (161.03)	 **281** $C_{21}H_{21}Cl$ (308.85)	20.5 : 1	86
2	 **243** C_7H_6ClF (144.57)	 **282** $C_{21}H_{21}F$ (292.40)	19.1 : 1	84
3	 **238** C_6H_6ClN (127.57)	 **283** $C_{20}H_{21}N$ (275.39)	20.6 : 1	61
4	 **244** $C_{11}H_9Cl$ (176.64)	 **284** $C_{25}H_{24}$ (324.47)	34.3 : 1	72
5	 **236** C_9H_7ClO (166.60)	 **285** $C_{23}H_{22}O$ (314.43)	2.3 : 1	40

Table 13 - Summary of benzyl carbenoids inserted into zirconacyle of enyne **227** followed by decomplexation using conditions specified in Scheme 73.

Interestingly, L. Norman reports no formation of the (*E*, *Z*)-dienes for **280** compounds[2] however, on close analysis of the GC and ^{1}H-NMR obtained of the crude products **281**-**285**, very small quantities of (*E*, *Z*)-dienes were observed (Table 13). An exception for this was the benzofuran compound **285** which had a much greater proportion of (*E*, *Z*)-diene than the other compounds, a 2.3:1 **285-*trans*** to **285-*cis*** respectively by crude ^{1}H-NMR and by GC peak ratio. This variation may be a result of coordination of the benzofuran oxygen onto the zirconocene resulting in a reduced preference for the formation of **285-*trans*** from the corresponding (*R*,*S*) zirconacycle (Section 1.3.2.3). Column chromatography allowed isolation of the pure (*E*, *E*)-dienes for compounds **281**-**284**. A lower yield of 40% for the benzofuran example **285** was a result of degradation. After storage at room temperature and in the presence of air before final purification, the **285** product with a 2.4:1 *trans* to *cis* ratio changed to 1.2:1 *trans* to *cis* by ^{1}H-NMR with the appearance of baseline impurities previously not present.

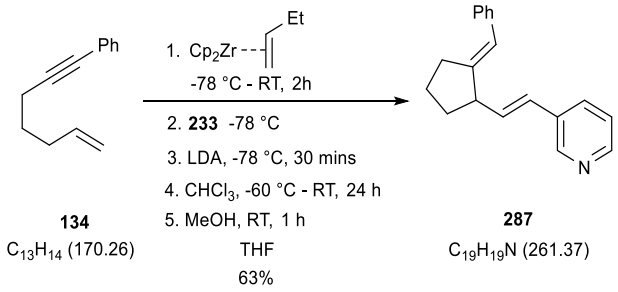
Section 3.3.1 showed how the presence of different zirconocene traps, particularly dichloromethane, affected the ratio between (*E*, *E)*- and (*E*, *Z)*-dienes from zirconocene decomplexation. L. Norman reports the synthesis of **286** dienes in 53% yield with a ratio of 3:1 between *trans* and *cis* respectively (Scheme 74).[2] To confirm that a greater proportion of (*E*, *E*)-diene is formed in this example, the reaction was repeated using chloroform as the zirconocene trap. ^{1}H-NMR of the crude compound showed a 2.6:1 ratio between dienes **286-*trans*** and **286-*cis*** respectively, which was consistent with the results reported by L. Norman with significantly greater (*E*, *E*)-alkene being formed.



Scheme 74 – Synthesis of compound **286** using chloroform as the zirconocene trap.

Furthermore, insertion of 3-pyridine benzyl chloride into the zirconacycle of enyne **134**, followed by decomplexation, was carried out to prepare compound **287** in 63% yield (Scheme 75). Unlike for the 5-membered ring compounds discussed in Section 3.3.1 for the test reactions which showed an average of 1.2:1 ratio between *trans* and *cis* dienes by ^{1}H-NMR, a larger ratio difference between the pyridine dienes **287** was obtained (6.5:1 ratio favouring the *trans* by ^{1}H-NMR). Introducing a pyridine made little difference on the 6-

membered ring system (compound **247**, Table 13) however, a significant difference was observed for the 5-membered ring system. This difference is speculated to be due to more (*R*,*S*) zirconacycle forming the (*E*, *E*)-diene, potentially caused by the pyridine reducing the energy of the (*R*,*S*) zirconacycle chair-like conformer (Section 1.3.2.3).

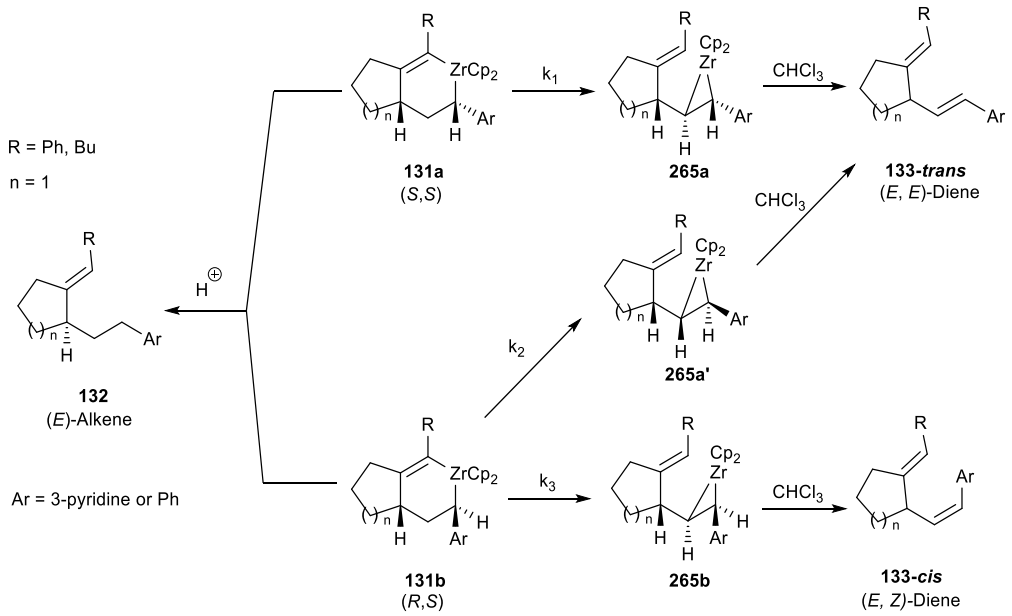


Scheme 75 – Synthesis of compound **287** from 3-pyridine benzyl chloride insertion and decomplexation with chloroform.

3.3.3 – (*E*, *E*)-/ (*E*, *Z*)-Diene Kinetics

Kinetic studies conducted by L. Norman showed the rate of formation for (*E*, *E*)-dienes was significantly faster than that of (*E*, *Z*)-dienes, by 1 or 2 orders of magnitude.[2] Furthermore, she also showed the kinetics are largely unaffected by the aryl group introduced from the carbenoid insertion. L. Norman only investigated the effect of the aryl group with *para*-methoxy and *para*-chloro phenyl, therefore kinetic studies were carried out on the 3-pyridine aryl group (a much stronger electron withdrawing aryl group), which affords dienes **287-*cis*** and **287-*trans*** (Scheme 75). In addition, for better quality results, the kinetics for the formation of dienes **286-*cis*** and **286-*trans*** was also investigated (Scheme 74).

As discussed in Section 1.3.3.3, zirconacycles **131a** and **131b** are formed from benzyl carbenoid insertion into unsaturated zirconacycles. After endocyclic cyclometallation and decomplexation, (*S*, *S*) zirconacycle **131a** affords diene **133-*trans*** (k_1) and (*R*, *S*) zirconacycle **131b** affords diene **133-*cis*** (k_3). However, DFT calculations showed (*R*,*S*) zirconacycle **131b** can also form **131-*trans*** (k_2) depending on which low energy conformation (*R*,*S*) zirconacycle **131b** adopts for the cyclometallation. The significance of pathway k_2 depends on the relative energy levels of (*R*,*S*) zirconacycle **131b** conformers. Therefore there are two pathways for the formation of diene **133-*trans*** (k_1 and k_2) which explains why greater amounts of (*E*,*E*)-dienes have been shown to form. This is summarised in Scheme 76.



Scheme 76 – Organozirconocene intermediates and pathways for the formation of (*E*)-alkene, (*E*,*E*)-diene and (*E*,*Z*)-diene.

Kinetic studies were conducted *via* GC monitoring of the reaction after benzyl carbenoid addition. All organozirconocenes in Scheme 76 are observed as (*E*)-alkene **132** upon protic quench, therefore directly observing the consumption of zirconacycles **131a** and **131b** for the formation of the dienes **133** was not possible. Furthermore, the following assumptions were made for the kinetic studies; (*E*)-alkene **132**, (*E*,*E*)- and (*E*,*Z*)-alkenes **133-*trans*** and **133-*cis*** all have the same response factor by GC-FID (as GC ratios were generally consistent with ^{1}H-NMR ratios), k_1 can be obtained from the initial slope of first order reaction plot and k_2+k_3 from the second slope (as effectively only zirconacycle **131a** is reacting initially as formation of **133-*trans*** immediately observed) and any remaining zirconacycle (which is observed as (*E*)-alkene **132** by GC) goes to the formation of (*E*,Z)-alkene **133-*cis***.

First order rate plots were obtained from monitoring the loss of zirconacycles **131a** and **131b** for the formation of the dienes **287** and **286** by GC (Figure 19 and Figure 20). Two slopes were observed in the graphs, the first for k_1 and the second for k_2+k_3. As L. Norman shows there are equal amounts of zirconacycles **131a** and **131b**, the rates for k_2 and k_3 can be obtained from the final ratios of the products (Table 14). On comparing the reaction rates of the pyridine compound with the *para*-methoxy and *para*-chloride phenyl examples conducted by L. Norman, the result was consistent with the reaction rates being largely unaffected by the aryl group. However, the aryl group does affect the ratio of (*E*,*E*)- and (*E*,*Z*)-alkenes (**133**) significantly and thus the amount of zirconacycle **131b** going to (*E*,*E*)-alkene **133-*trans*** (k_2). It appears that the presence of a greater electron-withdrawing aryl

group, results in more of zirconacycle **131b** adopting the conformation which results in the formation of (*E*,*E*)-alkene **133-*trans***.

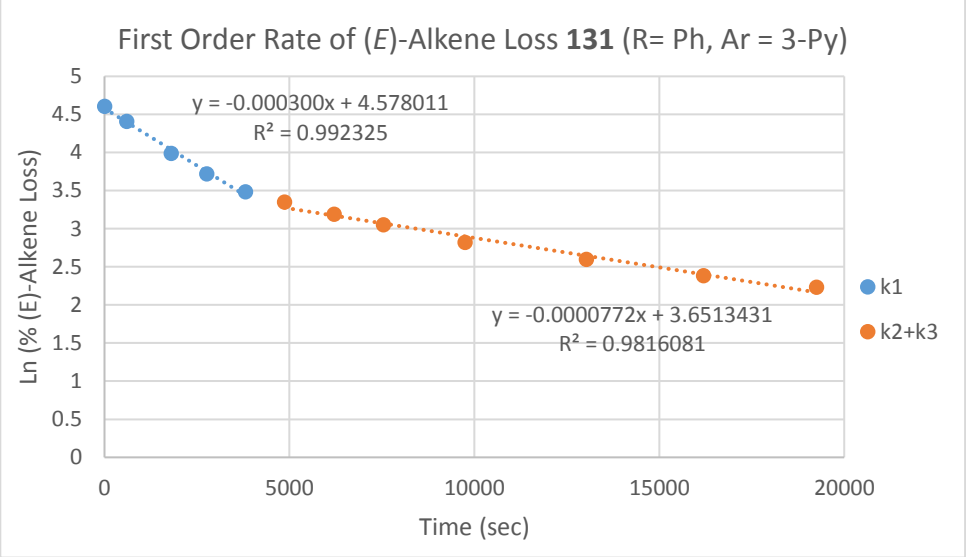


Figure 19 – First order kinetics plot of zirconacycles **131a** and **131b** consumption for the formation of (*E*,*E*)- and (*E*,*Z*)-alkenes **287 (**Scheme 75 and Scheme 76).

Entry	R	Ar	**132** : **133-*cis*** : **133-*trans*** GC Peak Ratio	k1 (s^{-1})	k2+k3 (s^{-1})	k2 (s^{-1})	k3 (s^{-1})
1	Ph	3-Py	1.5 : 1 : 15.5	3.00×10^{-4}	7.72×10^{-5}	5.56×10^{-5}	2.16×10^{-5}
2	Bu	Ph	1 : 6.0 : 18.0	7.76×10^{-4}	1.97×10^{-4}	8.47×10^{-5}	1.12×10^{-4}

Table 14 – Kinetics data obtained from first order plots for the synthesis of dienes **287** and **286** (Scheme 76, Figure 19 and Figure 20).

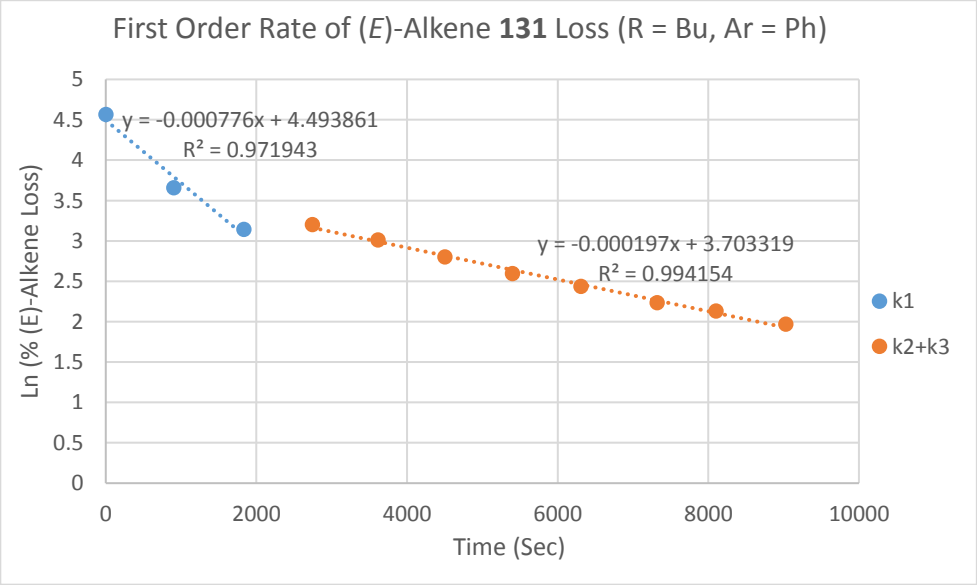


Figure 20 – First order kinetics plot of zirconacycles **131a** and **131b** consumption for the formation of (*E*,*E*)- and (*E*,*Z*)-alkenes **286 (**Scheme 74 and Scheme 76).

3.4 – Conclusions for Chapter 3

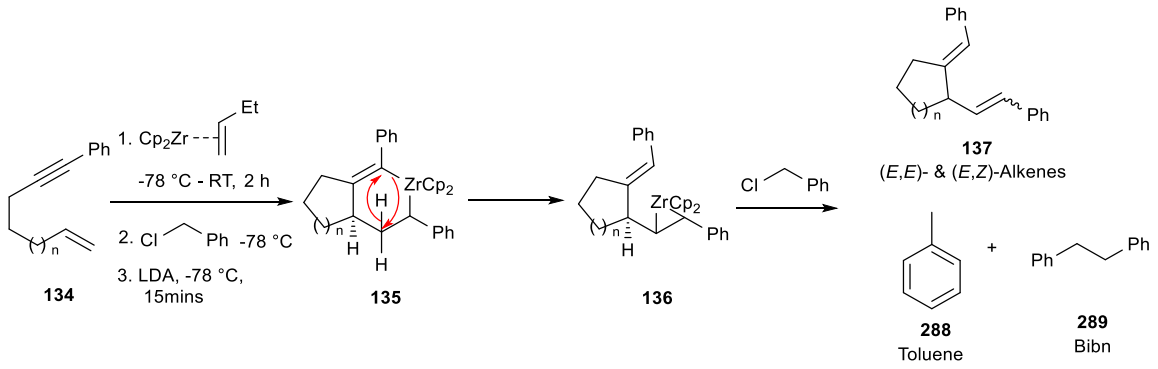
In conclusion, the scope for the insertion of benzyl carbenoids into unsaturated zirconacycles was broadened to include heteroaromatics, such as 3-pyridine and 2-benzofuran, but also naphthalene and 4-fluorobenzene. These benzyl carbenoids were inserted into zirconacycles with 5-membered and 6-membered rings fused by zirconocene, with particular focus on the 6-membered ring systems. Yields ranged from 68-91%. In order to synthesis (*E*, *E*)- and (*E*, *Z*)-dienes after carbenoid insertion, a series of potential zirconocene traps were trialled to identify one which allowed for clean formation of the dienes and no isomerisation. The best zirconocene traps were identified to be benzyl chlorides and chloroform, the latter being the most favourable due to the lack of products present in isolated crude compounds. Dienes were synthesised successfully for 6-membered (and some 5-membered) ring systems in yields ranging from 40-86%.

Chapter 4 – Insertion of Benzyl Chlorides into Zirconocene η^2-Alkene Complexes

The work described in this chapter probes the unprecedented reactivity of benzyl chloride with zirconocene(1-butene) initially introduced in Chapter 3. In addition to determining the scope of benzyl chloride reactions with zirconocene, such as functional group tolerance and subsequent insertion of carbenoids, mechanistic understanding of the reaction is explored. Ultimately, the utility of the reaction is demonstrated in the synthesis of tri-substituted alkenes from a novel one-pot three-component coupling reaction.

4.1 – Exploring the Reactivity of Benzyl Chloride with Zirconocene

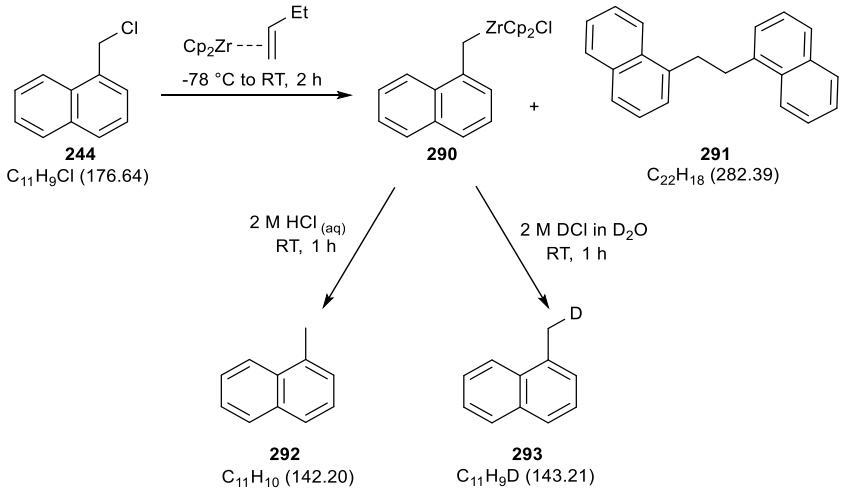
As discussed in Chapter 3, benzyl chloride was shown to react with η^2-alkene complexes of zirconocene. Benzyl chloride behaved as a zirconocene trap on organozirconocene species **136** allowing for clean dissociation of the zirconocene to yield (*E*, *E*)- and (*E*, *Z)*-alkenes **137-*trans*** and **137-*cis***, thus avoiding isomerisation of the alkene products. Consequently, two products were identified by GC and GCMS of the reaction mixture from this zirconocene trapping with benzyl chloride, toluene **288** and bibenzyl **289** (Scheme 77).



Scheme 77 – Benzyl carbenoid insertion into unsaturated zirconacyles followed by zirconocene decomplexation of organozirconocene **136** with the use of benzyl chloride as a zirconocene trap.

To further investigate the reactivity of benzyl chlorides with η^2-alkene complexes of zirconocene, a benzyl chloride that would yield an isolatable methylarene was required, allowing for better GCMS and NMR analysis of the products. Therefore, 1-naphthylmethyl chloride **244** was stirred in the presence of zirconocene(1-butene), generated *in situ* from the Negishi reagent Cp_2ZrBu_2, which resulted in the formation of two products, identified by ^{1}H-NMR and GCMS as 1-methylnaphthalene **292** and 1,2-di(1-naphthyl)ethane **291** (Scheme 78). The formation of these products demonstrated that the reaction was

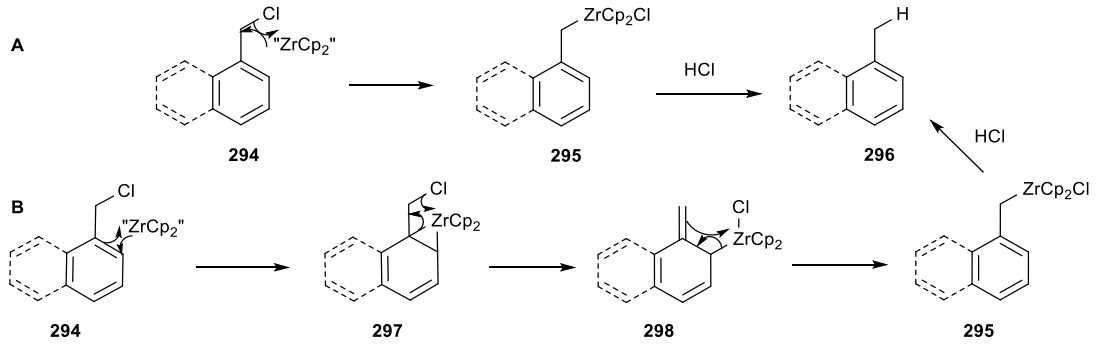
reproducible with a different benzyl chloride and a different alkene complex (Scheme 77). On repeating the reaction using DCl in D_2O instead of aqueous HCl as the quench, deuterium incorporation was observed for compound **293** (>90% by ^{13}C-NMR) but not on 1,2-di(1-naphthyl)ethane **291**. This showed that the 1-methylnaphthalene **292** product had a C-Zr bond prior to quench, organozirconocene intermediate **290**, whereas the bibenzyl **291** did not (Scheme 78). Repeating the reaction with frequent GC monitoring showed both products began to form at 0 °C, significantly the temperature at which zirconocene(η^2-1-butene) is formed from dibutylzirconocene and suggests that both products are formed from a reaction with zirconocene(1-butene). GC monitoring showed the reaction reached completion within 1.5 to 2 hours at room temperature. Adding a mixture of benzyl chloride and 1-naphthylmethyl chloride **244** (0.5 equivalents each) to zirconocene(1-butene) resulted in the cross-coupling of benzyl chlorides to yield 1-phenethylnaphthalene along with the homocoupled bibenzyls (**289** and **291**), toluene **288** and 1-methylnaphthalene **292**.



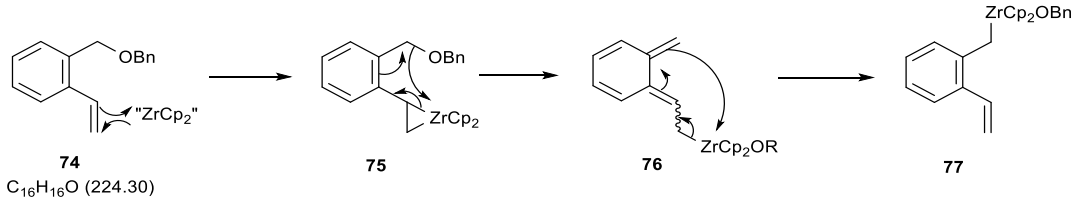
Scheme 78 – Reaction between 1-naphthylmethyl chloride and the zirconocene(1-butene).

A proposed mechanism for the formation of methylarene **296** is through insertion of the zirconocene into the benzyl C-Cl bond of **294** (A) or by insertion into the aryl ring followed by migration (B). Protic quench of the benzylzirconocene **295** cleaves the C-Zr bond forming the methylarene **296** (Scheme 79). Mechanism 'B' is similar to the insertion of zirconocene into allylic ethers as reported by Taguchi (Section 1.3.1.3), a methodology later extended to benzylic ethers with *ortho*-vinyl substituents, for which the vinyl group is indispensable for the reaction as no product formation occurs without it (Scheme 80).[81, 82, 84, 90-94, 96, 179, 180] Currently there is no literature precedent for the insertion of zirconocene directly to benzyl halides. The formation of benzylzirconocene chloride has only recently been reported but *via* the reaction of benzyl Grignard **300** with zirconocene dichloride (Scheme 81).[181]

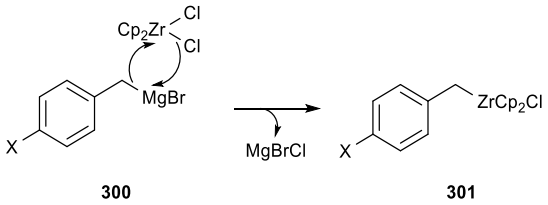
For the formation of the bibenzyl, Section 4.3 will discuss the experiments carried out to investigate the mechanism.



Scheme 79 – Proposed mechanism for zirconocene insertion into benzyl chloride where "$ZrCp_2$" refers to zirconocene(1-butene).



Scheme 80 – Zirconocene insertion into allylic ethers and *ortho*-vinylbenzyl ethers as reported by Taguchi.



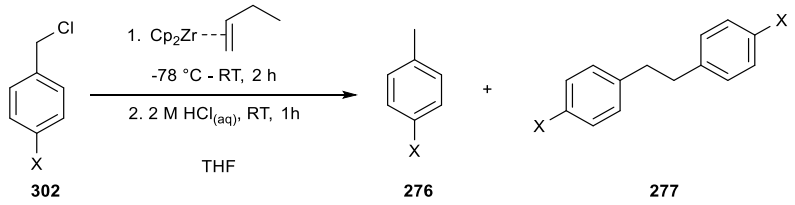
Scheme 81 – Benzylzirconocene chloride formation from benzyl Grignard and zirconocene dichloride.

4.2 – Assessment of the Reaction Scope

4.2.1 – Varying the Aryl Moiety

To determine the scope of benzyl chloride insertion into zirconocene, various *para*-substituted benzyl chlorides **302** were reacted with zirconocene(1-butene) to identify which functional groups were compatible with the reaction (Scheme 82 and Table 15). Entries 1 to 7 worked successfully and showed the formation of the corresponding methylarene **276** and bibenzyl **277** by GC, GCMS and ^{1}H-NMR. These results show the reaction tolerates electron-withdrawing substituents (such as trifluoromethyl and 4-pyridine) as well as electron-donating substituents (such as methoxy). However, the formation of the trifluoromethylbenzylzirconocene **317** was found to be unstable as disappearance of this product was observed by GC, most notably after 1.5 hours reaction time. This observation

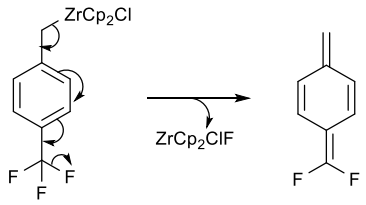
is assumed to be due to the loss of fluoride from the molecule as proposed in Scheme 83, however confirmation by GCMS was not possible due to volatility. For the *p*-vinylbenzyl chloride, corresponding methylarene **276** and bibenzyl **277** were observed by GC and GCMS along with other products formed from the insertion of zirconocene into the vinyl group. The *para*-nitro (entry 11) was unsuccessful and remained mostly unreacted over an extended reaction time of 40 hours, with some formation of an unknown compound of *m/z* 210 identified by GCMS (EI). The lack of reactivity of *para*-nitrobenzyl chloride with zirconocene in the desired manner presumable due to the nitro group reacting with zirconocene. Conversely, *para*-nitrile (entry 10) showed the formation of several unknown products by GCMS.



Scheme 82 – Reaction of *para*-substituted benzyl chlorides with the zirconocene(1-butene).

Entry	BnCl Substituent 'X'	Methylarene Compound No.	Bibenzyl Compound No.	Average GC Peak Ratio **276** : **277**	Isolated Bibenzyl **277** Yield (%)
1	H	**288**	**289**	2.2 : 1	14
2	Cl	**303**	**310**	2.0 : 1	19
3	F	**304**	**311**	1.9 : 1	12
4	Me	**305**	**312**	1.9 : 1	19
5	OMe	**306**	**313**	1.1 : 1	22
6	CF_3	**307**	**314**	0.83 : 1*	8
7	Ph	**308**	**315**	1.8 : 1	16
8	4-Pyridine	**309**	**316**	**	19
9	$HC=CH_2$	-	-	-	-
10	CN	-	-	-	-
11	NO_2	-	-	-	-

Table 15 – Insertion of *para*-substituted benzyl chlorides onto zirconocene as shown in Scheme 82 from a 1 mmol reaction. (*Ratios are not accurate due to eluting close to solvents or due to degradation, **pyridines did not elute well on the GC column).

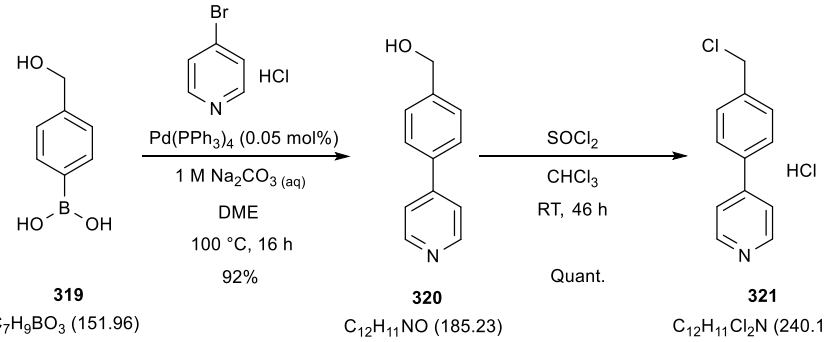


317 **318**

$C_8H_6F_2$ (140.13)

Scheme 83 – Fluoride loss from trifluorobenzylzirconocene.

All the benzyl chlorides trialled in Table 15 were commercially available, with the exception of pyridine **321** (entry 8) which was prepared *via* a Suzuki reaction and subsequently a chlorination to yield the hydrochloride salt (Scheme 84).[182, 183] No literature precedent was found for a Suzuki reaction synthesising alcohol **320**, the conditions used were from the synthesis of a range of substituted 2-pyridinephenyl methanol compounds.[182] Benzyl chloride **321** was washed with $NaHCO_3$ to yield the free amine before reaction with zirconocene(1-butene). Due to the likelihood of polymerisation of **321** (due to the polymerisation of 3-(chloromethyl)pyridine **238** as discussed in Section 3.2), the benzyl chloride was concentrated *in vacuo* at 0 °C after drying with anhydrous $MgSO_4$ and only left as the neat free amine for no longer than 15 minutes before addition to the dibutylzirconocene reaction mixture.

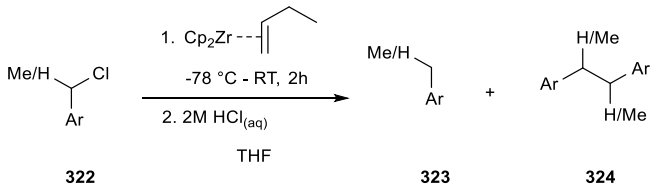


319 **320** **321**

$C_7H_9BO_3$ (151.96) $C_{12}H_{11}NO$ (185.23) $C_{12}H_{11}Cl_2N$ (240.13)

Scheme 84 – Synthesis of 4-(4-(chloromethyl)phenyl)pyridine hydrochloride **321**.

The reaction also proceeded with benzyl chlorides with steric hinderance on the aryl ring, as shown with 2-methylbenzyl chloride **325** and 1-(chloromethyl)naphthalene **244**, as well as on a secondary benzyl chloride **326** – demonstrating steric hindrance had little effect on the reaction (Scheme 85 and Table 16). Furthermore, the use of heteroaromatics (thiophene **327**, benzofuran **236** and 3-pyridine **238**) were all successful and showed the formation of their respective methylarene **323** and bibenzyls **324**.



Scheme 85 – Reaction of arylmethyl chlorides with zirconocene.

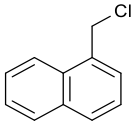
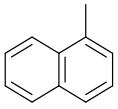
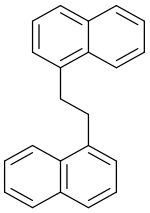
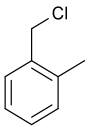
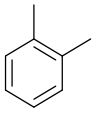
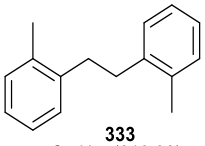
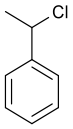
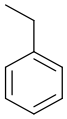
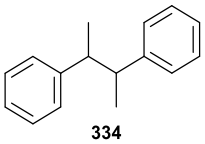
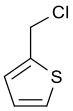
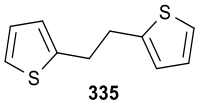
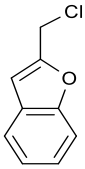
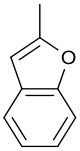
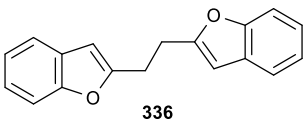
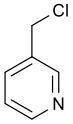
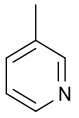
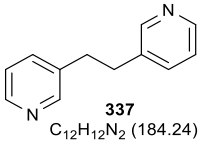
Entry	Benzyl Chloride **322**	Methylarene **323**	Bibenzyl **324**	GC Peak Ratio **323** : **324**	Isolated Bibenzyl **324** Yield (%)
1	 **244** $C_{11}H_9Cl$ (176.64)	 **292** $C_{11}H_{10}$ (142.20)	 **291** $C_{22}H_{18}$ (282.39)	1.8 : 1	16
2	 **325** C_8H_9Cl (140.61)	 **328** C_8H_{10} (106.17)	 **333** $C_{16}H_{18}$ (210.32)	2.0 : 1	9
3	 **326** C_8H_9Cl (140.61)	 **329** C_8H_{10} (106.17)	 **334** $C_{16}H_{18}$ (210.32)	1.6 : 1	18
4	 **327** C_5H_5ClS (132.61)	 **330** C_5H_6S (98.16)	 **335** $C_{10}H_{10}S_2$ (194.31)	1.5 : 1	8
5	 **236** C_9H_7ClO (166.60)	 **331** C_9H_8O (132.16)	 **336** $C_{18}H_{14}O_2$ (262.31)	2.4 : 1	10
6	 **238** C_6H_6ClN (127.57)	 **332** C_6H_7N (93.13)	 **337** $C_{12}H_{12}N_2$ (184.24)	**	7

Table 16 – Summary of sterically hindered benzyl chlorides and heteroaromatics with zirconocene(1-butene) in a 1 mmol scale (Scheme 85). (**Pyridines did not elute well on the GC column).

The 2-(chloromethyl)benzofuran **236** was prepared *via* the route described in Section 3.2. 2-(Chloromethyl)thiophene **327** was synthesised from the chlorination of thiophen-2-ylmethanol using thionyl chloride (57%) following literature procedure.[184] 3-(Chloromethyl)pyridine was purchased as the hydrochloride salt and required base washing before use in the reaction.

Detailed analysis into the ratios between methylarenes **323** and bibenzyls **324** formed for each benzyl chloride will be provided and discussed in Section 4.3.5.

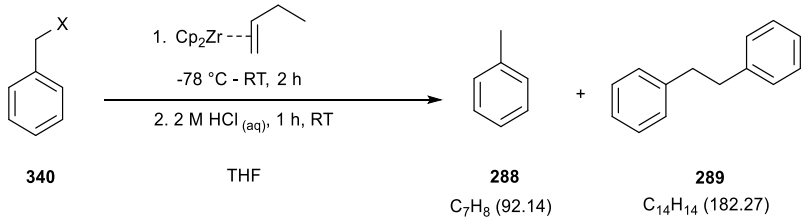
4.2.2 – Varying the Leaving Group Moiety

Subsequently, the effect of changing the identity of the leaving group on the benzyl was investigated.

Benzyl mesylate **338** and tosylate **339** can be readily prepared following literature conditions from benzyl alcohol.[185, 186] Mesylation of benzyl alcohol afforded mesylate **338** in yields of 63-91%. The lowest yields were due to decomposition on attempted purification by chromatography. Benzyl mesylate **338** was found to be unstable and would exothermically degrade on warming to room temperature after prolonged freezer storage. For the synthesis of benzyl tosylate **339**, purification by column chromatography was unavoidable due the removal of the unreacted tosyl chloride.

Three different groups were trialled (bromide, mesylate and tosylate) and compared to benzyl chloride to test the effect of the leaving group. The reaction with benzyl bromide resulted in the formation of toluene **288** and bibenzyl **289** as expected. However, on comparing the relative GC peak ratios of toluene **288** and bibenzyl **289**, using benzyl bromide consistently resulted in a greater proportion of bibenzyl **289** than with benzyl chloride by GC (Table 17). Conversely, benzyl mesylate **338** or tosylate **339** did not yield any bibenzyl **289**, only toluene **288**. These results implied that the bibenzyl may be a result of a radical reaction between benzyl halides and zirconocene as a greater proportion is observed with bromide and none is observed with benzyls directly bound to oxygen.

The potential formation of bibenzyl *via* a radical reaction will be investigated further in section 4.3.



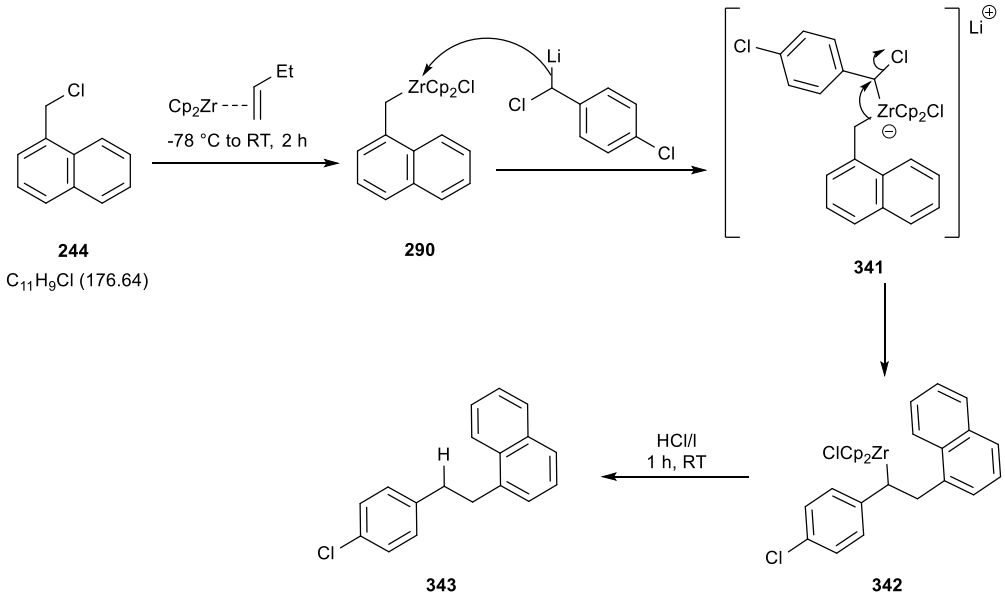
Scheme 86 – Reaction of benzyl chloride/bromide/mesylate/tosylate with the zirconocene(1-butene).

Entry	X	Average GC Peak Ratio **288** : **289**
1	Cl	2.2 : 1
2	Br	1.4 : 1
3	OMs	1 : 0
4	OTs	1 : 0

Table 17 – Summary of benzyl reactions with zirconocene(1-butene) as shown in Scheme 86.

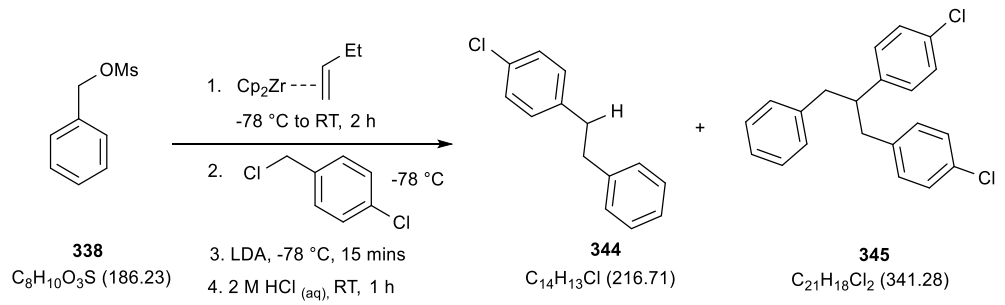
4.2.3 – Screening of Carbenoids for Insertion into Benzylzirconocenes

To determine the utility of forming benzylzirconocene chlorides, further functionalisation was attempted on the benzylzirconocene intermediate through the insertion of a carbenoid. As initially introduced in Chapter 3, benzyl carbenoids can insert into organozirconocenes when prepared *in situ* with LDA. Thus, insertion of 4-chlorobenzyl carbenoid was attempted on benzylzirconocene **290** before quenching with HCl and DCl (Scheme 87). GC monitoring showed the appearance of a new peak which GCMS and ^{1}H-NMR analysis were consistent with compound **343**. On quenching the reaction with DCl, deuterium incorporation was observed by NMR on compound **343** (>90% by ^{13}C-NMR). Isolation of the product was not attempted as it was inseparable from the naphthalene bibenzyl. The reactions confirmed 4-chlorobenzyl carbenoid inserted into benzylzirconocene **290** generating a subsequent organozirconocene **342** after 1,2-metallate rearrangement. Regenerating an organozirconocene is particularly beneficial as it allows for further functionalisation of the organozirconocene within the same reaction.



Scheme 87 – 4-Chlorobenzyl carbenoid insertion into naphthyl benzylzirconocene followed by HCl quench.

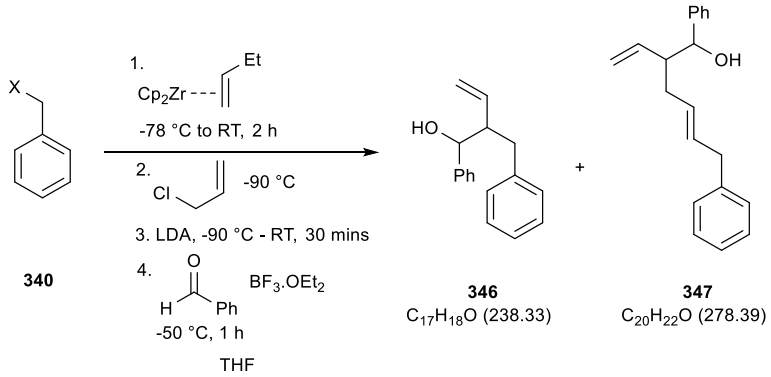
Section 4.2.2 showed how benzyl mesylate **338** resulted in no formation of bibenzyl. Thus, the equivalent 4-chlorobenzyl carbenoid insertion was repeated on benzylzirconocene mesylate as, without the formation of bibenzyl, more benzylzirconocene would be available to undergo carbenoid insertion to form the desired product **344** (Scheme 88). GC monitoring of the reaction showed the formation of the desired product **344** as well as a small quantity of a second product which appeared to be the result of double addition **345** (identified by GCMS). Furthermore, GC monitoring showed carbenoid insertion had not gone to completion as a significant amount of 4-chlorobenzyl chloride still remained, in a GC peak ratio of 4.8:7.4:1 between 4-chlorobenzyl chloride, mono-addition product **344** and double addition product **345** respectively. Repeating the reaction using the more sterically hindered naphthyl benzyl carbenoid did not prevent the double addition.



Scheme 88 – Insertion of 4-chlorobenzyl chloride into benzylzirconocene mesylate.

Subsequently, the addition of allyl chloride carbenoid was attempted on benzylzirconocene, a carbenoid which has also been shown previously within the group to insert well into zirconacycles.[1, 171] The insertion of allyl carbenoid was initially attempted on benzylzirconocene chloride followed by a benzaldehyde addition with the use of Lewis acid

$BF_3.OEt_2$ (Scheme 89 and Table 18). For entry 1, one equivalent of every reagent was used for the carbenoid insertion and resulted in the formation of two products, one from single carbenoid addition **346** and the second from double carbenoid addition **347**. On switching to benzylzirconocene mesylate (entry 2), despite improving the GC peak ratio between single and double insertion products **346** and **347**, poor insertion of the carbenoid into benzylzirconocene was observed. Using an excess of carbenoid (entry 3) resulted in a much larger proportion of double addition product **346** as well as two new products, identified by GCMS to be products from triple and quadruple carbenoid additions. The poor insertion of allyl carbenoid to benzylzirconocene mesylate was speculated to be potentially from coordination of an oxygen lone pair from the mesylate group into the empty orbital of the zirconocene, thus blocking this orbital for carbenoid insertion. Reverting back to benzylzirconocene chloride, the ratio of zirconocene(1-butene) and benzyl chloride was increased to 1.5 while the equivalents of allyl carbenoid was unchanged (entry 4) - an attempt to avoid the double addition product **347**. However, this modification showed no benefit by GC. Homoallylic alcohol **346** (entry 1) was isolated by HPLC purification in 8% isolated yield (17% estimated total due to impure samples from purification). The structure drawn for the double addition product **347** was not confirmed by ^{1}H-NMR, due to no clean sample of the compound being isolated which meant characterisation was not possible. Additional reactions form the insertion of the allyl chloride carbenoid into benzylzirconocene as well as discussion of region- and stereoselectivity is carried out in Section 4.4.3.



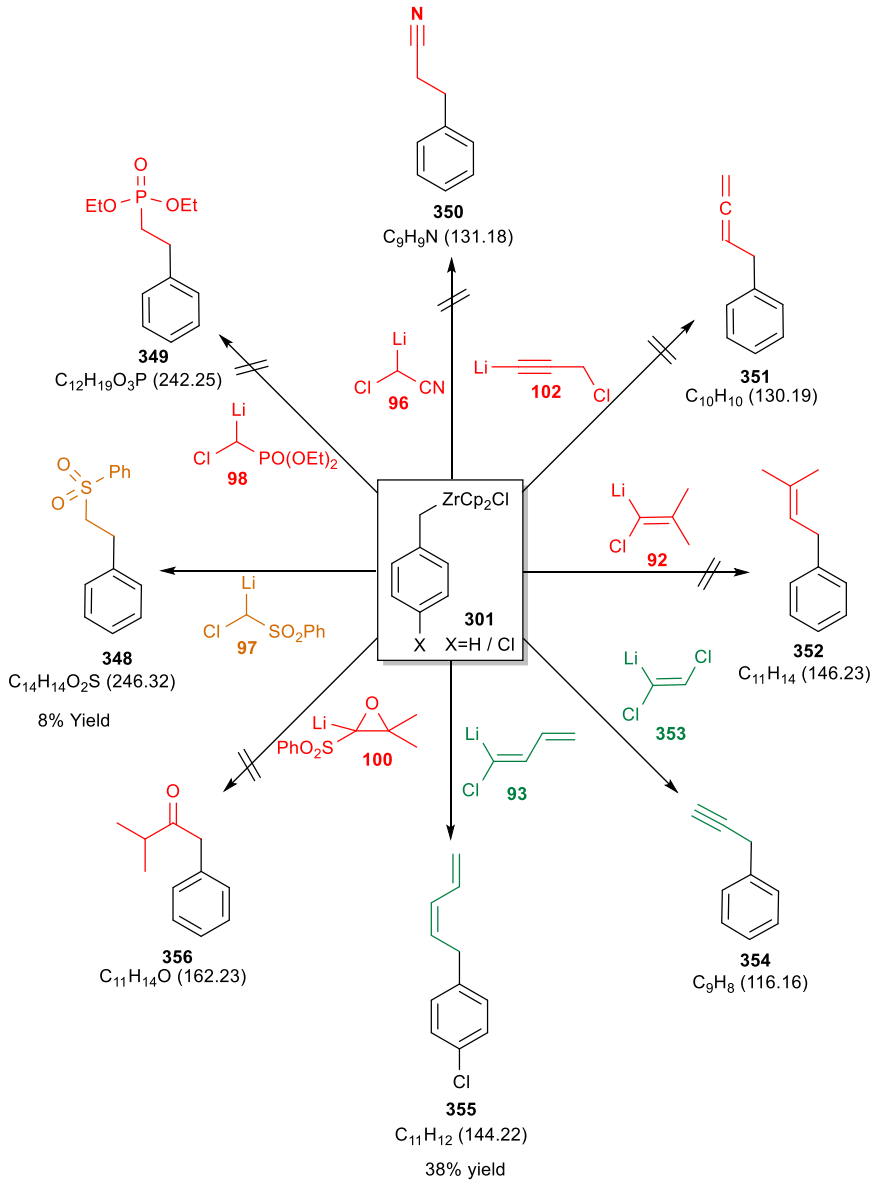
Scheme 89 – Allyl chloride carbenoid insertion into benzylzirconocene chloride/mesylate followed by benzaldehyde addition.

Entry	X	BnX & "$ZrCp_2$" Eq	Allyl Carbenoid Eq	PhCHO Addition Conditions	GC Peak Ratio **340** : **346** : **347**
1	Cl	1.0	1.0	-78 to -50 °C, 1 h	1 : 7.8 : 1
2	OMs	1.0	1.0	-78 to -50 °C, 1 h	30.6 : 10.9 : 1
3	OMs	1.0	1.2	-78 to -50 °C, 1 h	1 : 1 : 1.2 *
4	Cl	1.5	1.0	-78 to -50 °C, 1 h	1.3 : 2.3 : 1

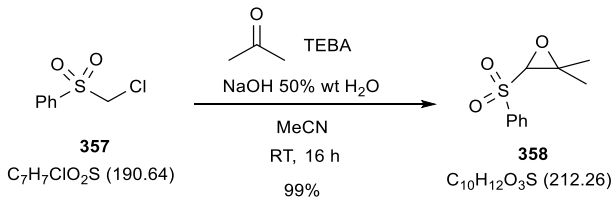
Table 18 – Summary of allyl carbenoid insertion reactions into benzylzirconocenes (Scheme 89). (*Plus more products from multiple carbenoid insertions).

Alternative carbenoids for insertion into benzylzirconocenes were trialled. The chosen carbenoids were used following the work published by A. Kasatkin on carbenoid insertion into acyclic organozirconocene chlorides formed from hydrozirconation (as introduced in Section 1.3.2.1).[106-112] From his work, the most successful carbenoids were chosen to trial insertion into benzylzirconocenes. Sulfonyl **97**, phosphonate **98** and nitrile **96** alkyl lithium carbenoids were trialled on benzylzirconocene as A. Kasatkin reports yields of 48%, 64% and 73% respectively on alkenylzirconocene from the hydrozirconation.[108] Despite this, no insertion was observed to yield products **346** and **347** and poor carbenoid insertion was observed to yield sulfonyl product **348** in 8% yield (Scheme 90). Product **348** was formed upon warming to room temperature suggesting the 1,2-metallate rearrangement was slow for this system. The structure was confirmed according to published characterisation of the compound.[187] For the propargyl **102** and dimethylalkene **92** carbenoids, no carbenoid insertion was observed on benzylzirconocene chloride **301** by GC at -78 °C and upon warming to room temperature despite successful insertion of these carbenoids into *n*-octylzirconocene by Negishi[104] and A. Kasatkin[106] respectively (Scheme 90). Dichloroalkene carbenoid **353** inserted well into benzylzirconocene chloride **301** with GCMS confirming the formation of desired product **354** (Scheme 90). However, alkyne product **354** was too volatile for isolation from THF, it also no longer retained the C-Zr bond and so does not allow for further functionalisation of the molecule.[106] The successful insertion of sulfonyl oxirane carbenoid **100** into an alkenylzirconocene was shown by A. Kasatkin in 87% yield (discussed in Section 1.3.1). This sulfonyl oxirane **358** was therefore prepared following literature conditions using acetone and sulfonyl chloride **357** with phase transfer catalyst triethylbenzylammonium chloride (TEBA) which afforded sulfonyl oxirane **358** in 99% yield (Scheme 91).[188, 189] Insertion of sulfonyl oxirane carbenoid **100** was attempted on benzylzirconocene chloride **301** however, no ketone product **356** was observed by GCMS. Alternatively, product **361** was observed, identified by GCMS and NMR, in 22% yield. Product **361** was likely to have occurred after carbenoid formation followed by

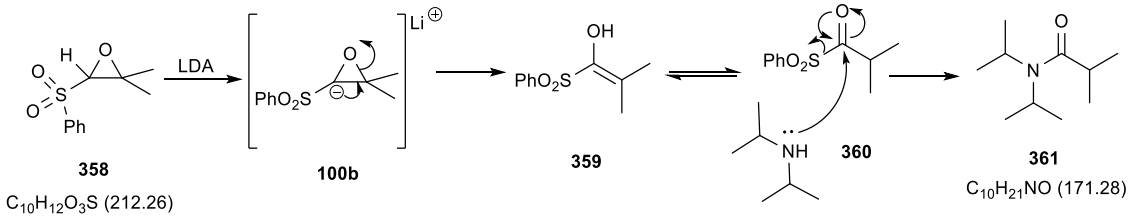
insertion of *i*PrNH$_2$ present in the reaction mixture from the *in situ* formation of the carbenoid (Scheme 92). The formation of this product **361** suggests that benzylzirconocene is less susceptible to carbenoid insertion compared to alkenylzirconocene chlorides.



Scheme 90 – Summary of carbenoid insertions attempted on benzylzirconocene chloride.



Scheme 91 – Synthesis of sulfonyl oxirane **358**.[188, 189]



Scheme 92 – Proposed formation of product **368** from sulfonyl oxirane carbenoid **100**.

Alkenyl carbenoid **93** was shown by A. Kasatkin to be a carbenoid that inserts well into organozirconocenes with yields ranging from 62-76%.[106] This carbenoid is prepared from *cis*-dichlorobut-2-ene **362** with two equivalents of LDA (Scheme 93). Insertion of this alkenyl carbenoid **93** was successful on 4-chlorobenzylzirconocene chloride showing full insertion by GC monitoring and the diene product was isolated in 38% yield (Scheme 90). Alkenyl carbenoid insertion was carried out on the *para*-chlorobenzylzirconocene system as this was later chosen as the parent system for alkenyl insertions which are described in Section 4.4.1 and Section 4.4.2.

Scheme 93 - *In situ* preparation of (*E*)-(1-chlorobuta-1,3-dien-1-yl)lithium alkenyl carbenoid

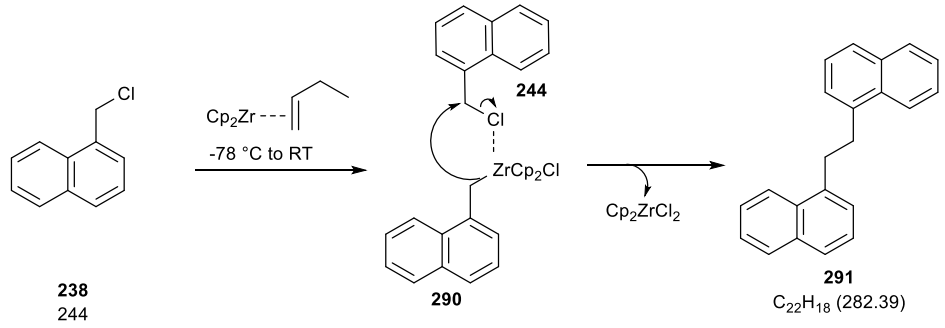
4.3 – Bibenzyl Formation Investigation

As shown from the carbenoid insertion trials into benzylzirconocene discussed in Section 4.2.3, although using benzyl mesylate **338** showed no formation of the bibenzyl, carbenoid insertion on benzylzirconocene mesylate appeared to be hindered by the mesylate group. Therefore, due to the greater stability of benzyl chlorides and their commercial availability, benzyl chlorides were used in further work. In doing so, the study of the mechanism of the bibenzyl formation was carried out in the hope of finding conditions to suppress its formation.

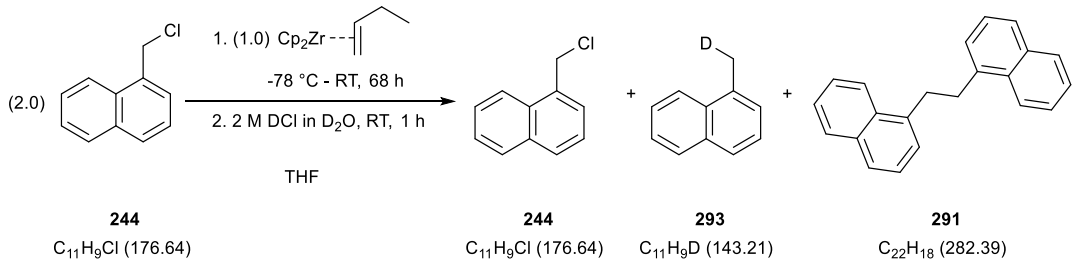
4.3.1 – Proposed Intermolecular Mechanism

It was initially proposed that the formation of the bibenzyl **291** was from the benzylzirconocene intermediate **290** *via* an intermolecular mechanism in which zirconocene, similarly to magnesium, renders its adjacent carbon negative. This negative carbon can then behave as a nucleophile and attack a second 1-naphthylmethyl chloride **244** which is brought in close proximity to the organozirconocene due to complexation of the chlorine. After

nucleophilic attack, chloride is eliminated which then reforms zirconocene dichloride and the bibenzyl **291** (Scheme 94). To test this hypothesis, two equivalents of 1-naphthylmethyl chloride **244** were added to one equivalent of zirconocene(1-butene). If the hypothesis was correct then all of the 1-naphthylmethyl chloride **244** would be converted to bibenzyl **291** after extended reaction time (Scheme 95). However, after 68 hours reaction time, the second equivalent of 1-naphthylmethyl chloride **244** remained and GC monitoring showed the ratios between starting material and products remained consistent from two hours onwards. On quenching the reaction with DCl, good deuterium incorporation (>90% by ^{13}C-NMR) was observed for the methylnaphthylene **293** suggesting the intermediate benzylzirconocene **290** remains stable at room temperature and in the presence of 1-naphthylmethyl chloride **244**, thus disproving the hypothesis (Figure 21).



Scheme 94 – Proposed mechanism for the formation of bibenzyl **291** from benzyl chloride and the zirconocene(1-butene).



Scheme 95 – Reaction testing the intermolecular mechanism hypothesis for the formation of bibenzyl **291**.

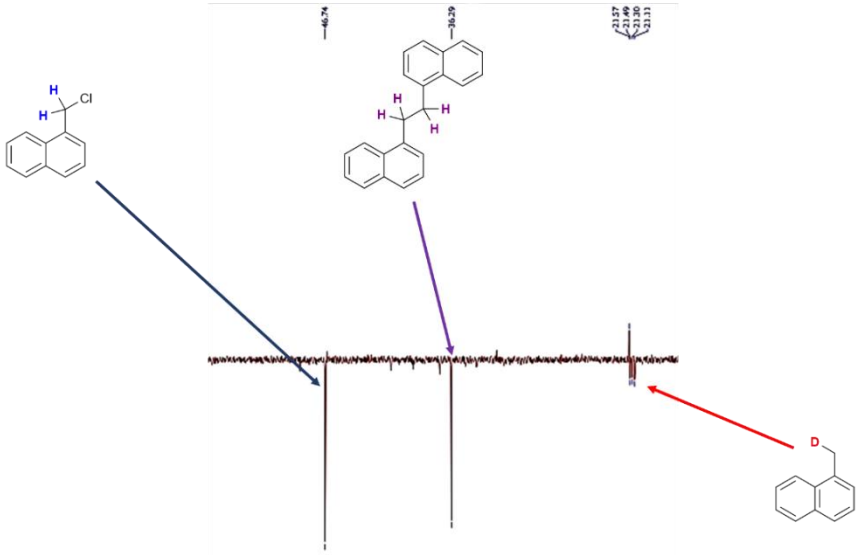
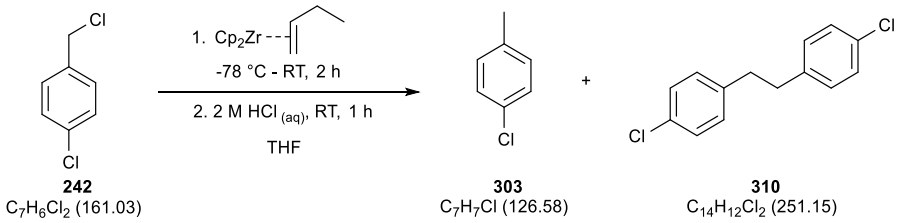


Figure 21 - ^{13}C-NMR of the product obtained from reaction of Scheme 95.

4.3.2 – Concentration Effects

The effect of reaction concentration on the formation of bibenzyl (**310**) was investigated (Scheme 96 and Table 19). Although the GC peak ratio appeared to show a moderate reduction in the amount of bibenzyl **310** formed at lower concentrations, the isolated yields did not. A greater difference would be expected from a second order reaction, therefore it was concluded that concentration did not have a significant effect on the formation of the bibenzyls.



242 $C_7H_6Cl_2$ (161.03) **303** C_7H_7Cl (126.58) **310** $C_{14}H_{12}Cl_2$ (251.15)

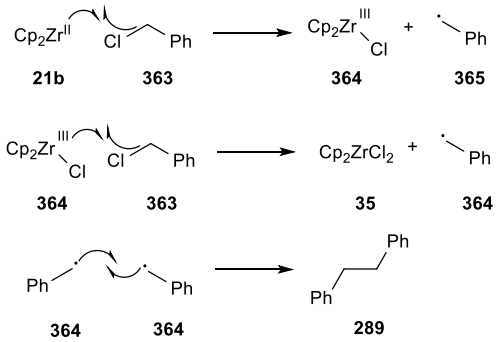
Scheme 96 – 4-Chlorobenzyl chloride reaction with zirconocene(1-butene) at different concentrations.

Entry	Concentration (mM)	GC Peak Ratio **303** : **310**	Isolated Bibenzyl **310** Yield (%)
1	120.5	1.6 : 1	19
2	34.1	2.6 : 1	13
3	17.5	3.1 : 1	16

Table 19 – Summary of 4-chlorobenzyl chloride reaction with zirconocene(1-butene) at different concentrations (Scheme 96).

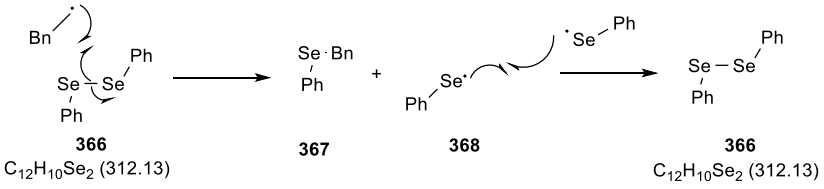
4.3.3 – Radical Traps

The formation of bibenzyl through a radical mechanism was considered to be a possibility since quenching with deuterium showed this product was not derived from an organozirconocene intermediate (Section 4.1). A proposed mechanism for formation of bibenzyl *via* radical steps is shown in Scheme 97. Literature precedent can be found for radical zirconium reactions however, examples found either used triethylborane as a radical initiator on the Schwartz reagent[190] or had Schiff base-type ligands.[190, 191] Although a radical-radical coupling reaction is a very improbably method for the formation of bibenzyls, it was deemed worth testing as it is a way of forming a carbon-carbon bond without the product having a carbon-zirconium bond. Therefore, to eliminate this route as a possible cause for the bibenzyl formation, suitable radical traps were considered for the reaction to observe their effect on the formation of the bibenzyl.



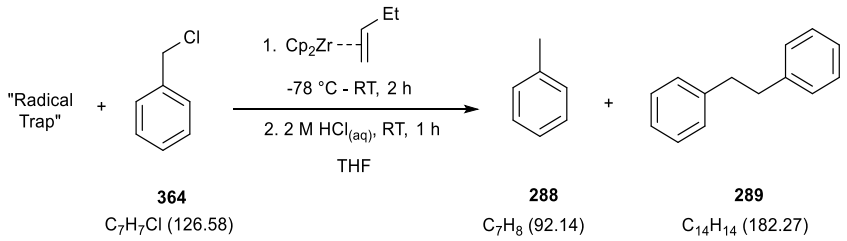
Scheme 97 - Proposed radical mechanism for the formation of bibenzyl.

Firstly, diphenyl diselenide **366** was trialled as selenium is known to be a potent alkyl radical trap, orders of magnitude faster at reacting with alkyl radicals than equivalent sulfur-containing compounds. Furthermore, once the phenyl selenide radical **368** is formed, it is unlikely to propagate radical reactions, alternatively preferring to react with another phenyl selenide radical **368** to reform the diselenide species **366** (Scheme 98).[192, 193] Although there is literature precedent for the reaction of organozirconocenes with phenyl selenide in hydrozirconation intermediates, only a very small equivalent of radical trap would be necessary to hinder a radical reaction pathway hence little material would be lost if some substitution occurred. [194-197]



Scheme 98 - Mechanism for the reaction between benzyl radical (an alkyl radical) and diphenyl diselenide.

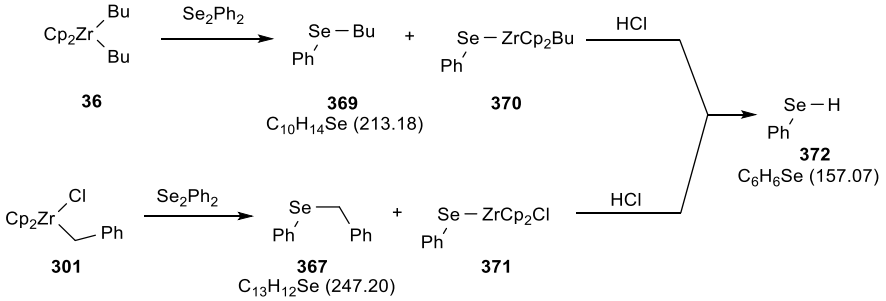
Thus, to test the use of diphenyl diselenide **366** as a radical trap for the formation of bibenzyl **289**, the reaction between benzyl chloride **364** and the zirconocene(1-butene) was repeated in the presence of diselenide **366** and monitored by GC (Scheme 99 and Table 20). Initially 0.03 equivalents were used (entry 1) but this proved to have no effect on the reaction. Therefore, the amount of diselenide **366** was increased by ten-fold (entry 2) which resulted in some inhibition of the reaction, identified by the presence of unreacted benzyl chloride **366** by GC, and no effect on the bibenzyl **289** formation. In addition to this, new products were observed in the reaction mixture which were identified by GCMS - phenyl selenol **372**, butyl(phenyl)selane **369** and benzyl(phenyl)selane **367**. This suggested that the diselenide **366** was inserting into organozirconocene intermediates (Scheme 100). Further increasing the equivalents of diselenide **366** to 1.0 resulted in complete inhibition of the formation of products **288** and **289** (entry 3).



Scheme 99 – Benzyl chloride reaction with the zirconocene(1-butene) in the presence of a radical trap.

Entry	Radical Trap	Equivalents	Effect on Bibn Formation
1	Se_2Ph_2	0.03	Negligible
2	Se_2Ph_2	0.30	Negligible
3	Se_2Ph_2	1.00	No reaction
4	$CBrCl_3$	0.30	Negligible
5	$CBrCl_3$	1.00	No reaction

Table 20 - Summary of benzyl chloride and zirconocene(1-butene) reaction in the presence of a radical trap, determined by GC monitoring.

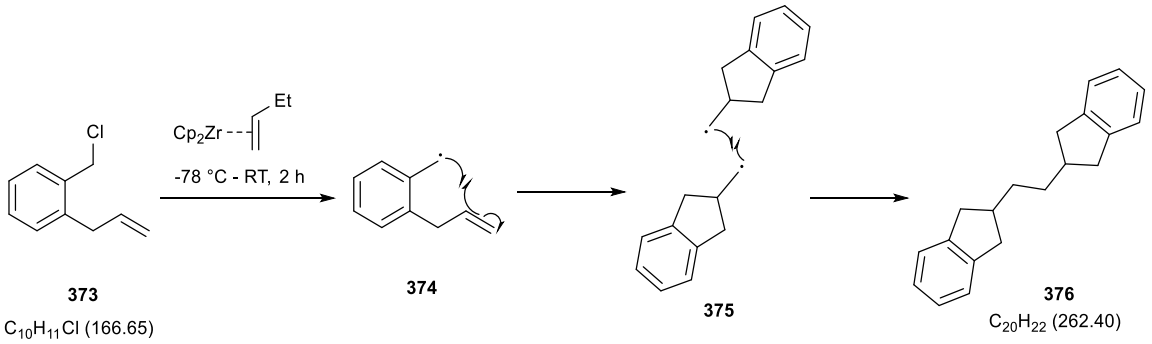


Scheme 100 - Proposed formation of butyl(phenyl)selane benzyl(phenyl)selane and phenyl selenol in the reaction of the zirconocene(1-butene) with benzyl chloride in the presence of diphenyl diselenide (Scheme 99).

Subsequently, bromotrichloromethane ($CBrCl_3$) was also trialled as a radical quench. [198-200] However, similar results were obtained to those of diselenide **366** with 0.03 equivalents leaving the reaction largely unaffected but with some inhibition and 1.0 equivalents completely inhibited the reaction. These results appeared to suggest the formation of bibenzyl was not *via* a radical reaction.

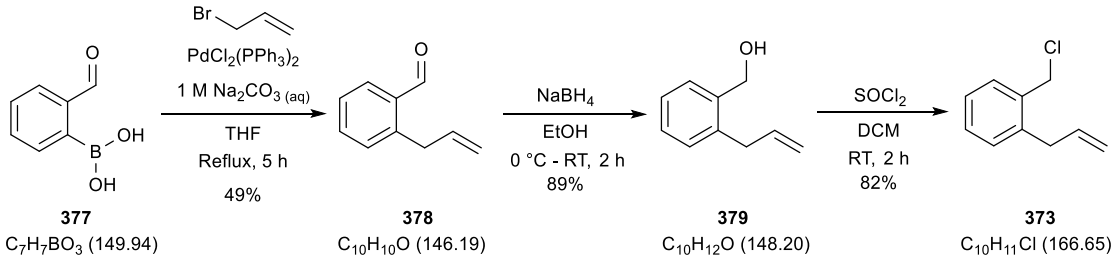
4.3.4 – Benzyl Chlorides with Potential for Internal Cyclisation

To further test the formation of the bibenzyl *via* a radical mechanism from the formation of a benzyl radical, the synthesis of a benzyl chloride with an *ortho* allyl group **373** was proposed as formation of a benzyl radical would result in an intramolecular 5-*exo*-*trig* cyclisation with the allyl group, before dimerization (Scheme 101).



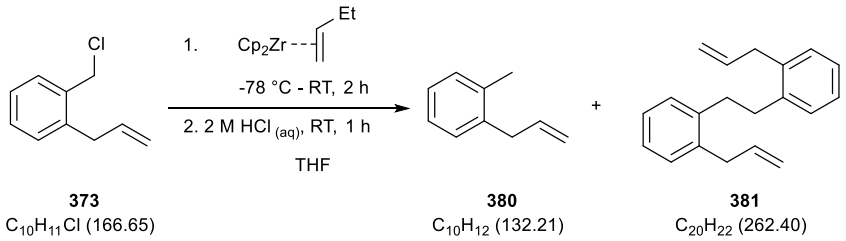
Scheme 101 – Proposed intramolecular 5-*exo*-*trig* radical cyclisation from 2-allylbenzyl chloride **373**.

2-Allylbenzyl chloride **373** was synthesised *via* a three-step route following literature conditions (Scheme 102).[201-203] Firstly a Suzuki reaction was carried out between (2-formylphenyl)boronic acid **377** and allyl bromide to yield aldehyde **378** in 49% yield. This aldehyde was reduced to the alcohol **379** using sodium borohydride which surprisingly also resulted in some reduction of the allyl alkene forming (2-propylphenyl)methanol **379**. The two alcohols (2-allylphenyl)methanol **379** and (2-propylphenyl)methanol gave a 20:1 ratio respectively by ^{1}H-NMR and were inseparable. Therefore chlorination was conducted on the mixture which resulted in the formation of allylbenzyl chloride **373** and 2-propylbenzyl chloride also in a 20:1 ratio by ^{1}H-NMR.



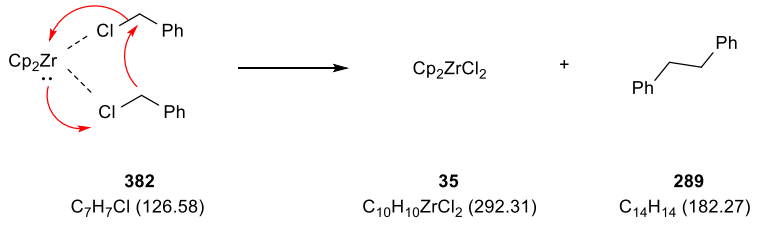
Scheme 102 – Synthesis of 2-allylbenzyl chloride **379** from (2-formylphenyl)boronic acid **377**.

2-Allylbenzyl chloride **373** was reacted with zirconocene(1-butene) (Scheme 103). GCMS analysis of the reaction confirmed the formation of products with *m/z* 132 and 262. ^{1}H-NMR analysis of the crude compound confirmed 2-allyltoluene **380** and bis-allylbibenzyl **381** to be the major products in a 4.2:1 ratio respectively (along with minor impurities most likely from the reduction of the alkene as observed for the *para*-allyl system in Section 4.2.1, Scheme 82 and Table 15). Therefore the reaction strongly indicated that the formation of the bibenzyl was not from a radical mechanism.

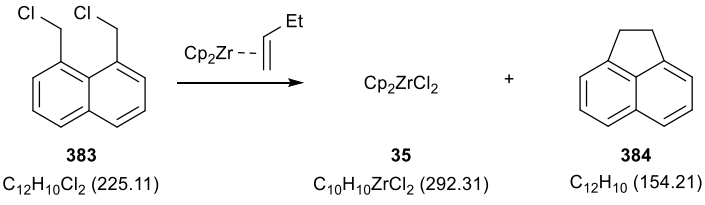


Scheme 103 – Reaction of 2-allylbenzyl chloride with the zirconocene(1-butene).

Another hypothesis for the formation of the bibenzyl was a possible sp^3 coupling between two benzyl chloride molecules and one Cp_2Zr^{II} (structure **382**, Scheme 104). To test the hypothesis, the synthesis of a bis-benzyl chloride was proposed as an intramolecular sp^3 coupling would be faster than an intermolecular coupling and the formation of benzylzirconocene, thus yielding the coupled product in greater proportion. The use of bis(chloromethyl)naphthalene **383** was suggested as a compound that could test the intramolecular coupling (Scheme 105).



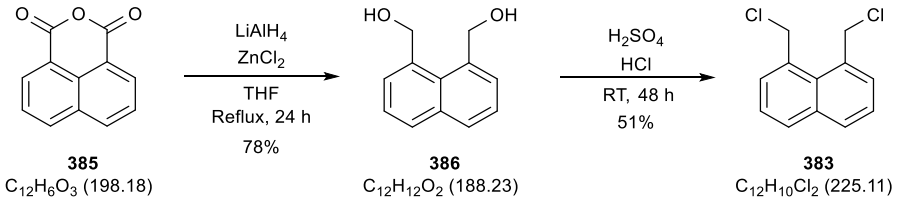
Scheme 104 – Proposed sp^3 coupling with zirconocene to form the bibenzyl.



Scheme 105 – Sp^3 coupling of **390** with zirconocene to form acenaphthene **383**.

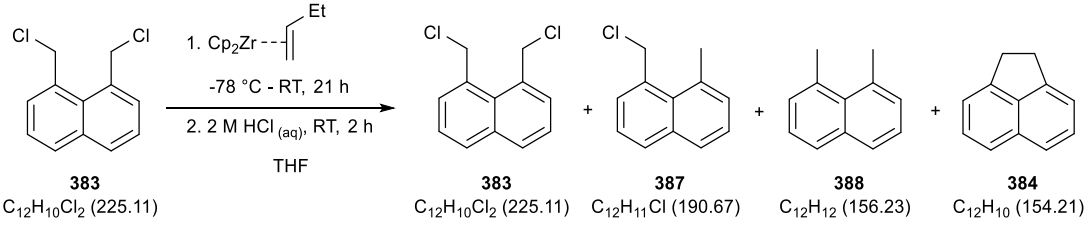
Bis(chloromethyl)naphthalene **383** was prepared *via* a two-step route following literature conditions (Scheme 106).[204, 205] Firstly 1,8-naphthalic anhydride **385** was reduced with lithium aluminium hydride in 78% yield to afford the diol **386**. Chlorination of diol **386** in

concentrated hydrochloric and sulphuric acid afforded dichloride **383** in 51% yield. The low yield for the chlorination was due to the poor solubility of diol **386** in concentrated acid. ^{1}H-NMR and GCMS of the crude compound from the chlorination showed the presence of diol **386** and dichloride **383** only, with no presence of the intermediate (mono-chloride alcohol). Despite the low yield, sufficient dichloride **383** was prepared to test the intramolecular sp^{3} coupling.



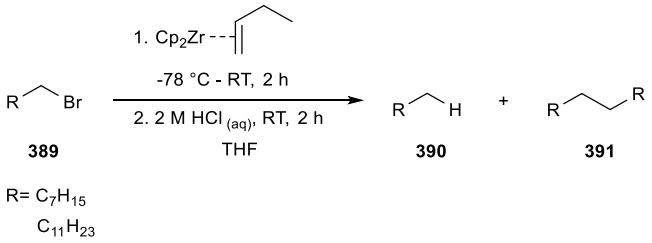
Scheme 106 – Synthesis of bis(chloromethyl)naphthalene **392** from 1,8-naphthalic anhydride **390**.

One equivalent of bis(chloromethyl)naphthalene **383** was reacted with one equivalent of the zirconocene(1-butene) over 72 hours reaction time and three major compounds were identified by GCMS and ^{1}H-NMR to be present in the reaction mixture (Scheme 107). As well as the acenaphthene **384** predicted, unreacted starting material **383** remained due to zirconocene insertion into Bn-Cl bonds which yielded compounds **387** and **388**. ^{1}H-NMR showed a 1.5:1.2:1:3.2 ratio between the starting material **383**, **387**, **388** and acenaphthene **384** respectively. Repeating the reaction with DCl as the quench showed deuterium incorporation into compounds **387** and **388** only. Although these four compounds were the major products, formation of various bibenzyls were identified in minor quantities by GCMS as a result of coupling between two bis-benzyl chlorides. Although the reaction showed acenaphthene **384** to be the major product, the observation of small quantities of bibenzyls formation was surprising as this would require an intermolecular process. Furthermore, the insertion of zirconocene into Bn-Cl bonds appears to be faster than expected as it competed with the intramolecular coupling. However, the rate of the intramolecular cyclisation may have been affected by the ring strain of forming the 5-membered ring of the acenaphthene **384**. Due to the variety of products formed, the outcome of the reaction was inconclusive.



Scheme 107 – Reaction between bis(chloromethyl)naphthalene **383** and the zirconocene(1-butene).

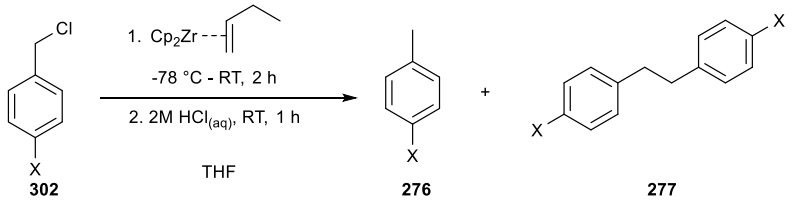
Subsequently, it was proposed that for the sp^3 coupling suggested, the reaction could equally occur between two alkyl halides in a similar manner. Furthermore, as Section 4.2.2 showed that benzyl bromides resulted in greater formation of bibenzyl compared to chlorides, it was proposed that an alkyl bromide could be exposed to zirconocene(1-butene) in order to observe the reaction outcome (Scheme 108). The reaction was attempted with octylbromide and dodecylbromide which showed the reaction products to be predominantly octane and dodecane respectively, GCMS detected baseline amounts of dimer products not visible by ^{1}H-NMR. The reaction appeared to show that the insertion of zirconocene into carbon-halide bonds was not specific to benzyls. Repeating the reaction with dodecyl bromide and a deuterium quench (D_2O) showed poor deuterium incorporation (<20% by ^{13}C-NMR) on the dodecyl product. The poor deuterium incorporation was partly attributed to the symmetry of the compound (as even with 100% deuterium incorporation only 50% of the terminal methyl groups would be deuterated) but also suggested the reaction of alkyl halides with zirconocene could proceed *via* a different mechanism as the benzyl halides. Overall, the reaction showed alkyl bromides also react with zirconocene(1-butene) and the formation of dimers from halogenated hydrocarbons was greatly influenced by the benzyl group.



Scheme 108 - Alkyl bromide reaction with the zirconocene(1-butene).

4.3.5 – Substituent Effects

In an attempt to determine the mechanism behind the formation of the bibenzyl, the effect of the benzyl chloride *para*-substituents on the formation of the respective bibenzyls was analysed (Scheme 109). In order to do this, the reaction between different benzyl chlorides and the zirconocene(1-butene) was set up and after 2 hours reaction time, NMR sampling of the reaction was taken without THF solvent removal. Attempting to remove solvent would alter the ratio between *para*-substituted toluene **276** and bibenzyl **277** due to the volatility of the *para*-substituted toluene **276**. ^{1}H-NMR analysis allowed for ratio comparison between **276** and bibenzyl **277** through their CH_3 and CH_2 peaks respectively which were found between the two THF solvent peaks. The ratios obtained are summarised in Table 21.



Scheme 109 – *Para*-substituted benzyl chloride reaction with the zirconocene(1-butene).

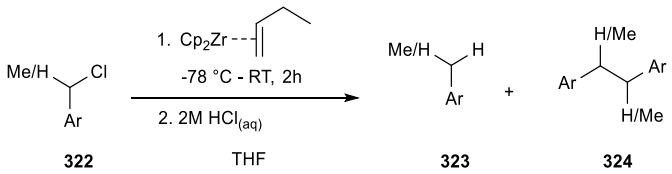
Entry	BnCl Substituent 'X'	Average **276** : **277** ^{1}H-NMR Ratio	Average Conversion from **302** to **276** (%)
1	H	2.4 : 1	55
2	Cl	2.4 : 1	55
3	F	2.3 : 1	53
4	Me	1.8 : 1	48
5	OMe	1.8 : 1	48
6	Ph	4.1 : 1	67
7	4-Py	1.6 : 1*	44*

Table 21 – Summary of *para*-substituted benzyl chloride reaction with the zirconocene(1-butene) product ratios (Scheme 109). (*Not an average value).

The ratios obtained for **276** and bibenzyl **277** formation for different *para*-substituents showed little difference between electron-withdrawing and electron-donating groups. The largest difference observed was between entries 6 and 7 in which *para*-4-pyridine appeared to increase the proportion of bibenzyl and 4-phenyl decreased the proportion of bibenzyl, suggesting an electron donating group may influence the reaction outcome. An average value was not obtained for the pyridine compound (entry 7) due to polymerisation of this benzyl chloride (discussed in Section 4.2.1).

The reaction was repeated with different aryl groups which showed the ratios were affected by steric factors (entries 1 and 2), increasing the steric hindrance of the aryl ring appeared to disfavour the bibenzyl **324** formation but increasing the steric hindrance of the benzyl carbon appeared disfavour it. However, it is important to note that for entry 3 the ^{1}H-NMR ratio is less accurate due to the formation of two diastereomeric bibenzyls in which the benzyl protons appeared as multiplets and so these peaks were observed at the baseline. Heteroaromatic compounds generally showed an increase in bibenzyl **324** formation,

excluding benzofuran which may also have been influenced by sterics due to the conjugated aryl ring (entries 5-6) (Scheme 110 and Table 22).



Scheme 110 – Variation of the aryl group for arylmethyl chlorides with zirconocene(1-butene) reaction.

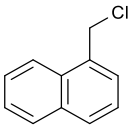
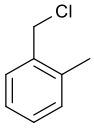
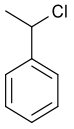
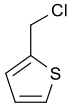
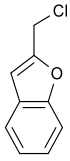
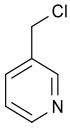
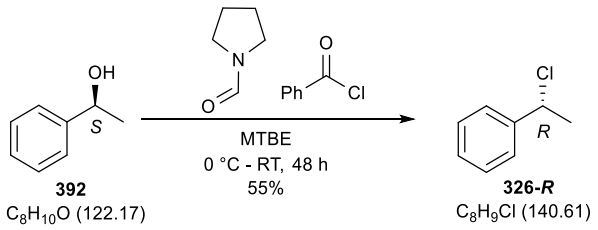
Entry	BnCl	Average **323** : **324** ^{1}H-NMR Ratio	Average Conversion from **322** to **323** (%)
1		4.0 : 1	66
2		5.2 : 1	72
3		1.7 : 1	45
4		1.6 : 1	45
5		3.6 : 1	64
6		1.5 : 1*	43*

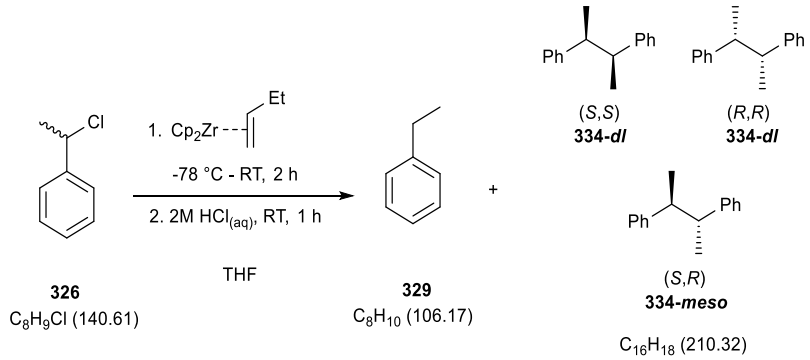
Table 22 – Summary benzyl chloride reaction with the zirconocene(1-butene) when varying the aryl group (Scheme 110). (*Not an average value).

It was considered that knowing the stereochemistry of a bibenzyl formed from a chiral benzyl chloride could elucidate the mechanism of the bibenzyl formation. Thus, ((*R*)-(1-chloroethyl)benzene **326-*R***) was synthesised from (*S*)-1-phenylethan-1-ol **392** in 55% yield following literature conditions with chiral GC showing >95% enantioselectivity (Scheme 111).[107, 206] Chiral benzyl chloride **326-*R*** was then reacted with zirconocene(1-butene) (Scheme 112). As with the racemic secondary benzyl chloride, two diastereoisomers of bibenzyl **334** were observed by GC in the same ratio, approximately 1:1 (Table 23).

Purification resulted in isolation of **334-*dl*** and **334-*meso*** diastereomers in a 1:1.2 ratio by ^{1}H-NMR respectively – consistent with the GC peak ratio of the purified compound. Upon chiral GC analysis of the post-column samples (PC) formed from the racemic and chiral benzyl chloride reactions, both samples showed a 1:1:2.7 peak ratio, the former two peaks assumed to correspond to the separate *RR*/*SS* enantiomers and the latter to the *meso* isomer. The reaction showed the stereochemistry is not retained in the formation of the bibenzyls.



Scheme 111 – Stereoselective synthesis of (*R*)-(1-chloroethyl)benzene.



Scheme 112 - Zirconocene insertion into chiral secondary benzyl chloride **326-*R*.**

Entry	Ethyl Benzyl Chloride **326**	GC Peak Ratio **334** (RM)	GC Peak Ratio **334** (PC)	Chiral GC Peak Ratio **334** (PC)
1	Racemic	1 : 1.0	1 : 1.4	1 : 1 : 2.7
2	R	1 : 1.1	1 : 1.3	1 : 1 : 2.7

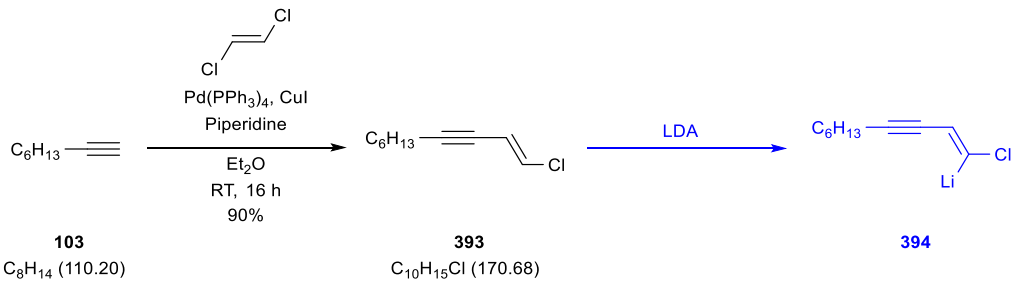
Table 23 – Summary GC data from secondary benzyl chloride reactions with zirconocene(1-butene) (GC columns used are specified in the experimental, RM = reaction mixture, PC= post-column).

4.4 – Multi-Component Couplings

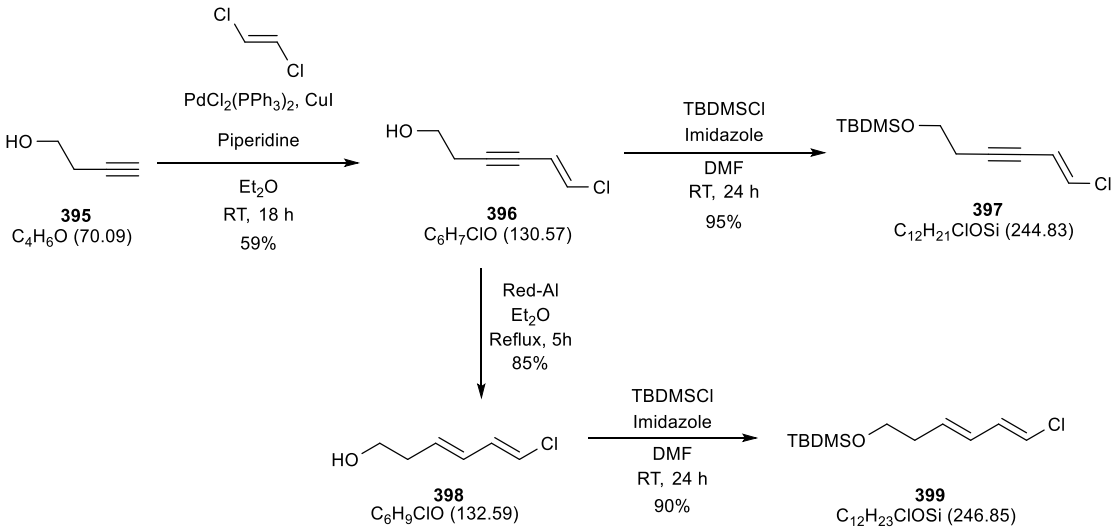
4.4.1 – Two-Component Couplings with Alkenyl Carbenoids

From the screening of carbenoids for insertion into benzylzirconocene (Section 4.2.3), alkenyl carbenoid **93** showed good insertion and only single carbenoid addition by GC monitoring, unlike the allyl chloride carbenoid (Section 4.2.3). Furthermore, A. Kasatkin reports yields of 65-82% for the insertion of a *trans*-enyne and *trans*-diene carbenoid into acyclic organozirconocenes.[106] Therefore, a range of *trans*-alkenyl carbenoid precursors were synthesised in order to be inserted into benzylzirconocene. Enyne **393** was synthesised *via* a Sonogashira reaction between octyne **103** and *trans*-1,2-dichloroethene in 90% yield following literature conditions (Scheme 113).[207] *In situ* deprotonation of vinyl halides (such as **393**) with LDA generates the corresponding alkenyl carbenoid (**394**).

In addition, TBDMS-protected *trans*-enyne **397** and *trans*-diene **399** were prepared following literature conditions (Scheme 114).[208, 209] A Sonogashira reaction between butyn-1-ol **395** and *trans*-1,2-dichloroethene afforded enyne alcohol **396** (59%) which, upon TBDMS protection, afforded enyne **397** (95%). To synthesise the diene **399**, enyne alcohol **396** was reduced to the diene alcohol **398** using Red-Al (85%) and then protected with TBDMS (97%). Diene alcohol **398** was found to be unstable as it degraded over time whilst in freezer storage, whereas TBDMS-protected diene **399** was found to be stable. The syntheses of **397** and **399** were to introduce polarity to the compounds synthesised from alkenyl carbenoid insertion into benzylzirconocene. Acidic quench of the organozirconocene could also cleave the TBDMS protecting group to afford products with a free alcohol group.



Scheme 113 - Synthesis of alkenyne carbenoid precursor *via* a Sonogashira reaction.

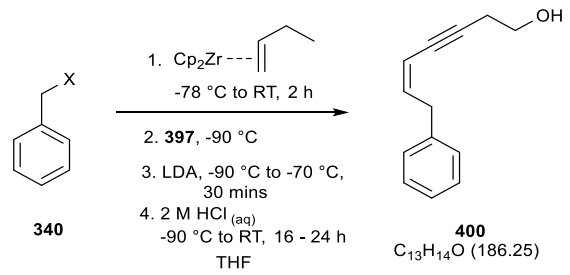


Scheme 114 – Synthesis of enyne **397** and diene **399**.

The carbenoid of enyne **397** was inserted into benzylzirconocene chloride and subsequently quenched with HCl (Scheme 115 and Table 24). Despite the HCl quench, complete removal of the TBDMS protecting group from the compound was not achieved as expected therefore, the crude compound was re-dissolved in THF and re-treated with aqueous 2 M HCl (4:1 ratio) to yield alcohol **400**. Column chromatography of the crude compound afforded the separation of product **400** and the expected bibenzyl **284** however, product **400** and unreacted enyne alcohol **396** were inseparable by column chromatography. Presence of enyne **396** in the crude compound is unavoidable as the carbenoid is added in excess due to the loss of starting material to the formation of bibenzyl. Clean isolation of product **400** was realised by Kugelrohr distillation in which the enyne **396** was distilled and removed, affording product **400** in 37% yield.

Results from Section 4.2.3 suggested carbenoid insertion into benzylzirconocene mesylate was inhibited. Therefore the reaction for the formation of **400** was repeated using benzylzirconocene mesylate which resulted in a yield of 34% (entry 2, Table 24). The yield was much lower than expected as no starting material was lost to the formation of bibenzyl. The reaction was repeated using 1.5 equivalents of carbenoid which yielded alcohol **400** in 36% (entry 3), a comparable yield to the benzyl chloride reaction (entry 1). In an attempt to exploit the lack of bibenzyl formation of the mesylate system and the good carbenoid insertion of the chloride system, ligand exchange was attempted on benzylzirconocene mesylate with the addition of excess lithium chloride (10 equivalents). The reaction was then stirred for 18 hours to allow the ligand exchange to take place before *in situ* preparation of the carbenoid. Due to increased dilution of the reaction (caused by poor solubility of LiCl in

THF), double the reaction time was provided for carbenoid insertion and subsequent 1,2-metallate rearrangement. Despite this, alcohol **400** was isolated in 20% yield.



Scheme 115 – Alkenyl carbenoid insertion from enyne **400** into benzylzirconocene.

Entry	X	Carbenoid Equivalents	Additional Reagents	Yield (%)
1	Cl	1.0	-	37
2	OMs	1.0	-	34
3	OMs	1.5	-	36
4	OMs	1.0	LiCl	20

Table 24 – Summary of alkenyl carbenoid insertion to synthesise alcohol **400** (Scheme 115).

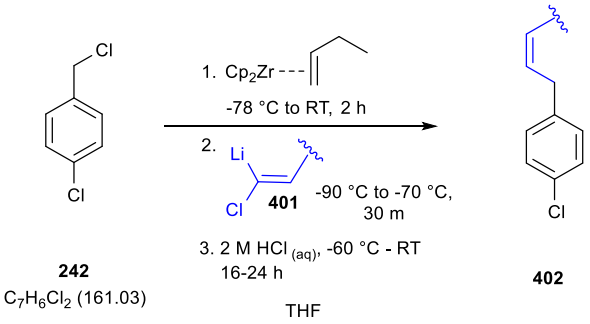
From the reactions summarised in Table 24, it was concluded that benzyl chloride and benzyl mesylate gave comparable yields of alcohol **400** from carbenoid insertion (entry 1 and entry 3). No successful method was identified which would either suppress the formation of bibenzyl for the benzyl chloride (Section 4.3) or achieve full carbenoid insertion for the benzyl mesylate. As benzyl chlorides are commercially available and more stable than the mesylates, syntheses of compounds herein were carried out on benzyl chlorides. 4-Chlorobenzyl chloride was chosen as the parent benzyl chloride as it allowed for easier GC monitoring of the carbenoid insertions.

Insertion of alkenyl carbenoids **93**, **394**, **403** and **404** and into 4-chlorobenzylzirconocene chloride, followed by HCl quench afforded compounds **355** and **405**-**407** in 33-45% yield (Scheme 116 and Table 25). The highest yields were obtained for the enyne carbenoids **394** and **403**. Considering Section 4.3.5 showed an average 55% of 4-chlorobenzyl chloride starting material converts to benzylzirconocene chloride and A. Kasatkin reports an average yield of 74% for enyne carbenoid insertions into acyclic organozirconocenes,[106] 44% and 45% yields for enyne compounds **394** and **403** were considered good yields.

Isolation of diene **355** was achieved by column chromatography whereas purification of enyne alcohol **406** was realised in the same manner described for enyne alcohol **400** with the use of column chromatography followed by Kugelrohr distillation. However, this method

was not successful for diene alcohol product **407** as heating resulted in some isomerisation of the product, likely occurring by a 1,5-hydride shift as proposed in Scheme 117. Due to the broad doublet at 3.41 ppm (*J* 7.0 Hz) observed for the hydride-shift isomer by ^{1}H-NMR, it was assumed the isomer formed is compound **407b**. Assignment of the alkene configuration for **407b** was not possible due to peak overlap with **407** by ^{1}H-NMR. Consequently, diene alcohol **407** was resynthesised and purified by HPLC to achieve separation from diene **398**. Enyne product **405** was also purified by HPLC as separation between bibenzyl, enyne **393** and product **405** was not possible by column chromatography.

All products from insertion of *trans*-alkenyl carbenoids into benzylzirconocenes (**400**, **355** and **405**-**407**) afforded only one alkene isomer product with *cis*-alkene geometry (as depicted in Scheme 115 and Scheme 116). ^{1}H-NMR showed coupling of 10.5-11.1 Hz between the alkene protons which was consistent with *cis*-coupling. The products formed were in accordance with the proposed mechanism in which, after formation of the 'ate' complex **408** from carbenoid insertion, 1,2-metallate rearrangement results in inversion of the vinyl halide geometry to afford organozirconocene **409** (Scheme 118). The isolation of *cis*-alkene products is also consistent with that observed and reported by A. Kasatkin.[106, 107]



Scheme 116 – Alkenyl carbenoid insertion into 4-chlorobenzylzirconocene chloride.

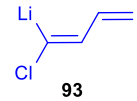
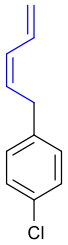
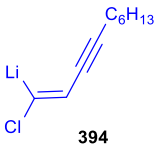
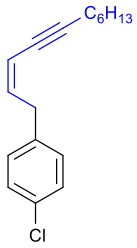
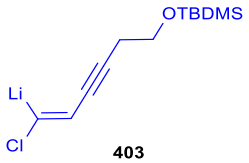
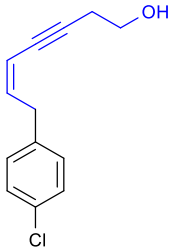
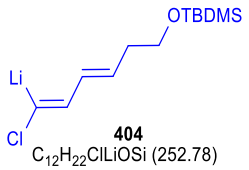
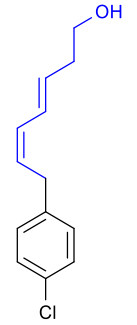
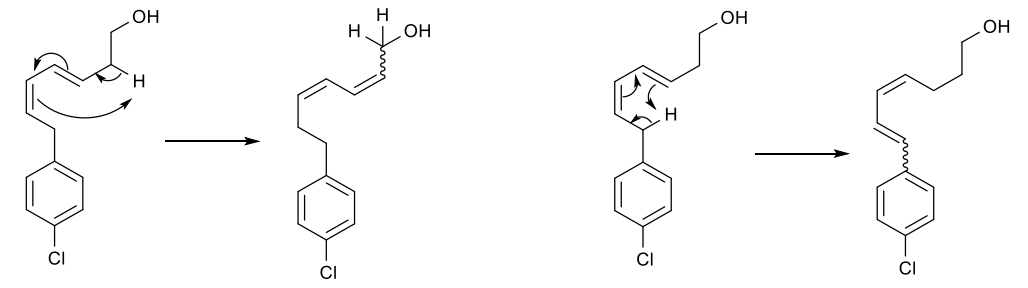
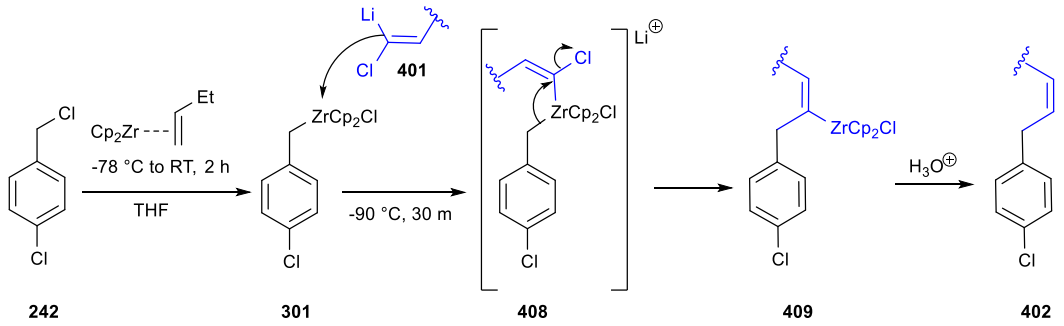
Entry	Alkenyl Carbenoid	Product	Yield (%)
1	 **93** C_4H_4ClLi (94.47)	 **355** $C_{11}H_{11}Cl$ (178.66)	38
2	 **394** $C_{10}H_{14}ClLi$ (176.61)	 **405** $C_{17}H_{21}Cl$ (260.81)	44
3	 **403** $C_{12}H_{20}ClLiOSi$ (250.77)	 **406** $C_{13}H_{13}ClO$ (220.70)	45
4	 **404** $C_{12}H_{22}ClLiOSi$ (252.78)	 **407** $C_{13}H_{15}ClO$ (222.71)	33

Table 25 – Summary of alkenyl carbenoid insertions into 4-chlorobenzylzirconocene chloride (Scheme 116).



407 $C_{13}H_{15}ClO$ (222.71) **407b** $C_{13}H_{15}ClO$ (222.71) **407** $C_{13}H_{15}ClO$ (222.71) **407c** $C_{13}H_{15}ClO$ (222.71)

Scheme 117 – Proposed mechanisms for 1,5-hydride shift of diene alcohol **407**.

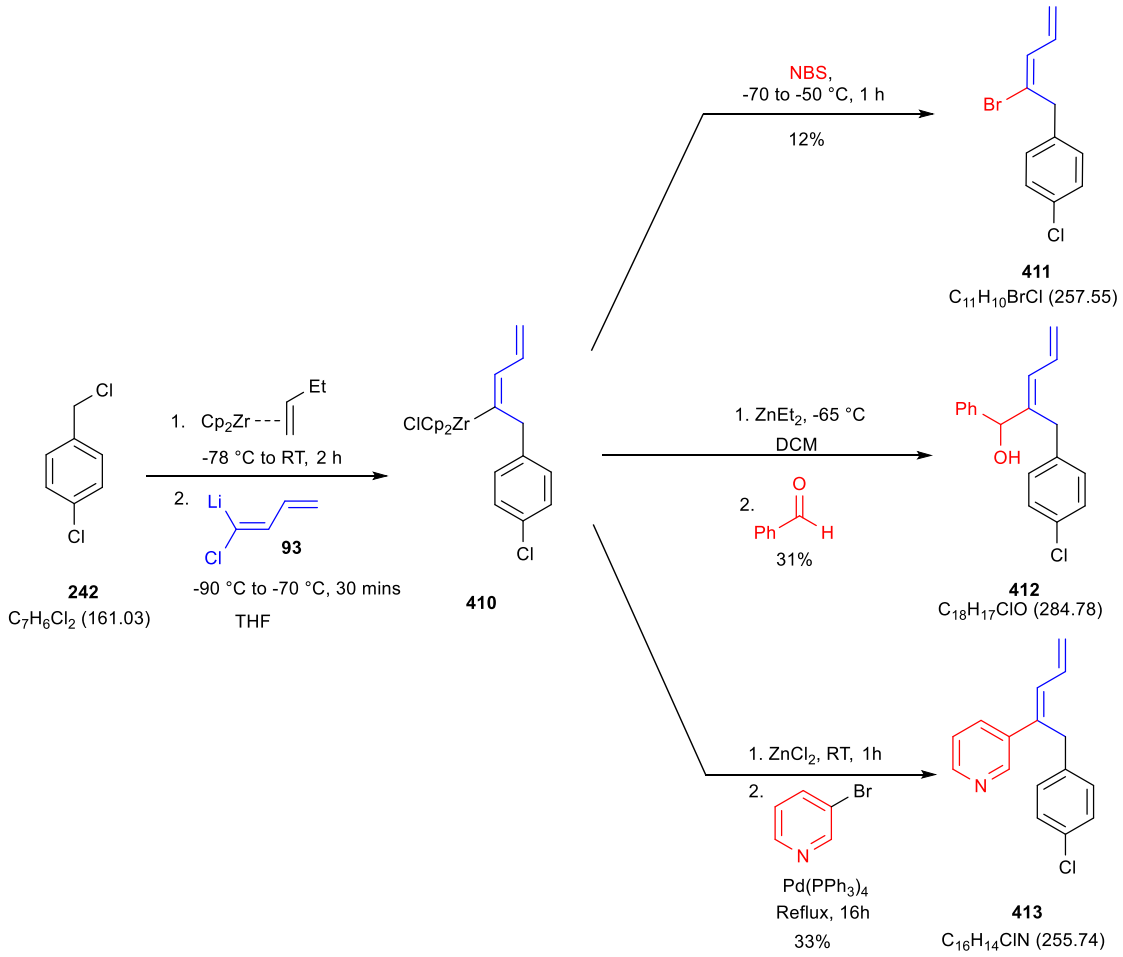


Scheme 118 – Mechanism of alkenyl carbenoid insertion into benzylzirconocene followed by 1,2-metallate rearrangement and consequently inversion of the vinyl halide geometry.

4.4.2 – Three-Component Couplings with Alkenyl Carbenoids

Insertion of alkenyl carbenoids into benzylzirconocenes results in a product which retains the zirconocene functionality, thus further elaboration can be conducted on the newly formed organozirconocene. Retention of the C-Zr bond allows for synthesis of complex compounds in a one-pot three-component coupling reaction. Thus, three alternative elaborations were trialled on the alkenylzirconocene **410**, a product formed from insertion of alkenyl carbenoid **93** which is prepared in situ from commercially available (*Z*)-1,4-dichlorobut-2-ene (Scheme 93, Section 4.2.3).

Bromination of alkenylzirconocenes can be achieved using *N*-bromosuccinimide (NBS) which was first demonstrated by Schwartz.[68] Therefore, after insertion of alkenyl carbenoid **93** into 4-chlorobenzylzirconocene chloride, the reaction was treated with one equivalent of NBS (Scheme 119). After one hour at low temperature and subsequently at room temperature for 16 hours, GC monitoring showed bromination of alkenylzirconocene **410** to give bromide **411** remained incomplete. Alternatively, degradation of the already formed bromide observed at low temperature began to occur, identified by the appearance of new peaks whilst monitoring by GC. Repeating the reaction with two equivalents of NBS resulted in full conversion of alkenylzirconocene **410** to bromide **411**. However, bromide **411** was found to be significantly unstable, degrading on a mildly warm rotary evaporator bath within 20 minutes, at room temperature if left for over two hours and in the freezer after more than two weeks. Consequently, on the fifth attempt at synthesising the compound, the reaction mixture was not warmed above 0 °C, the rotary evaporator bath was kept at 0 °C and purification was conducted quickly to avoid being at room temperature for longer than 2 hours. Clean bromide **411** was isolated in 12% yield after HPLC purification, the low yield most likely a result of the instability of the compound.



Scheme 119 – Insertion of carbenoid **93** onto 4-chlorobenzylzirconocene followed by three different elaborations cleaving the C-Zr bond.

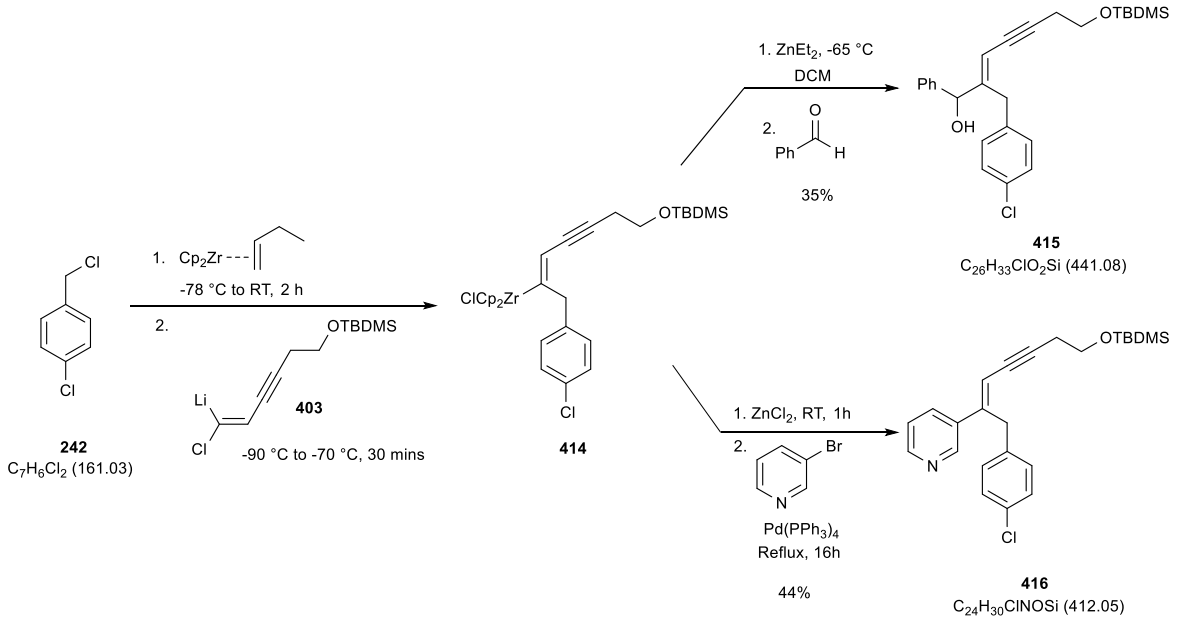
The second alternative elaboration attempted was addition of benzaldehyde onto alkenylzirconocene in a similar manner to that described for allylzirconocenes (Section 1.3.3.2). Quenching with benzaldehyde and $BF_3.OEt_2$ Lewis acid, as conducted for allylzirconocenes, was unsuccessful and did not yield any alcohol **412** product. Literature precedence was found for the addition of carbonyls onto alkenylzirconocenes after transmetallation to zinc in CH_2Cl_2 solvent.[132, 135] In order to follow these literature conditions, the solvent of the reaction was changed from THF to DCM after carbenoid insertion, achieved by concentration of the reaction mixture *in vacuo* whilst remaining under nitrogen. This was followed by the addition of diethyl zinc and freshly distilled benzaldehyde. The reaction was successful and showed formation of alcohol **412** in 31% yield for the three-component coupling (Scheme 119). In an attempt to avoid the delicate solvent exchange, the transmetallation was trialled in THF however, this proved to be unsuccessful. Alternative literature conditions were sought for the addition of carbonyls to alkenylzirconocenes which avoided solvent changes. However, precedent literature demonstrated that addition of carbonyls activated by Lewis acids (most successfully with

TMSOTf) onto alkenylzirconocenes only proceeded well in non-coordinating solvent such as CH_2Cl_2.[137]

For the final alternative elaboration demonstrated, transmetallation from zirconium to zinc was exploited once more. A Negishi coupling reaction was conducted on alkenylzirconocene **410**, after transmetallation using $ZnCl_2$, which added a 3-pyridine group at the former C-Zr bond under palladium catalysis.[210, 211] The reaction yielded pyridine **413** in 33% yield once the reaction was refluxed (Scheme 119). Both the Negishi coupling and the carbonyl addition gave comparable yields to the equivalent two-component coupling described in Section 4.4.1 demonstrating the final elaboration of the three-component coupling proceeded well.

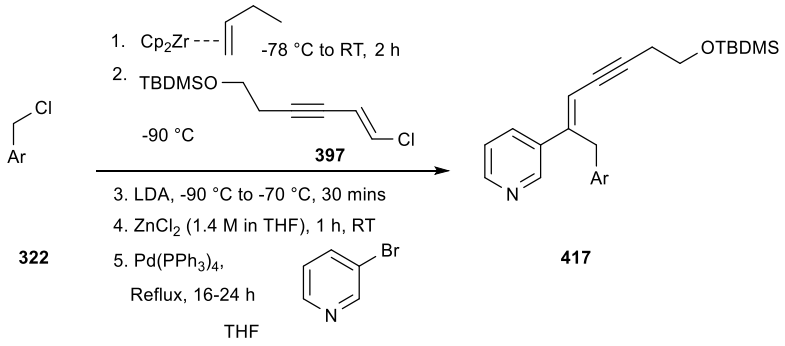
The three alkenylzirconocene elaborations resulting in C-Zr bond cleavage are known to proceed with retention of configuration (Section 1.3.3). Thus the structure of all three products (bromide **411**, alcohol **412** and pyridine **413)** have been drawn with the shown stereochemistry of the alkene (Scheme 119), which is in accordance with the two-component coupling reactions showing formation of a *cis*-alkene (Section 4.4.1). Only one three-component coupling product was observed for all three elaborations.

Both transmetallations to zinc for the addition of the third component gave similar yields. As insertion of carbenoid **403** gave the highest yield for the two-component coupling (Section 4.4.1), carbonyl addition and Negishi coupling was trialled on alkenylzirconocene **414** to identify the highest yielding combination for the three-component coupling (Scheme 120). For the addition of the benzaldehyde, a 35% yield was obtained for alcohol **415**. This was a lower yield than expected, likely due to losses from multiple purification attempts by column chromatography and the use of the HPLC to obtain clean compound. Furthermore, incomplete addition of benzaldehyde to alkenylzirconocene **414** was observed by GC monitoring, most likely due to the benzaldehyde not being freshly distilled on the day of use. For the 3-pyridine Negishi coupling, a good yield of 44% was obtained for pyridine **416**. Addition of a pyridine increased the polarity of the product and facilitated its purification and separation from remaining unreacted carbenoid and dichlorobibenzyl compounds. However, separation of product from minor quantities of 3-(4-chlorobenzyl)pyridine, a by-product formed from the coupling of transmetallated benzylzirconocene to pyridine if carbenoid addition is incomplete, was difficult. This was only eventually achieved by column chromatography using 5% EtOAc in DCM over silica to yield the clean product **416**.



Scheme 120 – Carbenoid **403** insertion into benzylzirconocene with benzaldehyde or 3-pyridine addition after transmetallation to zinc resulting in a three-component coupling.

The three-component coupling using the insertion of alkenyl carbenoid **403** into 4-chlorobenzylzirconocene chloride followed by transmetallation to zinc for a Negishi coupling to 3-bromopyridine was repeated on a variety of benzyl chlorides (Scheme 121 and Table 26). Yields for these benzyl chlorides ranged from 30 to 46%. The lowest yields were generally from the bulkier or sterically hindered benzyl chlorides for which carbenoid insertion was incomplete despite extended reaction time provided for the 1,2-metallate rearrangement to take place. For the synthesis of the trifluoromethyl compound **421**, GC monitoring (with an internal standard) was carried out on the reaction between 4-(trifluoromethyl)benzyl chloride and zirconocene(1-butene) to determine the optimum reaction time for the formation of the corresponding benzylzirconocene due to its observed degradation (as discussed in Section 4.2.1). GC monitoring identified the optimum reaction time to be 70 minutes thus this was the reaction time provided for the synthesis of **421** instead of the standard two hours provided for the other compounds (Scheme 121). Purification of compounds **418**-**427** was realised in the same manner described for pyridine **416**; column chromatography with 1% Et_3N, 20% EtOAc in hexane on silica followed by a second column using 5% EtOAc in DCM on silica. The latter purification allowed for separation of product from any minor amounts of corresponding 3-benzylpyridines.



Scheme 121 – Three-component couplings between varying benzyl chlorides, enyne **397** and 3-pyridines.

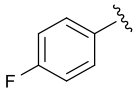
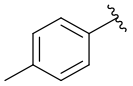
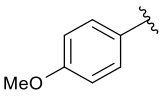
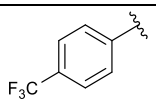
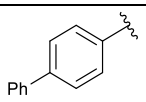
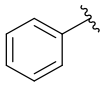
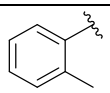
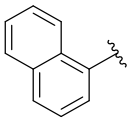
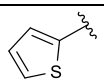
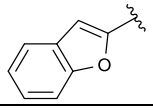
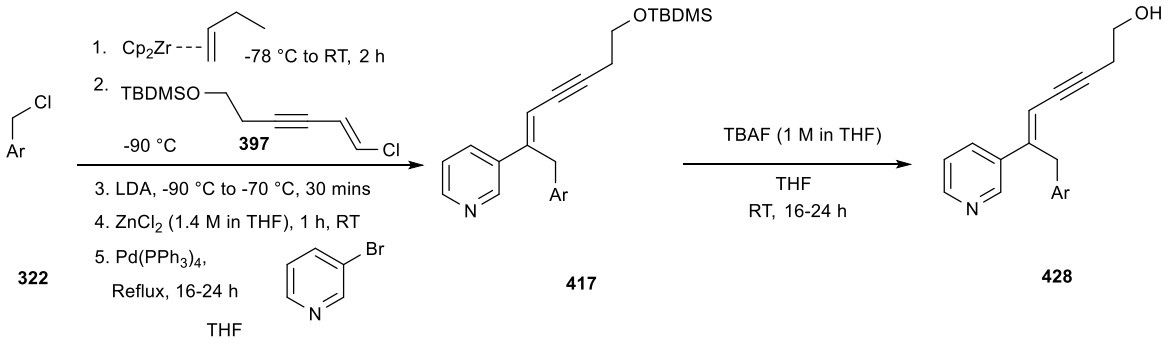
Entry	Ar	Product	Yield (%)
1		**418**	43
2		**419**	30
3		**420**	33
4		**421**	36
5		**422**	46
6		**423**	34
7		**424**	33
8		**425**	38
9		**426**	41
10		**427**	33

Table 26 – Summary of three-component coupling of benzylzirconocenes followed by carbenoid insertion and final transmetallation to zinc for Negishi coupling to 3-bromopyridine (Scheme 121).

Before the use of EtOAc in DCM was identified as the optimum solvent system for column separation of product from respective 3-benzylpyridines, purification of the Negishi coupling products were achieved after TBDMS removal using TBAF (Scheme 122 and Table 27). Removal of the protecting group increased the polarity of the desired Negishi coupling product allowing for easier separation from the small quantities of 3-benzylpyridines. Yields for the compounds **429**-**434** ranged from 26% to 40% across both steps, yields lower than those stated in Table 26 for compounds not deprotected. The lower yields were most likely due to losses associated from carrying out a second reaction on the compound before clean isolation, particularly when working on a small scale.

Upon purification on silica of deprotected thiophene **426** and benzofuran **427** three-component products, degradation of these products occurred. As a result, after resynthesis of benzofuran **426** and thiophene **427** compounds, extensive TLC analysis identified the EtOAc-DCM eluent system for the efficient purification of the three-component coupling products before deprotections (listed in Table 26). Consequently, the three-component coupling products already deprotected (Table 27) were resynthesized to allow for better comparison of the different aryl groups for the three-component coupling (Scheme 121).

One compound which was not possible to isolate cleanly before TBAF deprotection was bis-pyridine **435** (entry 7, Table 27). Due to similar polarities, separation of the product from its corresponding bibenzyl and 3-benzylpyridine compoundswas found to not be possible by column chromatography. Removal of the TBDMS group thus allowed isolation of product **435** in 12% yield. The low yield was presumably due to polymerisation of 4-(4-(chloromethyl)phenyl)pyridine when isolated as the free amine from the salt which may have occurred before reacting with zirconocene(1-butene).



Scheme 122 – Three-component coupling followed by TBAF deprotection.

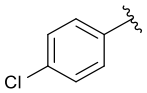
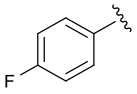
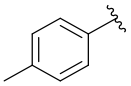
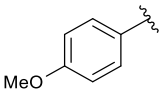
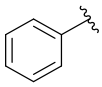
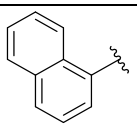
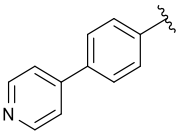
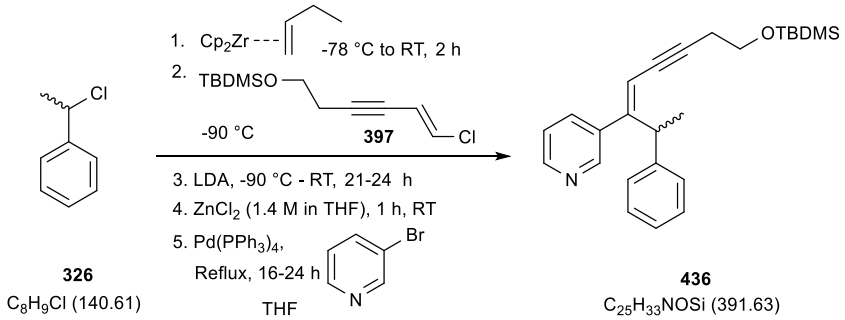
Entry	Ar	Product	Total Yield (%)
1		**429**	35
2		**430**	38
3		**431**	30
4		**432**	37
5		**433**	40
6		**434**	26
7		**435**	12

Table 27 – Summary of three-component couplings followed by TBAF deprotections (Scheme 122).

In addition to the different aryl compounds used for the three-component couplings already described, the reaction was also conducted on *Rac*-(1-chloroethyl)benzene **326**, a secondary benzyl chloride (Scheme 123). This was successful and afforded pyridine **436** in a 26% yield (Table 28). The lower yield was due to incomplete carbenoid insertion caused by steric hindrance of the methyl group as observed by GC monitoring, despite extended reaction time provided for the 1,2-metallate rearrangement. To determine the stereoselectivity of the reaction, the three-component coupling was carried out on (*R*)-(1-chloroethyl)benzene **326-*R*** yielding pyridine product **436** in 27% yield (Table 28). The *R*/*S* ratio for compound **436** prepared from chiral (*R*)-(1-chloroethyl)benzene **326-*R*** was identified using a NMR chiral solvating agent, (*R*)-(+)-1,1'-bi(2-naphthol), as *R*/*S* enantiomers of product **436** were inseparable by HPLC using CHIRALCEL® OD-H and CHIRALPAK® AD-H columns. ^{1}H-NMR analysis of compound **436b** with (*R*)-BINOL showed a 1:1.1 ratio between *R*/*S* compounds of **436**. The *R*/*S* ratio suggested the stereochemistry of the benzyl was lost before carbenoid insertion, either by configurational instability of the benzylzirconocene species or by non-stereoselective insertion of zirconocene into Bn-Cl bonds. The result is of mechanistic importance for the formation of benzylzirconocenes as retention of stereochemistry would be expected if the reaction were to proceed *via* the proposed mechanism shown in Section 4.1.



Scheme 123 - three-Component coupling on secondary benzyl chloride **326**.

Entry	Ethyl Benzyl Chloride **326**	Product No.	Yield (%)	*R*/*S* ^{1}H-NMR Ratio
1	Racemic	**436**	26	1:1
2	*R*	**436b**	27	1 : 1.1

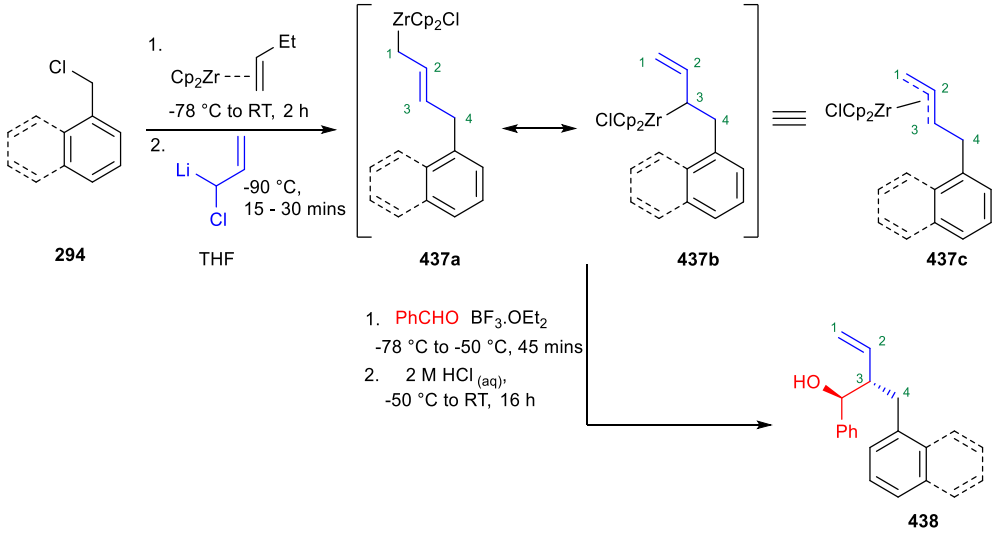
Table 28 – Summary of the three-component coupling on secondary benzyl chloride **326** (Scheme 123).

4.4.3 – Three-Component Couplings with an Allylic Carbenoid

As one of the carbenoids to have successfully inserted into benzylzirconocene chlorides (discussed Section 4.2.3), (1-chloroallyl)lithium was inserted into naphthyl and benzylzirconocene chlorides followed by benzaldehyde addition with Lewis acid $BF_3.OEt_2$ (Scheme 124). This reaction yielded homoallyl alcohols **346** and **439** in 8% and 26% isolated yields (17 and 29% estimated total yield respectively), as shown in Table 29. The low yields were suspected to be due to incomplete allyl carbenoid insertion into the benzylzirconocene as observed by GC monitoring, which was not improved by extended reaction time at room temperature to eliminate the possibility of a slow 1,2-metallate rearrangement. In addition, double carbenoid insertion was observed (identified by GCMS) as discussed in section 4.2.3. The yield for the naphthalene system **439** was greater than that of the benzyl chloride system **346**, the benzyl chloride system was more susceptible to double carbenoid addition as a consequence of steric effects.

Clean isolation of the homoallylic alcohols **346** and **439** was troublesome and required HPLC purification. Despite the use of HPLC, very poor separation was achieved between single and double carbenoid addition products, as well as some minor unknown impurities. Consequently, several mixed samples of product was isolated along with one clean sample, hence the estimated total yields. Only a single regioisomer was formed from the reaction in which benzaldehyde addition occurred at the γ-carbon (C3) of the allylzirconocene intermediate **437** instead of the α-carbon (C1), a consequence of the chair-like conformation

adopted for the addition of carbonyls onto allylzirconocenes (Scheme 124) as demonstrated and discussed in Section 1.3.3.2. ^{1}H-NMR analysis of the crude product confirmed a *syn*:*anti* ratio to be consistent and largely in favour of the *anti* diastereoisomer by an average of 88.5%, as expected from literature precedent for the preparation of homoallylic alcohols *via* organozirconocenes.[81, 124, 125, 212] The assignment of the *syn*/*anti* relative stereochemistry for benzyl **346** product was made in accordance with published literature for the benzyl compound.[213, 214] The relative stereochemistry of naphthalene homoallylic alcohol **439** was assigned based on the stereochemistry of the benzyl system as this compound was prepared *via* the same route.



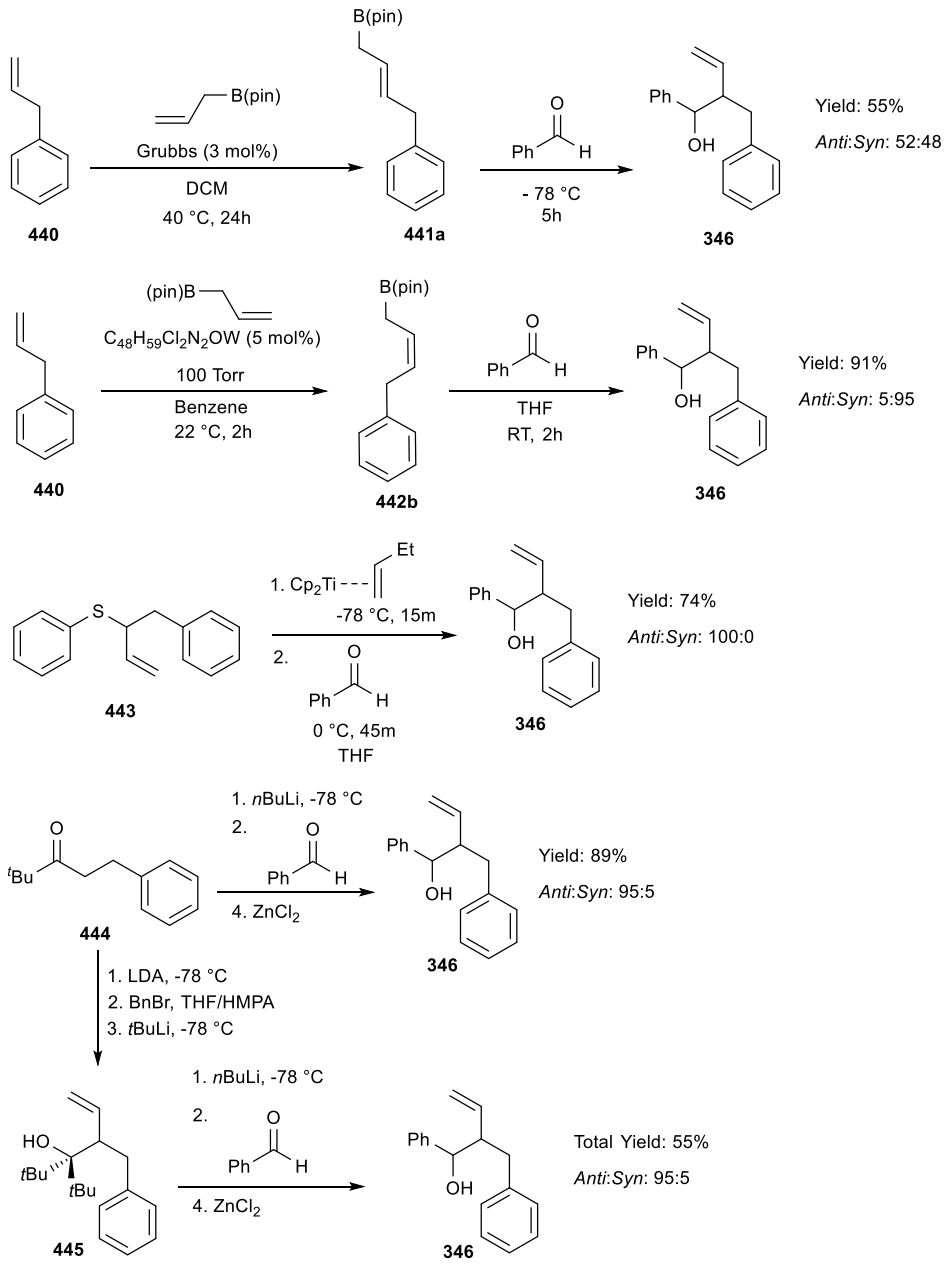
Scheme 124 - Allyl carbenoid insertion and benzaldehyde addition on benzylzirconocene chloride and naphthalenemethyl zirconocene chloride.

Entry	Ar	Compound No.	*Anti* : *Syn* Ratio	PhCHO Addition Conditions	Isolated Yield (%)	Estimated Total Yield (%)
1	Ph	**346**	88 : 12	-78 to -50 °C. 45 mins	8	17
2	Np	**439**	89 : 11	-78 °C to -50 °C, 30 mins	26	29

Table 29 – Allyl carbenoid insertion and benzaldehyde addition on benzyl and naphthylmethyl zirconocene chloride reaction products and yields (Scheme 124).

Although the synthesis of homoallylic alcohols with the use of organozirconoium chemistry is prevalent in the literature, none have had the benzyl moiety. Benzyl homoallyl alcohol **346** has been reported in the literature; with the use of Grubbs[215] or tungsten catalysts[214] with boronic esters in alkene cross metathesis, titanocene on an allyl sulphide[212] or with the use of organozinc chemistry[213, 216] in yields ranging from 55-91%, summarised in Scheme 125. Some of the literature reactions show high diastereomeric selectivity however, the reactions

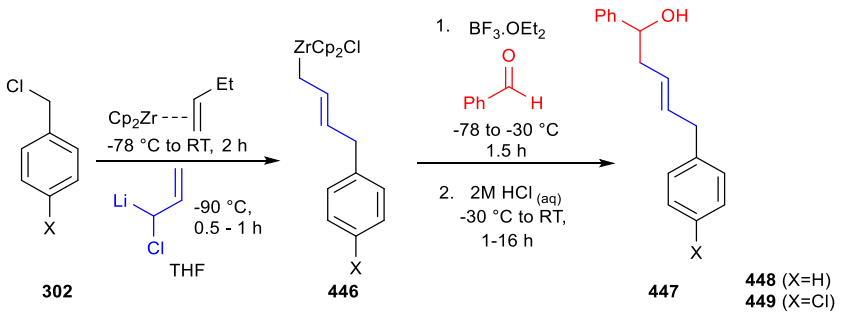
favouring the *anti* diastereoisomer are not begun from commercial starting materials. Furthermore, the organozinc reactions require the use of *t*-BuLi which poses practical difficulties.[213, 216]



Scheme 125 – Summary of *anti/syn* benzyl homoallylic alcohol synthesis reported in the literature.

Upon repeating the reaction on benzyl chloride (to obtain a better yield) and 4-chlorobenzyl chloride (the parent system) in parallel, the major product was found to be a regioisomer of the expected product in which benzaldehyde addition occurred at the α-carbon resulting in the linear product **447** as the major product (Scheme 126). Alcohols **448** and **449** were obtained in 15% and 12% isolated yields respectively (19% and 17% estimated total yields) (Table 30). Only the *trans* alkene was formed in both reactions, identified by ^{1}H-NMR from

the 14.8-15.8 Hz coupling between the alkene protons. Similarly for compounds **346** and **439** (Scheme 124), purification was troublesome and required HPLC purification resulting in isolation of mixed samples for compound **448** and **449** and only one clean sample.



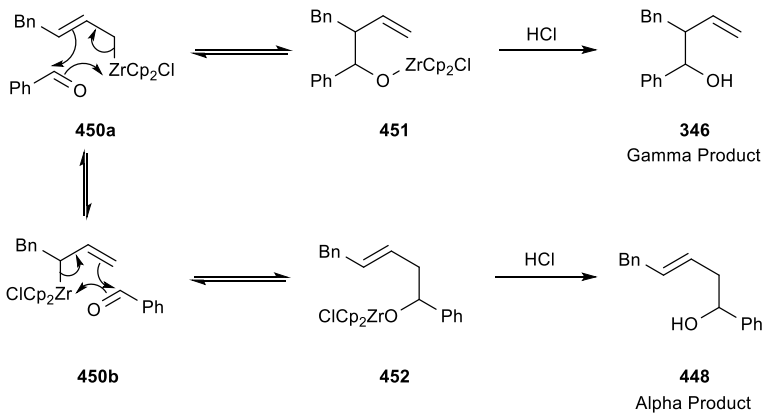
Scheme 126 – Allyl carbenoid insertion and benzaldehyde addition on benzylzirconocene chloride and 4-chlorobenzylzirconocene chloride.

Entry	X	Compound No.	Major Product	Isolated Yield (%)	Estimated Total Yield (%)
1	H	**448**	*E*-nternal Alkene	15	19
2	Cl	**449**	*E*-Internal Alkene	12	17

Table 30 - Allyl carbenoid insertion and benzaldehyde addition on benzyl and 4-chlorobenzylzirconocene chloride reaction products and yields (Scheme 126).

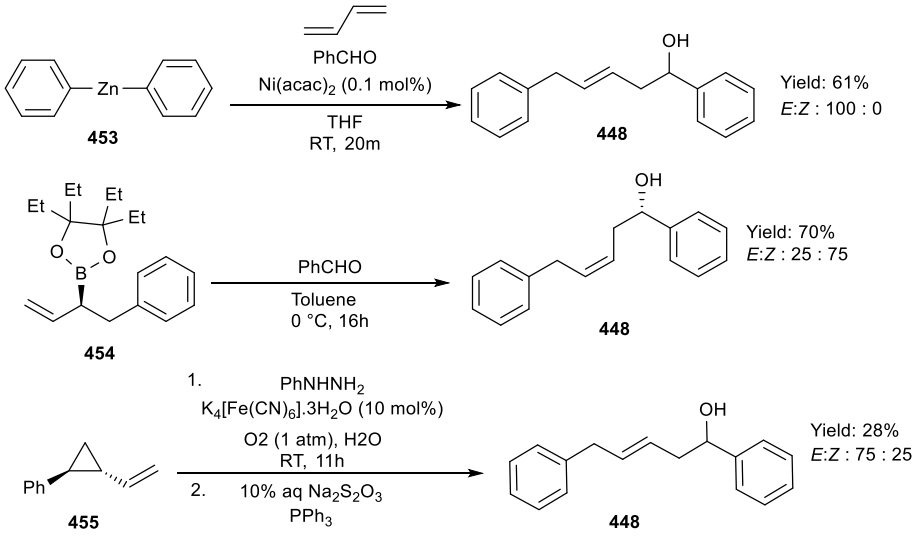
The key difference between the reactions yielding the γ-addition products and those yielding the α-addition products was the reaction time length and temperature between benzaldehyde addition and HCl quench. These reaction parameters were not maintained consistent as syntheses of γ-homoallylic alcohols have been prepared with the quench at below 0 °C and at room temperature. It appears that quenching at -50 °C affords the γ-homoallylic alcohols **447**, whereas allowing the reaction to warm to -30 °C before quenching affords the linear α-homoallylic alcohols **438**. The change in product isolated may be an example of kinetic (γ-product **447**) and thermodynamic products (α-product **438**) a consequence of the addition of benzaldehyde to allylzirconocene being reversible (Scheme 127). The reversibility of benzaldehyde addition to allylzirconocenes (termed retroallylation) has been reported in the literature for allylzirconocene with a OCH(*i*-Pr)$_2$ ligand - the temperature at which the HCl quench was conducted affected the product outcome (as discussed in Section 1.3.3.2).[126] However, the retroallylation reported only influenced the relative stereochemistry (*syn* and *anti*) of the product isolated not the regiochemistry and is reported only to have occurred for allylzirconocenes with OCH(*i*-Pr)$_2$ ligand on zirconocene.[126, 127] Thus, the reversibility of benzaldehyde addition onto allylzirconocene chloride resulting in different regioisomers is unprecedented and may be a result of the benzyl group. However, due to time constraints,

confirmation of the reversibility of the benzaldehyde addition and thus determination of the conditions affecting the regioselectivity was unfortunately not conducted.



Scheme 127 – Proposed reversible benzaldehyde addition to allylzirconocene to afford homoallylic alcohol regioisomers **346** and **448**.

Synthesis of linear homoallylic alcohol compounds is also reported in the literature but with the use of organozinc compounds with nickel catalysis, boron chemistry and by a radical aerobic oxidation. Only the organozinc with nickel showed the same stereoselectivity for the *E*-alkene as the zirconocene reaction described in this work (Scheme 128).[217-219]



Scheme 128 - Summary of α-linear benzyl homoallylic alcohol synthesis reported in the literature.

4.5 – Conclusions

In conclusion, the reactivity between benzyl chlorides and zirconocene(1-butene) was investigated and exploited for the synthesis of compounds through one-pot two-component and one-pot three-component couplings using alkenyl carbenoids in yields of 12-46%. The low yields are due to formation of bibenzyl from the reaction which uses 33-57% of the benzyl chloride starting material. With this in consideration, the yields were high for the

alkenyl carbenoid insertions. Various mechanisms were proposed for the formation of the bibenzyl, such as intermolecular couplings or radical reactions, however none of these theories were supported upon testing. Attempts to understand the mechanism through examining the influence of electron-donating and electron-withdrawing substituents suggested the reactions were relatively unaffected by electronic factors. The most plausible mechanism still remains the sp^3 coupling however, alternative reactions to test this would need to be devised.

Chapter 5 – Experimental

5.1 – General Experimental

Reactions:

Set-Up: All reactions were conducted in oven-dried (150 °C for at least 12 hours) Schlenk flasks, which were allowed to cool in a sealed desiccator with Drierite® before use. These were placed under inert atmosphere of nitrogen gas using standard Schlenk techniques. Reactions kept at -20 °C overnight were done so using an LTC2 Grant TC120 refrigerated circulating bath.

Solvents: All reaction solvents used were anhydrous. THF was freshly distilled over sodium wire-benzophenone. CH_2Cl_2 and MeCN were freshly distilled over CaH_2, $CHCl_3$ was dried over $CaCl_2$ (for at least 12 hours) and Et_2O was purchased anhydrous directly from commercial suppliers. Any other solvents were used in the form obtained from commercial suppliers.

Reagents: Acrolein was dried over 3 Å freshly activated molecular sieves overnight and distilled over molecular sieves at 58 °C under 1 atm. EtOH was also dried over 3 Å freshly activated molecular sieves overnight and distilled over molecular sieves at 78 °C under 1 atm. Et_3N, Et_2NH, *i*-Pr_2NH, TMP and commercial benzyl chlorides were dried over CaH_2, distilled and stored over CaH_2 before use. *n*-BuLi and $ZnEt_2$ were stored in Schlenk stock bottles under nitrogen. $ZnCl_2$ was dried at 0.1 mbar at 200 °C for 24 hours before dissolution in dry THF and stored in a Schlenk flask.

Purification:

Column Chromatography: Merck silica gel Geduran Si60 (40-63 μm) and with the eluent as specified in each procedure. Column purifications conducted on ISOLUTE®SiII pre-packed silica were done so on a Jones Chromatography Flash Master Personal 50-027-Ez.

HPLC: Compounds from Chapter 2 purified by HPLC were done so on a Hewlett Packard 1050 series HPLC, any other compounds were purified on a Shimadzu LC-20AR HPLC. Columns and eluents used are specified in the reaction procedures.

Kugelrohr Distillation: Compounds purified by Kugelrohr distillation were done so using a Buchi Gass Oven B-585 Kugelrohr at the temperature and pressure specified in the experimental procedure.

GC Monitoring:

GC analysis was carried out on a Hewlett Packard 6890 Series GC System. Samples were prepared from a small quantity of reaction mixture (normally 0.1 mL) which was subjected to a mini work up in a 1:1 ratio between Et_2O and H_2O. The Et_2O phase would be filtered over cotton wool before submission, aiming for 1 $mgmL^{-1}$ concentration.

Standard GC Programmes:

HP-5 (cross-linked 5% PH ME siloxane) 30 m length column, film thickness of 0.25 µm and 0.32 mm internal diameter. The carrier gas was helium with a flow rate of 2.7 mL min^{-1} and flame ionisation detector (FID) was used.

AP40: Starting temperature was 40 °C (maintained for 0 minutes) followed by a temperature gradient of 25 °C min^{-1} to 275 °C, remaining at 275 °C for 4 minutes.

AP40L: Starting temperature was 40 °C (maintained for 0 minutes) followed by a temperature gradient of 25 °C min^{-1} to 275 °C, remaining at 275 °C for 10 minutes.

AP240: Starting temperature was 240 °C (maintained for 0 minutes) followed by a temperature gradient of 1 °C min^{-1} to 260 °C, remaining at 260 °C for 0 minutes.

AP239: Starting temperature was 239 °C (maintained for 0 minutes) followed by a temperature gradient of 0.25 °C min^{-1} to 242 °C, remaining at 242 °C for 0 minutes.

Chiral GC Programmes:

HP-5 beta-cyclodextrin permethylate hydroxypropyl 30 m length column and 0.25 mm diameter. The carrier gas was helium with a flow rate of 1.3 mL min^{-1} and flame ionisation detector (FID) was used.

BP70: Starting temperature was 70 °C (maintained for 25 mins) followed by a temperature gradient of 20 °C min^{-1} to 150 °C (maintained for 0 minutes).

BP140: Starting temperature at 140 °C (maintained for 25 minutes) followed by a temperature gradient of 10 °C min^{-1} to 150 °C (maintained for 0 minutes).

Yields:

Yields were determined from the total mass of isolated clean compound from that reaction. Estimated yields were determined for compounds which were not isolated cleanly or where some samples of compound were found to be mixed. The value was calculated by using ^{1}H-NMR (if impurities were known) or LRMS UV absorbance integration (if impurities were unknown) to determine sample purity and, therefore yield of compound.

Characterisation:

NMR: Spectra were obtained using the Bruker AVIIHD400/ AVIII400 FT-NMR Spectrometer in which samples were dissolved in the specified deuterated solvent and filtered over cotton wool. ^{1}H-NMR spectra was referenced to residual solvent peak (7.26 ppm for $CHCl_3$ and 2.50 ppm for DMSO). Multiplicities were abbreviated as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), multiplet (m), broad peaks were denoted with 'br' and multiplets with fine splitting with 'fs'. Multiplet peaks integrating to more than 1H were reported as a ppm range, whereas other multiplicities or 'm' peaks only integrating to 1H were reported to the central ppm value. Peaks in ppm were reported to 2 decimal places and coupling constants (*J*) were reported in Hertz (Hz) to 1 decimal place, values <5 were rounded down and values ≥5 were rounded up. Specific assignment of peaks to the H-atoms of compound were aided by ^{1}H-^{1}H COSY NMR. Multiplets with second order effects have been marked with *.

^{13}C-NMR was referenced to the deuterated solvent used (middle peak at 77.16 ppm for $CHCl_3$, 39.52 ppm for DMSO and 7.16 ppm for C_6D_6). Peaks were reported in ppm to 2 decimal places, where values <5 were rounded down and values ≥5 were rounded up. Peaks were assigned C, CH, CH_2 or CH_3 according to the DEPT135-NMR and, when applicable, coupling constants (due to fluorine or deuterium presence) reported in Hertz. Specific assignment of peaks to the C-atoms of compound were aided by ^{1}H-^{13}C HSQC NMR. Compounds with deuterium incorporation which showed a weak signal for H incorporation on the same carbon were denoted with letter 'w' with neighbouring deuterium incorporated carbon labelled as a triplet and assigned CD.

For both ^{1}H- and ^{13}C-NMR containing a mixture of isomers, the major isomer was used as the reference for integration to denote 1H therefore minor isomer peaks will have integrations reported as less than 1H to 1 decimal place. Similarly, peaks of mixed major

and minor isomers will show exact integration values to 1 decimal place. If the quantity of the minor isomer was less than 20% in the isolated & characterised sample or the isomer is only observed in the crude sample, characteristic peaks of this isomer are reported separately from the peaks of the isolated major compound.

LRMS: Values of *m/z* were reported along with peak intensity (%) relative to the base peak to 0 decimal place. For compounds with bromine or chlorine, only the most abundant isotope was reported however all expected isotope patterns were observed for the compounds listed. Furthermore, the molecular masses beneath each compound structure is the average molecular mass which takes account isotope abundancies.

For EI or CI, Thermo (Hemel Hempstead, UK) Trace GC-MS single quadrupole mass spectrometer was used. Gas chromatography was performed using a Phenomenex ZB5-MS 30 m x 0.25 mm 0.25 µm thickness non-polar column using helium as a carrier gas at 1.2 mL min^{-1}. The injector temperature was set at 240 °C and 1 µL of sample was injected in splitless mode. Low resolution positive ion electron ionisation (or chemical ionisation using ammonia as a reagent gas) mass spectra were recorded over a mass range of *m/z* 40-500 at 70 eV.

For ESI reverse or normal phase, Waters (Manchester, UK) Acquity TQD mass tandem quadrupole mass spectrometer was used. For reverse phase, samples were introduced to the mass spectrometer via an Acquity H-Class quaternary solvent manager (with TUV detector at 254 nm, sample and column manager). Ultrahigh performance liquid chromatography was undertaken using Waters BEH C18 column (50 mm x 2.1 mm 1.7 µm). Gradient elution from 20-100% acetonitrile in water with 0.2% formic acid was performed over five/ten minutes at a flow rate of 0.6 mL/min. Low resolution positive/negative ion electrospray ionisation mass spectra were recorded. For normal phase, samples were introduced using a 2 µL Partial Loop with Needle Overfill (PLNO) injection. Ultrahigh performance supercritical fluid chromatography was undertaken using a UPC^2 BEH C18* column (Waters, 100 mm x 3.0 mm 1.7µm). Gradient elution from 90 % CO_2:10% methanol modifier (25 mM ammonium acetate) to 60% CO_2:40% methanol modifier (25 mM ammonium acetate) was performed over three minutes at a flow rate of 1.5 mL/min with an Active Back Pressure Regulator (ABPR) pressure of 150 bar. A make-up flow solvent (methanol 1% formic acid) was pumped at a flow rate of 0.45 mL min^{-1} into the mass

spectrometer. Low resolution positive/negative ion electrospray ionisation mass spectra were recorded.

HRMS: The *m*/*z* values are reported to 4 decimal places, the reporting of compounds with bromine or chlorine is conducted in the same manner as for LRMS.

For ESI, samples were analysed using a MaXis (Bruker Daltonics, Bremen, Germany) time of flight (TOF) mass spectrometer. Samples were introduced to the mass spectrometer *via* a Dionex Ultimate 3000 autosampler and uHPLC pump. Ultrahigh performance liquid chromatography was performed using a Waters UPLC BEH C18 (50 mm x 2.1 mm 1.7µm) column. Gradient elution from 20-100% acetonitrile in water with 0.2% formic acid was performed in five minutes at a flow rate of 0.6 mL min^{-1}.

For APPI, samples were analysed using a solariX (Bruker Daltonics, Bremen, Germany) mass spectrometer equipped with a 4.7 T magnet and FT-ICR cell. Samples were introduced to the mass spectrometer using a syringe driver at a flow rate of 5 µL min^{-1}. High resolution positive/negative ion electrospray ionisation or atmospheric pressure photoionisation mass spectra were recorded.

For EI, samples were analysed using a Thermo (Hemel Hempstead, UK) MAT900 XP double focusing sector mass spectrometer. Samples are introduced into the source using a solid heated probe. The source temperature is set to 150 °C and the filament is at 0.5 Ma. High resolution mass spectra positive ion electron ionisation were recorded at 70 eV.

Infra-Red: Spectra were obtained using a Thermo Fisher iD7ATR Diamond KBr Nicolet Is5 Infra-Red spectrometer. Absorptions are reported using wavenumbers (cm^{-1}) rounded to zero decimal places (*via* the same protocol as NMR). Intensities described with the following abbreviations; strong (s), medium (m), weak (w), very weak (vw) and broad (br). Only the strongest peaks were reported below 1400 cm^{-1}.

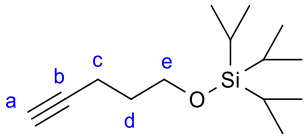
Melting Point: Values were measured using a Stuart® SMP20 digital melting point apparatus, melting point values were given to 1 decimal place.

Alpha-D: Values were recorded on Optical Activity LTD PolAAR 2001 polarimiter at 589 nm in which samples were dissolved in CH_2Cl_2 at known concentrations specified in the characterisation.

5.2 – Agonist Synthesis Targeting LRH-1 & SF-1 Receptors

5.2.1 – Synthesis of Target A

5.2.1.1 - 1-Triisopropylsilyloxypent-4-yne (166)



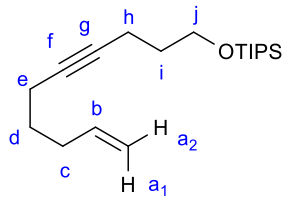
$C_{14}H_{28}OSi$ (240.46)

Procedure:[209] To a stirring solution of 1H-imidazole (3.06 g, 45.0 mmol) in DMF (30 mL), 4-pentyn-1-ol (2.80 mL, 30.0 mmol) and TIPSCl (7.06 mL, 33.0 mmol) were added at RT and stirred for 52 hours at RT. The reaction mixture was poured into sat. $NaHCO_{3\ (aq)}$ (100 mL) and extracted with Et_2O (3× 75 mL). The organic phases were combined, washed with $NaHCO_3$ (100 mL) and water (2× 100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 1% Et_2O in hexane over silica to afford the title compound as a colourless oil (6.79 g, 28.0 mmol, 94%).

GC (AP40):	Rt 5.78 mins.
^{1}H-NMR:	δ_H ppm (400 MHz, $CDCl_3$) 3.77 (2 H, t, *J* 6.0 Hz, He), 2.31 (2 H, td, *J* 7.1, 2.7 Hz, Hc), 1.92 (1 H, t, *J* 2.7 Hz, Ha), 1.75 (2 H, tt, *J* 7.0 6.0 Hz, Hd), 1.16 – 0.98 (21 H, m, TIPS).
^{13}C-NMR:	δ_C ppm (101 MHz, $CDCl_3$) 84.54 (C, Cb), 68.29 (CH, Ca), 61.86 (CH_2), 31.93 (CH_2, Cd), 18.15 (6 CH_3, TIPS), 15.03 (CH_2, Cc), 12.14 (3 CH, TIPS).
LRMS (CI):	*m/z*: 241 ($[M+H]^+$, 99%), 214 (17%), 197 ($[M-iPr]^{+\bullet}$, 89%), 172 ([M-*i*Pr&C≡C]$^{+\bullet}$, 28%), 155 ($[M-2(iPr)+H]^{+\bullet}$, 100%), 144 (14%), 127 (86%), 113 (24%).

Characterisation data was consistent with that reported in the literature.[209, 220]

5.2.1.2 - 1-Triisopropylsilyloxy-9-decen-4-yne (162)



$C_{19}H_{36}OSi$ (308.58)

Procedure:[166, 167] To a stirring solution of alkyne **166** (3.39 g, 14.1 mmol) in distilled THF (33 mL), *n*-BuLi (2.5 M in hexanes, 5.92 mL, 14.8 mmol) was added dropwise over 5 minutes at -78 °C under nitrogen. The reaction mixture was allowed to warm to -20 °C and was stirred at this temperature for 3 hours. HMPA (5 mL) was added dropwise over 10 minutes at -20 °C and the reaction mixture was subsequently stirred for 1 hour. 5-Bromo-1-pentene (2.17 mL, 18.3 mmol) in distilled THF (10 mL) was added dropwise to the reaction mixture at -30 °C, the reaction was allowed to warm to RT and stirred overnight. The reaction mixture was quenched with water (10 mL) and concentrated *in vacuo* for THF removal. The resulting mixture was washed with water (100 mL) and extracted with hexane (3× 80 mL). The combined organic phases were washed with water (3× 200 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 0 – 4% EtOAc in hexane over silica to afford the titled compound as a colourless oil (4.12 g, 13.3 mmol, 95%).

GC (AP40): Rt 7.96 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 5.79 (1 H, ddt, *J* 16.9, 10.2, 6.7 Hz, Hb), 5.03 (1 H, dq, *J* 17.2, 1.7 Hz, Ha_1), 4.97 (1 H, ddt, *J* 10.2, 2.2, 1.2 Hz, Ha_2), 3.76 (2 H, t, *J* 6.2 Hz, Hj), 2.26 (2 H, tt, *J* 7.0, 2.4 Hz, He/h), 2.20 – 2.09 (4 H, m, He/h & Hc), 1.71 (2 H, tt, *J* 6.9, 6.3 Hz, Hi/d), 1.57 (2 H, quin, *J* 7.2 Hz, Hi/d), 1.16 – 1.00 (21 H, m, TIPS).

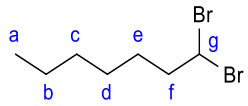
^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 138.26 (CH, Cb), 115.04 (CH_2, Ca), 80.27 (C, Cf/g), 80.04 (C, Cf/g), 62.16 (CH_2, Cj), 32.97 (CH_2, Cc/d), 32.51 (CH_2, Cd/c), 28.44 (CH_2. Cd), 18.34 (CH_2, Ce/h), 18.16 (3 CH, TIPS), 15.34 (CH_2, Ce/h), 12.16 (6 CH_3, TIPS).

LRMS (CI): *m/z*: 309 ($[M+H]^+$, 15%), 265 ($[M-i\text{Pr}]^{+\bullet}$, 44%), 223 ($[M-2(i\text{Pr})+H]^{+\bullet}$, 42%), 195 ($[M-2(i\text{Pr})\&HC{=}CH_2]^{+\bullet}$, 18%), 174 (23%), 157 ($[M-TIPS]^{+\bullet}$, 28%), 148 (17%), 135 ($[M-OTIPS]^{+\bullet}$, 100%).

HRMS (EI): Found *m/z*: 308.2517 $[M]^{+\bullet}$. Calculated 308.2530 Da.

IR (ATR): ν_{max}/ cm^{-1} 3077w (=C-H), 2941s (C-H), 2895s (C-H), 2865s (C-H), 1642m (C=C), 1464m (C-H), 1435m (C-H), 1105s (C-O), 881s, 679s, 658s.

5.2.1.3 - 1,1-Dibromoheptane (163)



$C_7H_{14}Br_2$ (258.00)

Procedure:[221] To a stirring solution of triphenyl phosphite (19.7 mL, 75.0 mmol) in CH_2Cl_2 (50 mL), bromine (3.33 mL, 65.0 mmol) was added dropwise over 20 minutes at -78 °C under nitrogen. Freshly distilled triethylamine (20.9 mL, 150 mmol) was added dropwise over 30 minutes followed by heptanal (6.99 mL, 50.0 mmol) over 10 minutes at -78 °C. The reaction was allowed to warm to RT and stirred for 16 hours. The reaction mixture was concentrated *in vacuo* and purified by column chromatography using 100% hexane over silica to afford the title compound as a colourless-pale yellow oil (10.4 g, 40.3 mmol, 80%).

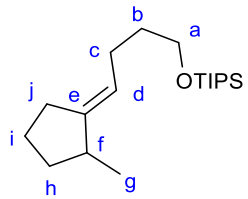
GC (AP40): Rt 4.83 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 5.70 (1 H, t, *J* 6.2 Hz, Hg), 2.45 – 2.30 (2 H, m, Hf), 1.61 – 1.45 (2 H, m), 1.42 – 1.20 (6 H, m), 0.89 (3 H, t, *J* 6.9 Hz, Ha).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 46.47 (CH, Cg), 45.61 (CH_2, Cf), 31.66 (CH_2), 28.19 (CH_2), 28.07 (CH_2), 22.63 (CH_2), 14.15 (CH_3, Ca).

Characterisation data was consistent with that reported in the literature.[141, 222]

5.2.1.4 – *Rac*-triisopropyl(4-(2-methylcyclopentylidene)butoxy)silane (168)



$C_{19}H_{38}OSi$ (310.60)

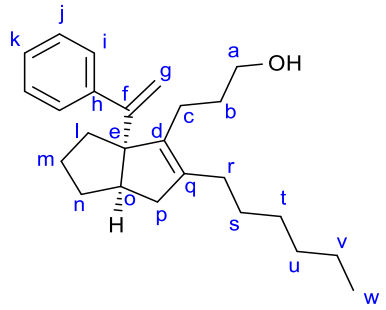
Procedure:[53] To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added at -78 °C under nitrogen and stirred for 35 minutes. Enyne **162** (309 mg, 1.0 mmol) in THF (3 mL) was added dropwise over 4 minutes at -78 °C and stirred for 30 minutes, the reaction was then

allowed to warm to RT and stirred for 3 hours. The reaction was cooled to -55 °C, methanol (10 mL) and sat. $NaHCO_{3\,(aq)}$ (10 mL) were added and the reaction was stirred at RT for 17 hours. The reaction mixture was poured into water (100 mL) and extracted with Et_2O (3× 75 mL). The organic phases were combined, washed with water (3× 100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 100% hexane over silica to afford the title compound as a colourless oil (96 mg, 0.31 mmol, 31%).

(Estimated total yield of 45% due to a mixed sample with unreacted enyne **162**; 142 mg, 1.4:1 ratio between enyne **162** to product **168** by ^{1}H-NMR).

GC (AP40):	Rt 8.03 mins.
^{1}H-NMR:	δ_H ppm (400 MHz, $CDCl_3$) 5.12 (1 H, tq, *J* 7.2, 2.4 Hz, Hd), 3.68 (2 H, t, *J* 6.6 Hz, Ha), 2.38 – 2.14 (3 H, m), 2.05 (1 H, qq, *J* 7.2, 1.3, Hc), 1.84 (1 H, m), 1.72 (1 H, m), 1.60 (2 H, tt, *J* 7.6, 6.7 Hz, Hb), 1.51 (1 H, m), 1.09 – 1.01 (23 H, m, TIPS), 1.03 (3 H, d, *J* 6.7 Hz, Hg).
^{13}C-NMR:	δ_C ppm (101 MHz, $CDCl_3$) 148.29 (C, Ce), 118.99 (CH, Cd), 63.16 (CH_2, Ca), 39.03 (CH, Cf), 35.70 (CH_2), 33.19 (CH_2), 29.12 (CH_2), 25.80 (CH_2), 24.14 (CH_2), 19.24 (CH_3, Cg), 18.19 (6 CH_3, TIPS), 12.20 (3 CH, TIPS).
LRMS (CI):	*m/z*: 311 ($[M+H]^+$, 18%), 284 (5%), 267 ($[M-i\text{Pr}]^{+\bullet}$, 39%), 225 ($[M-2(i\text{Pr})+H]^{+\bullet}$, 7%), 185 (7%), 160 (7%), 143 (11%), 135 (100%).
HRMS (EI):	Found *m/z*: 310.2681 $[M]^{+\bullet}$. Calculated 310.2687 Da.
IR (ATR):	ν_{max}/ cm^{-1} 2940s (C-H), 2891m (C-H), 2864s (C-H), 1675vw (C=C), 1461m (C-H), 1104s (C-O), 881s, 678s, 657s.

5.2.1.5 - *Rac*-(3*R*, 6*S*)-1-(1-phenylvinyl)-2-(propyl-3-ol)-3-hexyl-bicyclo[3.3.0]oct-2-ene (11)



$C_{25}H_{36}O$ (352.56)

Procedure:[53, 223] To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added

dropwise over 1.3 minutes at -78 °C under nitrogen and the reaction was stirred for 30 minutes at -78 °C. Enyne **162** (309 mg, 1.0 mmol) in THF (3 mL) was added dropwise at -78 °C. The reaction was stirred at -78 °C for 30 minutes and then at RT for 3 hours. The reaction was re-cooled to -78 °C, 1,1-dibromoheptane **163** (284 mg, 1.1 mmol) in THF (1 mL) was added followed by a dropwise addition of LiTMP [*n*-BuLi (2.5 M in hexanes, 0.44 mL, 1.1 mmol) was added dropwise to TMP (0.19 mL, 1.1 mmol) in THF (2 mL) at 0 °C and stirred for 20 minutes]. The reaction was stirred 15 minutes at -78 °C before lithium phenyl acetylide [*n*-BuLi (2.5 M in hexanes, 1.20 mL, 3.0 mmol) was added to phenylacetylene (0.33 mL, 3.0 mmol) in THF (3 mL) dropwise and stirred for 25 minutes at 0 °C] was added dropwise at -78 °C and the reaction was stirred for 1 hour whilst allowing to warm to -55 °C. MeOH (10 mL) followed by sat. $NaHCO_{3\,(aq)}$ (10 mL) were added to the reaction at -55 °C, the reaction was warmed to RT and stirred for 14 hours. The reaction mixture was poured into water (100 mL) and extracted with Et_2O (3× 75 mL). The organic phases were combined, washed with water (3× 100 mL), brine (100 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 100% hexane over silica. The isolated oil was dissolved in THF (2 mL) and TBAF (1 M in THF, 1.19 mL, 1.19 mmol) was added dropwise at RT under nitrogen and stirred at RT for 22 hours. The reaction mixture was poured into water (100 mL) and extracted with Et_2O (3× 80 mL). The organic phases were combined, washed with water (3× 100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography twice, first using 50% Et_2O in hexane over silica and secondly using by 5-10% Et_2O in hexane over ISOLUTE®SiII pre-packed silica to afford the title compound as a yellow oil (121 mg, 0.34 mmol, 34%).

GC (AP40): Rt 10.49 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.23 – 7.14 (5 H, m, ArH), 5.13 (1 H, d, *J* 1.7 Hz, Hg), 4.97 (1 H, d, *J* 1.7 Hz, Hg), 3.64 (2 H, t, *J* 6.5 Hz, Ha), 2.33 (1 H, tt, *J* 9.0, 2.0 Hz, Ho), 2.23 (1 H, dd, *J* 16.2, 8.9 Hz, Hp), 2.06 (4 H, t, *J* 8.3 Hz, Hc & Hr), 1.85 – 1.62 (6 H, m), 1.55 (1 H, m), 1.46 – 1.12 (11 H, m), 0.89 (3 H, t, *J* 6.9 Hz, Hq).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 156.11 (C, Cf), 144.53 (C, Ch), 139.98 (C, Cd/q), 136.35 (C, Cd/q), 127.98 (2 CH, Ci/j), 127.54 (2 CH, Ci/j), 126.50 (CH, Ck), 113.44 (CH_2, Cg), 70.53 (C, Ce), 63.80 (CH_2, Ca), 44.10 (CH, Co), 43.96 (CH_2, Cp), 36.71 (CH_2), 36.22 (CH_2), 33.61

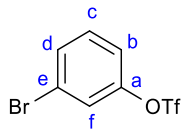
(CH_2), 32.00 (CH_2), 2968 (CH_2), 29.43 (CH_2), 27.88 (CH_2), 25.48 (CH_2), 22.81 (CH_2), 22.67 (CH_2), 14.27 (CH_3, Cq).

LRMS (CI): *m/z*: 353 ($[M+H]^+$, 28%), 335 ($[M\text{-}OH]^{+\bullet}$, 100%), 321 ($[M\text{-}CH_2OH]^{+\bullet}$, 16%), 307 ($[M\text{-}(CH_2)_2OH]^{+\bullet}$, 8%), 291 (12%), 277 (8%), 263 (20%), 249 (36%).

Characterisation data was consistent with that reported in the literature.[41, 53]

5.2.2 – Synthesis of Target B

5.2.2.1 - 3-Bromophenyl triflate (179)



$C_7H_4BrF_3O_3S$ (305.07) Procedure:[224] To a stirring solution of 3-bromophenol (5.19 g, 30.0 mmol) in CH_2Cl_2 (50 mL), anhydrous pyridine (6.73 mL, 83.2 mmol) was added at RT and under nitrogen. The reaction mixture was cooled to +5 °C before triflic anhydride (6.06 mL, 36.0 mmol) was added dropwise over 2 minutes. The reaction was stirred at +5 °C for 10 minutes and subsequently at RT for 18 hours. The reaction mixture was passed through silica (60 g) eluted with a 1:1 hexane to CH_2Cl_2 solution (400 mL). The filtrate was concentrated *in vacuo*, dissolved in Et_2O (200 mL), washed with sat. $CuSO_{4\,(aq)}$ (2× 300 mL) and brine (200 mL). The organic phase was dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by Kugelrohr distillation at 60 °C under 0.3 mbar to afford the title compound as a colourless oil (8.05 g, 26.4 mmol, 88%).

GC (AP40): Rt 4.64 mins.

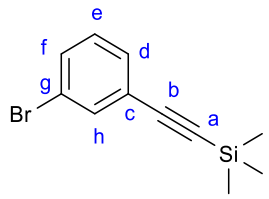
^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.55 (1 H, ddd, *J* 8.0, 1.7, 1.0 Hz, Hd), 7.46 (1 H, t, *J* 2.1 Hz, Hf), 7.34 (1 H, t, *J* 8.2 Hz, Hc), 7.25 (1 H, ddd, *J* 5.1, 2.4, 0.9 Hz, Hb).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 149.66 (C, Ca), 131.92 (CH, Cc/d), 131.41 (CH, Cc/d), 125.02 (CH, Cb/f), 123.26 (C, Ce), 120.34 (CH, Cb/f).* *CF_3 not visible, expected as 118.6 ppm (q, *J* 320.9 Hz).[225]

LRMS (EI): *m/z*: 306 ($[M]^{+\bullet}$, 54%), 240 (45%), 171 ($[M\text{-}Tf]^{+\bullet}$, 22%), 161 (22%), 143 (65%), 117 (20%), 95 (44%), 69 (100%).

Characterisation data was consistent with that reported in the literature.[225]

5.2.2.2 - ((3-Bromophenyl)ethynyl)trimethylsilane (180)



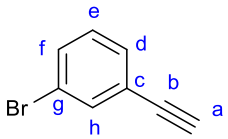
$C_{11}H_{13}BrSi$ (253.21)

Procedure: To a stirring solution of $Pd(dppf)Cl_2.CH_2Cl_2$ (710 mg, 0.87 mmol) and CuI (663 mg, 3.48 mmol) in degassed DMF (30 mL), 3-bromophenyl triflate **179** (5.30 g, 17.4 mmol) in DMF (25 mL), degassed triethylamine (12 mL, 86.1 mmol) and degassed ethynyl trimethylsilane (2.54 mL, 18.3 mmol) was added at RT and under nitrogen. The reaction was stirred at RT for 24 hours before it was poured into sat. $NH_4Cl_{(aq)}$ (400 mL) and extracted with Et_2O (3× 350 mL). The organic layers were washed separately with sat. $NH_4Cl_{(aq)}$ (300 mL each) before they were combined, dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 100% hexane over silica to afford the title compound as a colourless oil (3.57 g, 14.1 mmol, 81%).

GC (AP40):	Rt 6.00 mins.
^{1}H-NMR:	δ_H ppm (400 MHz, $CDCl_3$) 7.62 (1 H, br t, *J* 1.7 Hz, Hh), 7.44 (1 H, ddd, *J* 8.1, 2.0, 1.1 Hz, Hd/f), 7.38 (1 H, ddd, 7.8, 1.6, 1.0 Hz, Hd/f), 7.16 (1 H, t, *J* 7.9 Hz, He), 0.25 (9 H, s, Hz, TMS).
^{13}C-NMR:	δ_C ppm (101 MHz, $CDCl_3$) 134.85 (CH), 131.77 (CH), 130.60 (CH), 129.79 (CH), 125.28 (C, Cc/g), 122.16 (C, Cc/g), 103.43 (C, Ca/b), 96.02 (C, Ca/b), 0.00 (3 CH_3, TMS).
LRMS (EI):	*m/z*: 252 ($[M]^+$, 50%), 237 ($[M\text{-}CH_3]^{+\bullet}$, 100%), 223 (11%), 207 ($[M\text{-}3(CH_3)]^{+\bullet}$, 32%), 158 (26%), 143 (56%), 128 (45%), 115 (34%).

Characterisation data was consistent with that reported in the literature.[226]

5.2.2.3 - 3-Bromophenyl acetylene (177)



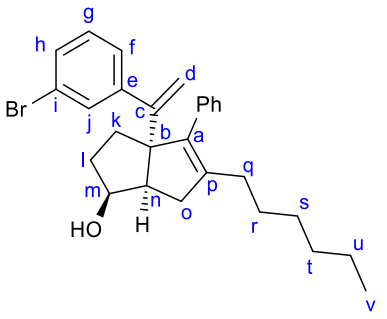
C_8H_5Br (181.03)

Procedure:[227] To a stirring suspension of K_2CO_3 (3.12 g, 22.6 mmol) in 1:1 THF: MeOH (42 mL), ((3-bromophenyl)ethynyl)trimethylsilane **180** (4.76 g, 18.8 mmol) in 1:1 THF: MeOH (42 mL) was added under nitrogen and at RT and the reaction was stirred at RT overnight. The reaction mixture was concentrated *in vacuo*, and dissolved in Et_2O (120 mL) and washed with water (150 mL). The phases were separated and the aqueous phase was extracted further with Et_2O (2× 120 mL). All organic phases were combined, washed with water (2× 150 mL) and brine (150 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by Kugelrohr distillation at 117 °C and under 2 cm Hg to afford the title compound as a colourless oil (3.16 g, 17.5 mmol, 93%).

GC (AP40):	Rt 4.63 mins.
^{1}H-NMR:	δ_H ppm (400 MHz, $CDCl_3$) 7.64 (1 H, t, *J* 1.7 Hz, Hh), 7.48 (1 H, ddd, *J* 8.1, 1.9, 1.0 Hz, Hd/f), 7.42 (1 H, dt, *J* 7.7, 1.2 Hz, Hd/f), 7.19 (1 H, t, *J* 7.9 Hz, He), 3.12 (1 H, s, Ha).
^{13}C-NMR:	δ_C ppm (101 MHz, $CDCl_3$) 135.02 (CH), 132.17 (CH), 130.84 (CH), 129.91 (CH), 124.26 (C, Cc/g), 122.25 (C, Cc/g), 82.18 (C, Cb), 78.67 (CH, Ca).
LRMS (EI):	*m/z*: 180 ($[M]^{+\bullet}$, 100%), 176 (7%), 163 (6%), 101 ($[M\text{-}Br]^{+\bullet}$, 78%), 90 (23%), 74 (84%), 62 (41%), 50 (57%).

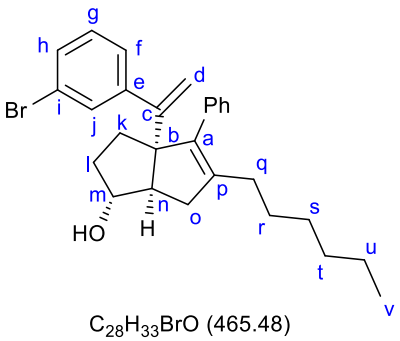
Characterisation data was consistent with that reported in the literature.[227, 228]

5.2.2.4 - *Rac*-(1*R*, 5*R*, 6*S*)-1-(1-(3-bromophenyl)vinyl)-2-phenyl-3-hexyl-bicyclo[3.3.0]oct-2-en-6-ol (175-*endo*) and *Rac*-(1*R*, 5*R*, 6*R*)-1-(1-(3-bromophenyl)vinyl)-2-phenyl-3-hexyl-bicyclo[3.3.0]oct-2-en-6-ol (175-*exo*)



$C_{28}H_{33}BrO$ (465.48)

Endo



$C_{28}H_{33}BrO$ (465.48)

Exo

Procedure:[53] To a stirring solution of Cp_2ZrCl_2 (599 mg, 2.05 mmol) in THF (10 mL) was added *n*-BuLi (2.5 M in hexane, 1.64 mL, 4.1 mmol) dropwise over 7 minutes at -78 °C under nitrogen and stirred for 30 minutes. Enyne **175** (617 mg, 2.0 mmol) in THF (6 mL) was added dropwise over 7.5 minutes at -78 °C and stirred for 15 minutes. The reaction was allowed to warm to RT and subsequently stirred for 4 hours at RT. The reaction was re-cooled to -78 °C and 1,1-dibromoheptane **163** (568 mg, 2.2 mmol) in THF (2 mL) was added dropwise over 1 minute followed by LDA (1 M in THF, 2.20 mL, 2.2 mmol) dropwise over 4 minutes and stirred for 15 minutes. Lithium 3-bromophenyl acetylide [LDA (1 M in THF, 6.0 mL, 6.0 mmol) was added dropwise over 4 minutes to 3-bromophenyl acetylene **177** (1.09 mg, 6.0 mmol) in THF (6 mL) at 0 °C and stirred at 0 °C for 30 minutes] was added dropwise over 4.5 minutes at -78 °C and stirred for 1 hour, allowing the reaction mixture to warm from -78 to -55 °C. MeOH (15 mL) followed by sat. $NaHCO_{3\,(aq)}$ (15 mL) was added at -55 °C and stirred at RT for 20 hours. The reaction mixture was poured into water (150 mL) and extracted with Et_2O (3× 120 mL). The organic phases were combined, washed with water (2× 150 mL), brine (150 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 10-20% Et_2O in hexane over silica. The isolated oil was dissolved in THF (8 mL) and TBAF (1 M in THF, 5.21 mL, 5.21 mmol) was added dropwise over 1 minute at RT and under nitrogen. The reaction was stirred at RT overnight. The reaction was poured into water (160 mL) and extracted with Et_2O (3× 100 mL). The organic phases were combined, washed with water (200 mL), brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 100% $CHCl_3$ over ISOLUTE®SiII pre-packed silica to afford the the title compound as three pale orange oils **175-*endo*** (167 mg, 0.36 mmol, 18%), **175-*exo*** (176

mg, 0.38 mmol, 19%,) and mixed **175** *endo*:*exo* in a 1:2.2 ratio (243 mg, 0.52 mmol, 26%) in 63% combined yield. (Ratio by ^{1}H-NMR).

(Estimated total yields for the separate diastereoisomers: **175-*exo*** (327 mg, 0.70 mmol, 35%) and **175-*endo*** (256 mg, 0.55 mmol, 28%).

(^{1}H-NMR of the crude mixture showed a 1:1.4 ratio between **175-*endo*** and **175-*exo*** diastereoisomers respectively).

175-*endo*

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.50 (1 H, t, *J* 1.8 Hz, Hj), 7.39 (1 H, ddd, *J* 7.9, 2.0, 1.1 Hz, Hf/h), 7.34 – 7.22 (4 H, m, ArH), 7.19 – 7.10 (3 H, m, ArH), 5.07 (1 H, d, *J* 1.1 Hz, Hd), 4.94 (1 H, d, *J* 1.1 Hz, Hd), 4.18 (1 H, ddd, *J* 14.2, 9.2, 5.3 Hz, Hm), 2.65 (1 H, dd, *J* 17.5, 1.8 Hz, Ho), 2.44 (1 H, td, *J* 9.1, 1.9 Hz, Hn), 2.11 – 2.00 (3 H, m), 1.86 (1 H, ddt, *J* 11.1, 5.5, 2.8 Hz, Hl), 1.79 – 1.61 (2 H, m), 1.55 (1 H, m), 1.47 – 1.33 (3 H, m), 131 – 1.11 (6 H, m, $H_{aliphatic}$ & OH), 0.85 (3 H, t, *J* 6.9 Hz, Hv).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 153.71 (C, Cc), 146.21 (C, Ca/p), 143.93 (C, Ca/p), 139.13 (C, Ce/*i*-Ph), 136.95 (C, Ce/*i*-Ph), 130.75 (CH, Cj), 129.93 (CH, Cf/h), 129.90 (2 CH, *o*/*m*-Ph), 129.42 (CH), 127.85 (2 CH, *o*/*m*-Ph), 126.84 (CH), 126.56 (CH), 122.06 (C, Ci), 115.92 (CH_2, Cd), 74.56 (CH, Cm), 68.83 (C, Cb), 49.01 (CH, Cn), 33.94 (CH_2), 33.43 (CH_2), 32.03 (CH_2), 31.78 (CH_2), 30.07 (CH_2), 29.69 (CH_2), 28.13 (CH_2), 22.73 (CH_2), 14.22 (CH_3, Cv).

LRMS (ESI^{+}): *m/z*: 465 ($[M+H]^{+}$, 100%).

HRMS (ESI^{+}): Found *m/z*: 465.1783 $[M+H]^{+}$. Calculated 465.1788 Da

IR (ATR): ν_{max}/ cm^{-1} 3307brm (OH), 3079w (=C-H), 3055w (=C-H), 3026w (=C-H), 3018w (=C-H), 2953m (C-H), 2927m (C-H), 2854m (C-H), 1589m (C=C), 1557m (C=C), 1491m (Ar), 1467m (Ar), 1441m (Ar), 1070s (C-O), 905s, 787s, 731s, 670s.

175-*exo*

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.52 (1 H, t, *J* 1.8 Hz, Hj), 7.39 (1 H, ddd, *J* 7.9, 2.0, 1.0 Hz, Hf/h), 7.34 – 7.24 (4 H, m, ArH), 7.17 – 7.09 (3 H,

m, ArH), 5.08 (1 H, d, *J* 1.1 Hz, Hd), 4.99 (1 H, d, *J* 1.0 Hz, Hd), 3.97 (1 H, brs, Hm), 2.40 (1 H, dd, *J* 17.1, 9.4 Hz, Ho), 2.25 (1 H, dq, *J* 9.3, 1.2 Hz, Hn), 2.12 – 1.98 (4 H, m), 1.79 – 1.62 (3 H, m), 1.43 – 1.13 (9 H, m, $H_{aliphatic}$ & OH), 0.85 (3 H, t, *J* 7.0 Hz, Hv).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 153.51 (C, Cc), 146.41 (C, Ca/p), 141.81 (C, Ca/p), 139.00 (C, Ce/*i*-Ph), 137.31 (C, Ce/*i*-Ph), 130.67 (CH, Cj), 129.89 (CH), 129.80 (2 CH, *o*/*m*-Ph), 129.45 (CH), 127.86 (2 CH, *o*/*m*-Ph), 126.87 (CH), 126.60 (CH), 122.06 (C, Ci), 116.03 (CH_2, Cd), 82.21 (CH, Cm), 69.43 (C, Cb), 55.75 (CH, Cn), 40.50 (CH_2), 34.07 (CH_2), 32.32 (CH_2), 31.78 (CH_2), 29.91 (CH_2), 29.60 (CH_2), 28.04 (CH_2), 22.72 (CH_2), 14.21 (CH_3, Cv).

LRMS (ESI$^+$): *m/z*: 465 ($[M+H]^+$, 100%.

HRMS (ESI$^+$): Found *m/z*: 465.1783 $[M+H]^+$. Calculated 465.1788 Da

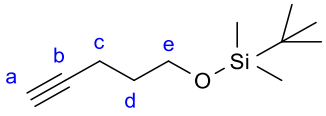
IR (ATR): ν_{max}/ cm^{-1} 3321mbr (OH), 3078w (=C-H), 3054w (=C-H), 3017w (=C-H), 3026w (=C-H), 2952s (C-H), 2923s (C-H), 2870s (C-H), 2853s (C-H), 1589m (C=C), 1557m (C=C), 1491m (Ar), 1468m (Ar), 1439m (Ar), 1067m (C-O), 787s,763s, 699s.

Compound **175-*exo*** (75 mg, 0.15 mmol) underwent chiral separation using 1.5% IPA in hexane on a 4.6 × 250 mm Daicel OD-H column at 1 mL min^{-1} using multiple injections. The enantiomers eluted at 10.87 minutes for the levorotary (colourless oil, 32 mg, 0.07 mmol) and 17.94 minutes for the dextrorotary (colourless oil, 31 mg, 0.07 mmol).

[α]$_D$ (28 °C): -21.1° (C = 0.03 M, CH_2Cl_2), +23.8 ° (C = 0.03 M, CH_2Cl_2).

5.2.3 – Synthesis of Target C

5.2.3.1 - 1-*tert*-Butyldimethylsilyloxy pent-4-yne (194)



$C_{11}H_{22}OSi$ (198.38)

Procedure:[229] To a stirring solution of 1H-imidazole (599 mg, 8.80 mmol) in DMF (4 mL), 4-pentyne-1-ol (0.37 mL, 4.0 mmol) and TBDMSCl (663 mg, 4.4 mmol) was added at RT and stirred for 62 hrs. The reaction was re-treated with TBDMSCl

(332 mg, 2.2 mmol) and stirred at RT for 24 hours. The reaction mixture was poured into sat. $NaHCO_{3\,(aq)}$ (40 mL) and extracted with Et_2O (3× 30 mL). The organic phases were combined, washed with sat. $NaHCO_{3\,(aq)}$ (40 mL), brine (40 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 0 – 20% Et_2O in hexane over silica to afford the title compound as a colourless oil (695 mg, 3.50 mmol, 88%).

GC (AP40): Rt 4.04 mins.

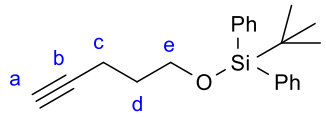
^{1}H-NMR: δ_H (400 MHz, $CDCl_3$) 3.70 (2 H, t, *J* 6.0 Hz, He), 2.27 (2 H, td, *J* 7.1, 2.7 Hz, Hc), 1.92 (1 H, t, *J* 2.7 Hz, Ha), 1.79 – 1.65 (2 H, m, Hd), 0.89 (9 H, s, *t*-Bu), 0.05 (6 H, s, $SiMe_2$).

^{13}C-NMR: δ_C (101 MHz, $CDCl_3$) 84.41 (C, Cb), 68.36 (CH, Ca), 61.58 (CH_2, Ce), 31.68 (CH_2, Cd), 26.07 (3 CH_3, *t*Bu), 18.47 (C, *t*Bu), 14.99 (CH_2, Cc), -5.21 (2 CH_3, $SiMe_2$).

LRMS (CI): *m/z*: 199 ($[M+H]^+$, 100%), 183 ($[M\text{-}CH_3]^{+\bullet}$, 5%), 158 ($[M\text{-}CH_3\&C{\equiv}C]^{+\bullet}$, 35%), 141 ($[M\text{-}t\text{Bu}]^{+\bullet}$, 88%), 132 (24%), 111 (24%), 91 (27%), 74 (57%).

Characterisation data was consistent with that reported in the literature.[230]

5.2.3.2 - 1-*tert*-Butyldiphenylsilyloxypent-4-yne (195)



$C_{21}H_{26}OSi$ (322.52)

Procedure:[229] To a stirring solution of 1H-imidazole (8.99 g, 132 mmol) in DMF (60 mL), 4-pentyn-1-ol (5.58 mL, 60.0 mmol) and TBDPSCl (17.2 mL, 66.0 mmol) was added at RT and stirred for 20 hours. The reaction mixture was poured into sat. $NaHCO_{3\,(aq)}$ (400 mL) and extracted with Et_2O (3× 250 mL). The organic phases were combined, washed with sat. $NaHCO_{3\,(aq)}$ (300 mL), water (300 mL), brine (300 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 20% Et_2O in hexane over silica to afford the title compound as a colourless oil (18.5 g, 57.5 mmol, 96%).

GC (AP40): Rt 8.68 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.74 – 7.64 (4 H, m, ArH), 7.50 – 7.34 (6 H, m, ArH), 3.76 (2 H, t, *J* 6.0 Hz, He), 2.36 (2 H, td, *J* 7.2, 2.6 Hz,

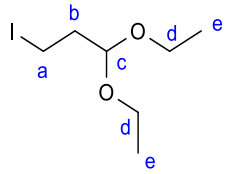
Hc), 1.92 (1 H, t, *J* 2.7 Hz, Ha), 1.79 (2 H, quin, *J* 6.6 Hz, Hd), 1.07 (9 H, s, *t*Bu).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 135.72 (4 CH, *o*/*m*-Ph), 133.98 (2 C, *i*-Ph), 129.73 (2 CH, *p*-Ph), 127.77 (4 CH, *o*/*m*-Ph), 84.40 (C, Cb), 68.42 (CH, Ca), 62.42 (CH_2, Ce), 31.59 (CH_2, Cd), 26.99 (3 CH_3, *t*Bu), 19.38 (C, *t*Bu), 15.12 (CH_2, Cc).

LRMS (CI): *m/z*: 323 ($[M+H]^+$, 63%), 282 ($[M-CH_3\&C{\equiv}C]^{+\bullet}$, 48%), 265 ($[M-t\text{Bu}]^{+\bullet}$, 100%), 247 (40%), 239 ($[SiPh_{2t}\text{Bu}]^{+\bullet}$, 32%), 199 (49%), 187 (53%), 181 (30%).

Characterisation data was consistent with that reported in the literature.[229]

5.2.3.3 - 1,1-Diethoxy-3-iodopropane (192)



$C_7H_{15}IO_2$ (258.10)

Procedure:[41] A solution of NaI (21.6 g, 144 mmol) in dry MeCN (240 mL) was stirred at RT and under nitrogen for 30 minutes. The reaction mixture was cooled to -5 °C and freshly distilled acrolein (8.02 mL, 120 mmol) was added dropwise over 2 minutes under nitrogen. This was followed by TMSCl (18.3 mL, 144 mmol) over 2 minutes and distilled EtOH (14.7 mL, 252 mmol) over 1 minute. The reaction was stirred at -5 °C for 15 minutes before warming to RT and stirred for 3 hours. The reaction was poured into 5% $NaHCO_{3\,(aq)}$ (240 mL) and extracted with hexane (3× 120 mL). The organic phases were combined, washed with 5% $Na_2S_2O_{3\,(aq)}$ (180 mL), brine (120 mL), dried over K_2CO_3, filtered, concentrated *in vacuo* and immediately purified by column chromatography using 10% Et_2O in hexane over basic deactivated alumina (grade III) to afford the title compound as a colourless oil (17.9 g, 69.2 mmol, 58%).

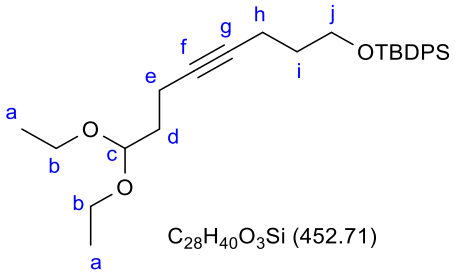
GC (AP40): Rt 4.51 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 4.56 (1 H, t, *J* 5.5 Hz, Hc), 3.67 (2 H, dq, *J* 9.4, 7.0 Hz, Hd), 3.53 (2 H, dq, *J* 9.4, 7.0 Hz, Hd), 3.17 (2 H, t, *J* 7.0 Hz, Ha), 2.11 (2 H, td, *J* 7.0, 5.5 Hz, Hb), 1.19 (6 H, t, *J* 7.1 Hz, He).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 102.97 (CH, Cc), 62.22 (2 CH_2, Cd), 37.75 (CH_2, Cb), 15.49 (2 CH_3, Ce), 0.66 (CH_2, Ca).

Characterisation data was consistent with that reported in the literature.[41]

5.2.3.4 - 1-*tert*-Butyldiphenylsilyloxy-8,8-diethoxy-oct-4-yne (196)



Procedure:[166, 167] To a stirring solution of enyne **195** (8.23 g, 25.5 mmol) in THF (75 mL), *n*-BuLi (2.5 M in hexanes, 10.2 mL, 25.5 mmol) was added dropwise over 3 minutes at -78 °C under nitrogen. The reaction was allowed to warm to -20 °C and was stirred at this temperature for 2 hours. HMPA (6 mL) was added dropwise over 2 minutes at -20 °C and the reaction mixture was stirred for 20 minutes. 1,1-Diethoxy-3-iodopropane **192** (8.56 g, 33.2 mmol) in THF (38 mL) was added dropwise at -30 °C and the reaction was allowed to warm to RT and stirred for 17 hours. The reaction mixture was quenched with water (5 mL) and concentrated *in vacuo* for THF removal. The resulting mixture was poured into water (300 mL) and extracted with Et_2O (3× 250 mL). The organic phases were combined, washed with water (300 mL), brine (300 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 0 – 30% Et_2O in hexane over basic deactivated alumina (grade III) to afford the title compound as a colourless oil (10.1 g, 22.3 mmol, 88%).

GC (AP40): Rt 12.02 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.71 – 7.63 (4 H, m, ArH), 7.46 – 7.32 (6 H, m, ArH), 4.58 (1 H, t, *J* 5.7 Hz, Hc), 3.73 (2 H, t, *J* 6.1 Hz, Hj), 3.64 (2 H, dq, *J* 9.4, 7.1 Hz, Hb), 3.49 (2 H, dq, *J* 9.4, 7.1 Hz, Hb), 2.29 (2 H, tt, *J* 7.1, 2.3 Hz, He/h), 2.20 (2 H, tt, *J* 7.2, 2.3 Hz, He/h), 1.76 (2 H, td, *J* 7.2, 5.8 Hz, Hd), 1.73 (2 H, tt, *J* 7.1, 6.1 Hz, Hi), 1.20 (6 H, t, *J* 7.1 Hz, Ha), 1.04 (9 H, s, *t*Bu).

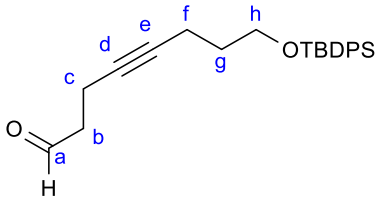
^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 135.72 (4 CH, *o*/*m*-Ph), 134.09 (2 C), 129.69 (2 CH, *p*-Ph), 127.75 (4 CH, *o*/*m*-Ph), 102.04 (CH, Cc), 80.13 (C, Cf/g), 79.55 (C, Cf/g), 62.69 (CH_2, Cj), 61.58 (2 CH_2, Cb), 33.26 (CH_2, Cd/i), 32.18 (CH_2, Cd/i), 26.99 (3 CH_3, *t*Bu), 19.39 (C, *t*Bu), 15.50 (2 CH_3, Ca), 15.43 (CH_2, Ce/h), 14.56 (CH_2, Ce/h).

LRMS (ESI$^+$): *m/z*: 476 ([M+Na]$^+$, 100%).

HRMS (ESI$^+$): Found *m/z*: 475.2646 [M+Na]$^+$. Calculated 475.2639 Da.

IR (ATR): ν_{max}/ cm^{-1} 3070w (=C-H), 3048w (=C-H), 2958s (C-H), 2929s (C-H), 2896s (C-H), 2857s (C-H), 1472m (Ar), 1444m (Ar), 1427m (C-H), 1105s (C-O), 1060s (C-O), 699s, 503s, 487s.

5.2.3.5 - 8-*tert*-Butyldiphenylsilyloxy-oct-4-ynal (197)



$C_{24}H_{30}O_2Si$ (378.59)

Procedure:[41] To a stirring solution of acetal **196** (9.38 g, 20.7 mmol) in THF (83 mL), 2 M HCl $_{(aq)}$ (20.7 mL) was added and the reaction was stirred at RT for 3 hours. The reaction mixture was quenched with sat. $NaHCO_{3\ (aq)}$ (40 mL), poured into sat. $NaHCO_{3\ (aq)}$ (250 mL) and extracted with Et_2O (3× 250 mL). The organic phases were combined, washed with sat. $NaHCO_{3\ (aq)}$ (200 mL), water (200 mL), brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 10-20% Et_2O in hexane over silica to afford the title compound as a colourless oil (6.39 g, 16.9 mmol, 81%).

GC (AP40): Rt 10.69 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 9.76 (1 H, t, *J* 1.4 Hz, Ha), 7.73 – 7.65 (4 H, m, ArH), 7.48 – 7.34 (6 H, m, ArH), 3.74 (2 H, t, *J* 6.1 Hz, Hh), 2.61 – 2.53 (2 H, m, Hb), 2.49 – 2.42 (2 H, m, Hc/f), 2.30 (2 H, tt, *J* 7.1, 2.4 Hz, Hc/f), 1.74 (2 H, tt, *J* 7.0, 6.1 Hz, Hg), 1.07 (9 H, s, *t*Bu).

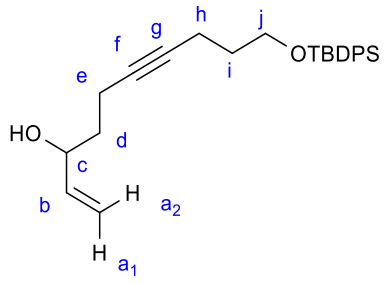
^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 201.07 (CH, Ca), 135.69 (4 CH, *o*/*m*-Ph), 134.02 (2 C, *i*-Ph), 129.68 (2 CH, *p*-Ph), 127.73 (4 CH, *o*/*m*-Ph), 81.10 (C, Cd/e), 78.13 (C, Cd/e), 62.58 (CH_2, Ch), 43.07 (CH_2, Cb), 31.92 (CH_2, Cg), 26.97 (3 CH_3, *t*Bu), 19.36 (C, *t*Bu), 15.34 (CH_2, Cc/f), 12.25 (CH_2, Cc/f).

LRMS (ESI$^+$): *m/z*: 396 ([M+NH_4]$^+$, 100%), 379 ([M+H]$^+$, 18%), 301 ([M-Ph]$^{+\bullet}$, 25%).

HRMS (ESI$^+$): Found *m/z*: 379.2088 [M+H]$^+$. Calculated 379.2088 Da.
Found *m/z*: 401.1910 [M+Na]$^+$. Calculated 401.1907 Da.

IR (ATR): ν_{max}/ cm^{-1} 3070w (=C-H), 3047w (=C-H), 2952m (C-H), 2929m (C-H), 2895m (C-H), 2856m (C-H), 2724w (H-C=O), 1726m (C=O), 1589w (Ar), 1472m (Ar), 1427m (C-H), 1104s (C-O), 700s, 503s, 487s.

5.2.3.6 – *Rac*-10-*tert*-butyldiphenylsilyloxy dec-1-en-6-yn-3-ol (198)



$C_{26}H_{34}O_2Si$ (406.64)

Procedure:[41] To a stirring solution of aldehyde **197** (5.87 g, 15.5 mmol) in THF (62 mL), vinyl magnesium bromide (1 M in THF, 19.4 mL, 19.4 mmol) was added dropwise over 12 minutes at -78 °C under nitrogen. The reaction was stirred at this temperature for 10 minutes and subsequently stirred at RT for 17 hours. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ (20 mL), poured into water (100 mL) and extracted with Et_2O (3× 80 mL). The organic phases were combined, washed with water (2× 100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 20% Et_2O in hexane over silica to afford the title compound as a colourless oil (4.88 g, 12.0 mmol, 77%).

GC (AP40): Rt 11.64 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.78 – 7.60 (4 H, m, ArH), 7.52 – 7.31 (6 H, m, ArH), 5.86 (1 H, ddd, *J* 17.2, 10.4, 5.9 Hz, Hb), 5.26 (1 H, dt, *J* 17.2 Hz, 1.5, Ha_2), 5.13 (1 H, dt, *J* 10.4, 1.4 Hz, Ha_1), 4.25 (1 H, q, *J* 6.1 Hz, Hc), 3.75 (2 H, t, *J* 6.1 Hz, Hj), 2.32 (2 H, tt, *J* 7.1, 2.3 Hz, He/h), 2.29 – 2.18 (2 H, m, He/h), 1.85 (1 H, s, OH), 1.76 (2 H, tt, *J* 6.9, 6.2 Hz, Hi), 1.72 – 1.64 (2 H, m , Hd), 1.07 (9 H, s, *t*Bu).

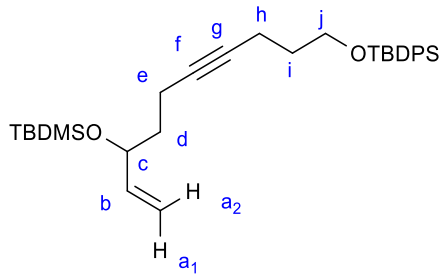
^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 140.67 (CH, Cb), 135.70 (4 CH, *o*/*m*-Ph), 134.04 (2 C, *i*-Ph), 129.68 (2 CH, *p*-Ph), 127.74 (4 CH, *o*/*m*-Ph), 114.92 (CH_2, Ca), 80.67 (C, Cf/g), 79.84 (C, Cf/g), 72.19 (CH, Cc), 62.65 (CH_2, Cj), 36.01 (CH_2, Cd/i), 32.07 (CH_2, Cd/i), 26.97 (3 CH_3, *t*Bu), 19.36 (C, *t*Bu), 15.41 (CH_2, Ce/h), 15.16 (CH_2, Ce/h).

LRMS (ESI$^+$): *m/z*: 424 ($[M+NH_4]^+$, 51%), 329 ($[M-Ph]^{+\bullet}$, 100%).

HRMS (ESI$^+$): Found *m/z*: 429.2228 $[M+Na]^+$. Calculated 429.2220 Da.

IR (ATR): ν_{max}/ cm^{-1} 3390wbr (OH), 3070w (=C-H), 3048w (=C-H), 2929m (C-H), 2856m (C-H), 1646vw (C=C), 1589w (C=C), 1472m (Ar), 1427m (C-H), 1104s (C-O), 1067s (C-O), 699s, 503s, 487s.

5.2.3.7 – *Rac*-3-*tert*-butyldimethylsilyloxy-10-*tert*-butyldiphenylsilyloxy-dec-1-en-6-yne (199)



$C_{32}H_{48}O_2Si_2$ (520.90)

Procedure:[231] To a stirring solution of enyne alcohol **198** (4.00 g, 9.84 mmol) in DMF (9.8 mL), 1H-imidazole (1.47 g, 21.6 mmol) and TBDMSCl (1.63 g, 10.8 mmol) were added and the reaction was stirred at RT for 64 hours. The reaction was retreated with TBDMSCl (75 mg, 0.50 mmol) and stirred at RT for 2 hours. The reaction mixture was poured into sat. $NaHCO_{3\,(aq)}$ (120 mL) and extracted with Et_2O (3× 100 mL). The organic phases were combined, washed with sat. $NaHCO_{3\,(aq)}$ (120 mL), brine (120 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 1% Et_2O in hexane over silica to afford the title compound as a colourless oil (4.83 g, 9.28 mmol, 94%).

GC (AP40L): Rt 14.15 mins.

^{1}H-NMR: δ_H (400 MHz, $CDCl_3$) 7.71 – 7.64 (4 H, m, ArH), 7.46 – 7.34 (6 H, m, ArH), 5.79 (1 H, ddd, *J* 17.0, 10.6, 6.1 Hz, Hb), 5.16 (1 H, dt, *J* 17.2, 1.5 Hz, Ha_2), 5.04 (1 H, dt, *J* 10.4, 1.4 Hz, Ha_1), 4.21 (1 H, brq, *J* 6.1 Hz, Hc), 3.75 (2 H, t, *J* 6.1 Hz, Hj), 2.31 (2 H, tt, *J* 7.1, 2.3 Hz, He/h), 2.22 – 2.15 (2 H, m, He/h), 1.74 (2 H, tt, *J* 6.8, 6.3 Hz, Hi), 1.69 – 1.58 (2 H, m, Hd), 1.06 (9 H, s, *t*Bu), 0.91 (9 H, s, *t*Bu), 0.07 (3 H, s, SiMe), 0.04 (3 H, s, SiMe).

^{13}C-NMR: δ_C (101 MHz, $CDCl_3$) 141.4 (CH, Cb), 135.7 (4 CH, *o*/*m*-Ph), 134.1 (2 C, *i*-Ph), 129.7 (2 CH, *p*-Ph), 127.8 (4 CH, *o*/*m*-Ph), 114.1 (CH_2, Ca), 80.1 (C, Cf/g), 80.1 (C, Cf/g), 72.6 (CH, Cc), 62.7 (CH_2, Cj), 37.4 (CH_2, Cd/i), 32.2 (CH_2, Cd/i), 27.0 (3 CH_3, *t*Bu), 26.0 (3 CH_3, *t*Bu),

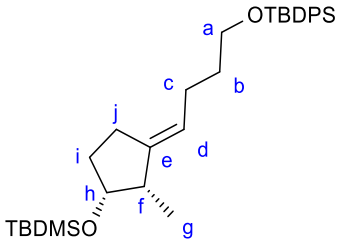
19.4 (C, *t*Bu), 18.4 (C, *t*Bu), 15.4 (CH_2, Ce/h), 14.9 (CH_2, Ce/h), -4.2 (CH_3, SiMe), -4.7 (CH_3, SiMe).

LRMS (ESI$^+$): *m/z*: 539 ($[M+NH_4]^+$, 100%).

HRMS (ESI$^+$): Found *m/z*: 543.3089 $[M+Na]^+$. Calculated 543.3085 Da.

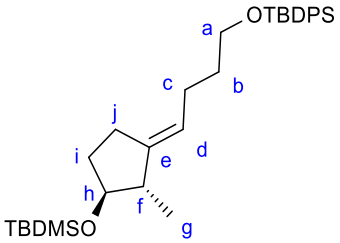
IR (ATR): ν_{max}/ cm^{-1} 3071w (=C-H), 2951m (C-H), 2928s (C-H), 2894m (C-H), 2856s (C-H), 1644w (C=C), 1589w (Ar), 1472m (Ar), 1462m (Ar), 1427m (C-H), 1105s (C-O), 1070s (C-O), 834s, 775s,700s, 503s, 488s.

5.2.3.8 - *Rac*-(2*S*, 3*R*)- *tert*-butyl((*E*)-4-(3-((*tert*-butyldimethylsilyl)oxy)-2-methylcyclopentylidene)butoxy)diphenylsilane (200-*syn*) and *Rac*-(2*S*, 3*R*)- *tert*-butyl((*E*)-4-(3-((*tert*-butyldimethylsilyl)oxy)-2-methylcyclopentylidene)butoxy)diphenylsilane (200-*anti*)



$C_{32}H_{50}O_2Si_2$ (522.92)

Syn



$C_{32}H_{50}O_2Si_2$ (522.92)

Anti

Procedure:[53] To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. Enyne **199** (521 mg, 1.0 mmol) in THF (3 mL) was added dropwise over 4 minutes at -78 °C; the reaction was allowed to warm to RT and stirred for 4 hours. The reaction was quenched with MeOH (10 mL) and sat. $NaHCO_{3\,(aq)}$ (10 mL). The reaction mixture was poured into water (100 mL) and extracted with Et_2O (3× 80 mL). The organic phases were combined, washed with water (2× 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 20-30% CH_2Cl_2 in hexane over silica to afford the title compounds as two colourless oils **200-*syn*** (141 mg, 0.27 mmol, 27%), **200-*anti*** (208 mg, 0.40 mmol, 40%) in 67% combined yield.

(Estimated total yield for **200-*anti*** was 48% due to a mixed sample of enyne **199** and **200-*anti*** in a 1.7:1 ratio respectively by ^{1}H-NMR (colourless oil, 107 mg)).

(Estimated total yield comprising all isomers is 392 mg, 0.75 mmol, 75%).

(^{1}H-NMR of the crude mixture showed a 1:1.6 ratio between diastereoisomers **200**-*syn* and **200**-*anti*).

200-*syn*

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.70 – 7.63 (4 H, m, ArH), 7.47 – 7.32 (6 H, m, ArH), 5.08 (1 H, tq, *J* 7.2, 2.4 Hz, Hd), 4.10 (1 H, q, *J* 4.1 Hz, Hh), 3.67 (2 H, t, *J* 6.4 Hz, Ha), 2.45 – 2.24 (2 H, m, Hj & Hf), 2.19 (1 H, m, Hj), 2.06 (2 H, qq, *J* 7.4, 1.1 Hz, Hc), 1.73 – 1.56 (4 H, m, Hi & Hb), 1.05 (9 H, s, *t*Bu), 0.96 (3 H, d, *J* 6.9 Hz, Hg), 0.87 (9 H, s, *t*Bu), 0.04 (3 H, s, SiMe), 0.04 (3 H, s, SiMe).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 145.94 (C, Ce), 135.74 (4 CH, *o*/*m*-Ph), 134.37 (C, *i*-Ph), 134.34 (C, *i*-Ph), 129.61 (2 CH, *p*-Ph), 127.71 (4 CH, *o*/*m*-Ph), 119.97 (CH, Cd), 76.12 (CH, Ch), 63.73 (CH_2, Ca), 44.37 (CH, Cf), 33.01 (CH_2, Ci/b), 32.74 (CH_2, Ci/b), 27.03 (3 CH_3, *t*Bu), 26.05 (CH_2, Cc/j), 26.01 (3 CH_3, *t*Bu), 25.54 (CH_2, Cc/j), 19.38 (C, *t*Bu), 18.35 (C, *t*Bu), 13.68 (CH_3, Cg), -4.46 (CH_3, SiMe), -4.71 (CH_3, SiMe).

LRMS (ESI$^+$): *m/z*: 540 ($[M+NH_4]^+$, 100%.

HRMS (ESI$^+$): Found *m/z*: 545.3243 $[M+Na]^+$. Calculated 545.3242 Da.

IR (ATR): ν_{max}/ cm^{-1} 3071w (=C-H), 3050w (=C-H), 2955m (C-H), 2928m (C-H), 2894m (C-H), 2856m (C-H), 1590vw (C=C), 1472m (Ar), 1462m (Ar), 1428m (C-H), 1107s (C-O), 1064s (C-O), 834s, 772s, 700s, 686s.

200-*anti*

^{1}H-NMR: δ_H (400 MHz, $CDCl_3$) 7.72 – 7.62 (4 H, m, ArH), 7.48 – 7.33 (6 H, m, ArH), 5.09 (1 H, tq, *J* 7.2, 2.4 Hz, Hd), 3.67 (2 H, t, *J* 6.4 Hz, Ha), 3.51 (1 H, td, *J* 8.6, 6.1 Hz, Hh), 2.35 (1 H, br dd, *J* 17.3, 10.4 Hz, Hj), 2.21 – 2.10 (2 H, m, Hj & Hf), 2.06 (2 H, q, *J* 7.2 Hz, Hc), 1.90 (1 H, dddd, *J* 11.8, 8.8, 6.0, 2.9 Hz, Hi), 1.62 (2 H, quin, *J* 6.9 Hz, Hb), 1.52 (1 H, m, Hi), 1.06 (9 H, s, *t*Bu), 1.01 (3 H, d, *J* 6.6 Hz, Hg), 0.90 (9 H, s, *t*Bu), 0.10 – 0.05 (6 H, m, $SiMe_2$).

^{13}C-NMR: δ_C (101 MHz, $CDCl_3$) 144.03 (C, Ce), 135.73 (4 CH, *o*/*m*-Ph), 134.30 (C, *i*-Ph), 134.28 (C, *i*-Ph), 129.64 (2 CH, *p*-Ph), 127.72 (4 CH, *o*/*m*-Ph), 120.32 (CH, Cd), 79.93 (CH, Ch), 63.62 (CH_2, Ca), 46.93 (CH,

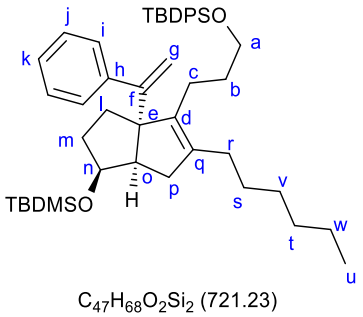
Cf), 32.90 (CH_2, Ci/b), 32.63 (CH_2, Ci/b), 27.02 (3 CH_3, *t*Bu), 26.05 (3 CH_3, *t*Bu), 25.53 (CH_2, Cc/j), 24.87 (CH_2, Cc/j), 19.34 (C, *t*Bu), 18.30 (C), *t*Bu, 15.85 (CH_3, Cg), -4.25 (CH_3, SiMe), -4.52 (CH_3, SiMe).

LRMS (ESI$^+$): *m/z*: 540 ($[M+NH_4]^+$, 100%.

HRMS (ESI$^+$): Found *m/z*: 523.3422 $[M+H]^+$. Calculated 523.3422 Da.

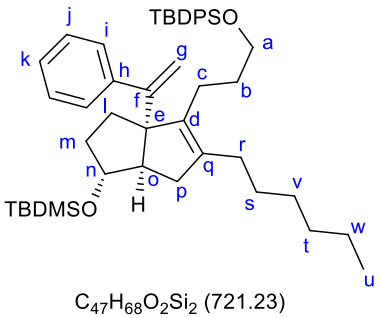
IR (ATR): ν_{max}/ cm^{-1} 3071w (=C-H), 3050w (=C-H), 2955m (C-H), 2929m (C-H), 2894m (C-H), 2856m (C-H), 1590w (C=C), 1472m (Ar), 1462m (Ar), 1428m (C-H), 1105brs (C-O), 834s, 773s, 700s.

5.2.3.9 - *Rac-(1R, 5R, 6S)*-1-phenylvinyl)-2-(3-*tert*-butyldiphenylsilyloxy)propyl-3-hexyl-6-*tert*-butyldimethylsilyloxy-bicyclo[3.3.0]oct-2-ene (201-*endo*) and *Rac-(1R, 5R, 6R)*-1-phenylvinyl)-2-(3-*tert*-butyldiphenylsilyloxy)propyl-3-hexyl-6-*tert*-butyldimethylsilyloxy-bicyclo[3.3.0]oct-2-ene (201-*exo*)



$C_{47}H_{68}O_2Si_2$ (721.23)

Endo



$C_{47}H_{68}O_2Si_2$ (721.23)

Exo

Procedure:[53] To a stirring solution of Cp_2ZrCl_2 (599 mg, 2.05 mmol) in THF (10 mL), *n*-BuLi (2.5 M in hexane, 1.64 mL, 4.1 mmol) was added dropwise over 3 minutes at -78 °C under nitrogen and stirred for 30 minutes. Enyne **199** (1.04 g, 2.0 mmol) in THF (6 mL) was added dropwise over 7 minutes at -78 °C and stirred for 20 minutes, and subsequently stirred for 4 hours at RT. The reaction was re-cooled to -78 °C and 1,1-dibromoheptane **163** (568 mg, 2.2 mmol) in THF (2 mL) was added dropwise over 1 minute followed by LDA (1 M in THF, 2.20 mL, 2.2 mmol) dropwise over 4 minutes and stirred for 15 minutes. Lithium phenylacetylide [*n*BuLi (2.5 M in hexane, 2.40 mL, 6.0 mmol) was added dropwise over 3.5 minutes to phenylacetylene (0.66 mL, 6.0 mmol) in THF (6 mL) at 0 °C for 30 minutes] was added dropwise over 3 minutes at -78 °C and stirred for 1 hour, allowing to warm from -78 to -55 °C. MeOH (15 mL) followed by sat. $NaHCO_{3\,(aq)}$ (15 mL) were added at -55 °C under nitrogen and stirred at RT for 18 hours. The reaction mixture was poured into water (150 mL) and extracted with Et_2O (3× 120 mL). The organic phases were combined, washed with water (2× 150 mL), brine (150 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and

purified by column chromatography using 20-30% CH_2Cl_2 in hexane over silica to afford the title compounds as a yellow oil (1.07 g, 1.48 mmol, 74%, 1:1.4 *endo*:*exo* ratio by ^{1}H-NMR).

The **201** *endo*/*exo* mixture was separated by column chromatography twice using 5% DCM in hexane over pre-packed ISOLUTE®SiII silica to afforded the two pure samples **201-*endo*** (139 mg, 0.19 mmol, 10%) and **201-*exo*** (143 mg, 0.20 mmol, 10%). The following samples were mixed **201** diastereomers; *endo*:*exo* in a 8.9:1 ratio (67 mg, 0.09 mmol, 5%), *endo*:*exo* in a 1:1.9 ratio (226 mg, 0.31 mmol, 16%) and *endo*:*exo* in a 1:13.7 ratio (109 mg, 0.15 mmol, 8%).

(^{1}H-NMR of the crude compouned showed a 1:1.4 ratio between **201**-*endo* and **201**-*exo* diastereoisomers respectively).

The following characterisation was conducted on the pure samples of diastereomers isolated.

201-*endo*

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.70 – 7.63 (4 H, m, ArH), 7.44 – 7.32 (6 H, m, ArH), 7.24 – 7.14 (5 H, m, ArH), 5.07 (1 H, d, *J* 1.6 Hz, Hg), 4.98 (1 H, d, *J* 1.6 Hz, Hg), 4.03 (1 H, ddd, 10.3, 8.7, 5.4 Hz, Hn), 3.70 – 3.58 (2 H, m, Ha), 2.59 (1 H, d, *J* 16.8 Hz, Hp), 2.28 (1 H, td, *J* 9.0, 2.1 Hz, Ho), 2.16 – 1.97 (4 H, m), 1.82 – 1.56 (6 H, m), 1.44 – 1.20 (9 H, m), 1.06 (9 H, s, *t*Bu), 0.89 (3 H, t, *J* 6.9 Hz, Me), 0.85 (9 H, m, *t*Bu), 0.01 (3 H, s, SiMe), -0.03 (3 H, s, SiMe).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 156.05 (C, Cf), 144.45 (C, Cd/q), 140.90 (C, Cd/q), 136.16 (2 C, *i*-Ph), 135.74 (4 CH, *o*/*m*-Ph), 134.26 (C, Ch), 129.63 (2 CH, *p*-Ph/Ci/j), 127.85 (2 CH, *p*-Ph/Ci/j), 127.71 (4 CH, *o*/*m*-Ph), 127.59 (2 CH, *p*-Ph/Ci/j), 126.54 (CH, Ck), 113.58 (CH_2, Cg), 74.86 (CH, Cn), 68.64 (C, Ce), 64.54 (CH_2, Ca), 47.70 (CH, Co), 33.92 (CH_2), 33.71 (CH_2), 33.21 (CH_2), 32.08 (CH_2), 31.95 (CH_2), 29.71 (CH_2), 29.46 (CH_2), 27.9 (CH_2), 27.04 (3 CH_3, *t*Bu), 26.04 (3 CH_3, *t*Bu), 22.84 (CH_2), 22.21 (CH_2), 19.38 (C, *t*Bu), 18.28 (C, *t*Bu), 14.30 (CH_3, Hu), -4.51 (CH_3, SiMe), -4.75 (CH_3, SiMe).

LRMS (ESI$^+$): *m/z*: 739 ($[M+NH_4]^+$, 100%), 722 ($[M+H]^+$, 16%).

HRMS (ESI$^+$): Found *m/z*: 743.6451 $[M+Na]^+$. Calculated 743.4650 Da.
Found *m/z*: 759.4390 $[M+K]^+$. Calculated 759.4389 Da.

IR (ATR): ν_{max}/ cm^{-1} 3070w (=C-H), 3050w (=C-H), 2952s (C-H), 2927m (C-H), 2894s (C-H), 1590vw (C=C), 1489m (Ar), 1471m (Ar), 1462m (Ar), 1427m (C-H), 1105brs (C-O), 773s, 699s, 503s.

201-*exo*

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.71 – 7.63 (4 H, m, ArH), 7.45 – 7.33 (6 H, m, ArH), 7.23 – 7.14 (5 H, m, ArH), 5.12 (1 H, d, *J* 1.7 Hz, Hg), 4.96 (1 H, d, *J* 1.7 Hz, Hg), 3.76 (1 H, brs, Hn), 3.64 (2 H, td, *J* 6.1, 1.7 Hz, Ha), 2.32 – 1.97 (6 H, m), 1.80 (1 H, d, *J* 15.4 Hz, Hp), 1.74 – 1.56 (3 H, m), 1.53 – 1.18 (11 H, m), 1.06 (9 H, s, *t*Bu), 0.89 (3 H, t, *J* 6.9 Hz, Me), 0.85 (9 H, s, *t*Bu), -0.02 (3 H, s, SiMe), -0.06 (3 H, s, SiMe).

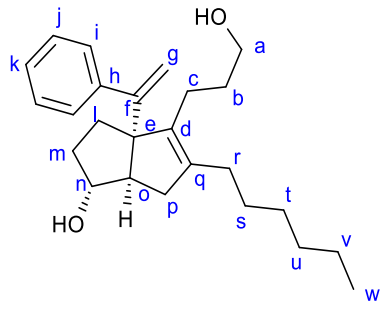
^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 155.87 (C, Cf), 144.71 (C, Cd/q/k), 137.88 (C, Cd/q/k), 137.37 (C, Cd/q/k), 135.75 (4 CH, *o*/*m*-Ph), 134.24 (2 C, *i*-Ph), 129.64 (2 CH), 127.98 (2 CH, *p*-Ph/Ci/j), 127.72 (4 CH, *o*/*m*-Ph), 127.49 (2 CH, *p*-Ph/Ci/j), 126.39 (CH, Ck), 113.51 (CH_2, Cg), 82.18 (CH, Cn), 69.52 (C, Ce), 64.53 (CH_2, Ca), 54.65 (CH, Co), 40.01 (CH_2), 34.14 (CH_2), 33.51 (CH_2), 32.69 (CH_2), 32.02 (CH_2), 29.67 (CH_2), 29.27 (CH_2), 27.95 (CH_2), 27.04 (3 CH_3, *t*Bu), 25.97 (3 CH_3, *t*Bu), 22.82 (2 CH_2), 19.38 (C, *t*Bu), 18.13 (C, *t*Bu), 14.27 (CH_3, Hu), -4.52 (CH_3, SiMe), -4.62 (CH_3, SiMe).

LRMS (ESI$^+$): *m/z:* 722 ($[M+H]^+$, 32%), 739 ($[M+NH_4]^+$, 100%).

HRMS (ESI$^+$): Found *m/z*: 721.4826 $[M+H]^+$. Calculated 721.4831 Da.
Found *m/z*: 743.4649 $[M+Na]^+$. Calculated 743.4650 Da.

IR (ATR): ν_{max}/ cm^{-1} 3070w (=C-H), 3050w (=C-H), 3014w (=C-H), 2953s (C-H), 2926s (C-H), 2894m (C-H), 2855s (C-H), 1590vw (C=C), 1490m (Ar), 1471m (Ar), 1462m (Ar), 1427m (C-H), 1091s (C-O), 1092s (C-O), 832s, 773s, 699s, 504s.

5.2.3.10 - *Rac-(1R, 5R, 6R)*-1-(1-phenylvinyl)-2-(propyl-3-ol)-3-hexyl-bicyclo[3.3.0]oct-2-en-6-ol (186-*exo*)



$C_{25}H_{36}O_2$ (368.56)

Exo

Procedure:[223] To a stirring solution of **201-*exo*** (90 mg, 0.12 mmol) in THF (1.9 mL), TBAF (1 M in THF, 0.50 mL, 0.50 mmol) was added dropwise over 1 minute at RT under nitrogen and stirred overnight at RT. The reaction mixture was poured into water (15 mL) and extracted with Et_2O (3× 10 mL). The organic phases were combined, washed with water (15 mL), brine (15 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 30% EtOAc in hexane over ISOLUTE®SiII pre-packed silica to afford the title compound as a colourless oil (26 mg, 0.07 mmol, 59%).

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.23 – 7.17 (5 H, m, ArH), 5.20 (1 H, d, *J* 1.5 Hz, Hg), 5.03 (1 H, d, *J* 1.5 Hz, Hg), 3.87 (1 H, d, *J* 3.1 Hz, Hn), 3.64 (2 H, t, *J* 6.5 Hz, Ha), 2.36 – 1.99 (7 H, m), 1.87 (1 H, brd, *J* 16.2 Hz, Hp), 1.84 (1 H, ddd, *J*, 12.5, 6.2, 2.0 Hz, Hm), 1.74 – 1.59 (4 H, m), 1.38 – 1.17 (10 H, m), 0.89 (3 H, t, *J* 6.9 Hz, Me).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 155.52 (C, Cf), 144.30 (C, Cd/q/h), 138.51 (C, Cd/q/h), 136.58 (C, Cd/q/h), 127.84 (2 CH, Ci/j), 127.72 (2 CH, Ci/j), 126.70 (CH, Ck), 113.79 (CH_2, Cg), 82.04 (CH, Cn), 69.68 (C, Ce), 63.66 (CH_2, Ca), 54.36 (CH, Co), 40.28 (CH_2), 33.64 (CH_2), 33.55 (CH_2), 32.73 (CH_2), 31.96 (CH_2), 29.67 (CH_2), 29.30 (CH_2), 27.84 (CH_2), 22.79 (CH_2), 22.48 (CH_2), 14.26 (CH_3, Cw).

LRMS (ESI$^+$): *m/z*: 391 ($[M+Na]^+$, 8%), 386 ($[M+NH_4]^+$, 7%), 369 ($[M+H]^+$, 100%).

HRMS (ESI$^+$): Found *m/z*: 351.2683$[M\text{-}OH]^{+\bullet}$. Calculated 351.2682 Da.
Found *m/z*: 369.2791 $[M+H]^+$. Calculated 369.2788 Da.
Found *m/z*: 391.2609 $[M+Na]^+$. Calculated 391.2608 Da.

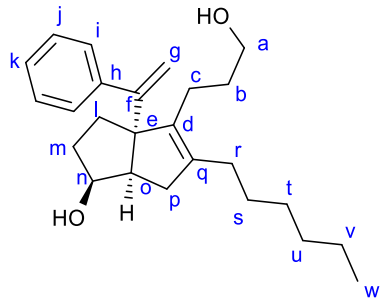
IR (ATR): ν_{max}/ cm^{-1} 3311brs (OH), 3078w (=C-H), 3052w (=C-H), 3017w (=C-H), 2951m (C-H), 2923s (C-H), 2870m (C-H), 2853m (C-H), 1621vw

(C=C), 1490m (Ar), 1456m (Ar), 1441m (Ar), 1055m (C-O), 1028m (C-O), 899s, 773s, 700s.

Compound **186-*exo*** underwent chiral separation using 5% IPA in hexane on a 4.6 × 250 mm Daicel OD-H column at 1 mL min^{-1} using multiple injections, enantiomers eluting at 9.51 and 11.11 minutes for the levorotary and dextrorotary enantiomers respectively. Two colourless oils were isolated (14 mg and 14 mg, 0.08 mmol).

[α]D (25 °C): -83.9 ° (C = 0.02 M, CH_2Cl_2), +85.2 ° (C = 0.02 M, CH_2Cl_2).

5.2.3.11 - *Rac*-(1*R*, 5*R*, 6*S*)-1-(1-phenylvinyl)-2-(propyl-3-ol)-3-hexyl-bicyclo[3.3.0]oct-2-en-6-ol (186-*endo*)



$C_{25}H_{36}O_2$ (368.56)

Endo

Procedure:[223] To a stirring solution of **201-*endo*** (122 mg, 0.33 mmol) in THF (5 mL), TBAF (1 M in THF, 1.32 mL, 1.32 mmol) was added dropwise at RT under nitrogen and the reaction was stirred overnight at RT. The reaction was poured into water (40 mL) and extracted with Et_2O (3× 25 mL). The organic phases were combined, washed with water (40 mL), brine (40 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 10-20% EtOAc in hexane over silica to afford the title compound as a colourless oil (59 mg, 0.16 mmol, 49%).

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.25 – 7.13 (5 H, m, ArH), 5.13 (1 H, d, *J* 1.5 Hz, Hg), 5.03 (1 H, d, *J* 1.5 Hz, Hg), 4.12 (1 H, ddd, *J* 9.3, 7.9, 5.1 Hz, Hn), 3.63 (2 H, t, *J* 6.5 Hz, Ha), 2.50 – 2.35 (2 H, m), 2.15 – 2.03 (4 H, m), 1.93 (1 H, brdd, *J* 16.5, 9.1 Hz, Hp), 1.88 – 1.61 (6 H, m), 1.48 – 1.18 (10 H, m), 0.90 (3 H, t, *J* 6.8 Hz, Me).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 155.58 (C, Cf), 144.09 (C, Cd/q/h), 140.50 (C, Cd/q/h), 136.96 (C, Cd/q/h), 127.83 (2 CH, Ci/j), 127.72 (2 CH, Ci/j), 126.75 (CH, Ck), 113.81 (CH_2, Cg), 74.76 (CH, Cn), 69.01 (C,

Ce), 63.69 (CH_2, Ca), 47.89 (CH, Co), 33.67 (CH_2), 33.59 (CH_2), 33.09 (CH_2), 32.53 (CH_2), 31.97 (CH_2), 29.77 (CH_2), 29.48 (CH_2), 27.94 (CH_2), 22.80 (CH_2), 22.23 (CH_2), 14.27 (CH_3, Cw).

LRMS (ESI$^+$): *m/z*: 391 ($[M+Na]^+$, 7%), 386 ($[M+NH_4]^{+\bullet}$, 7%), 369 ($[M+H]^+$, 100%), 351 ($[M-OH]^{+\bullet}$, 20%).

HRMS (ESI$^+$): Found *m/z*: 351.2683$[M-OH]^{+\bullet}$. Calculated 351.2682 Da.
Found *m/z*: 369.2791 $[M+H]^+$. Calculated 369.2788 Da.
Found *m/z*: 391.2611 $[M+Na]^+$. Calculated 391.2608 Da.

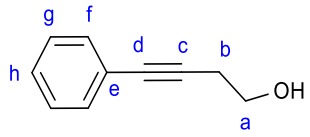
IR (ATR): ν_{max}/ cm^{-1} 3320brs (OH), 3078w (=C-H), 3052w (=C-H), 3017w (=C-H), 2950m (C-H), 2924s (C-H), 2852m (C-H), 1621vw (C=C), 1490m (Ar), 1453m (Ar), 1058brm (C-O), 899s, 774s, 699s.

Compound **186-*endo*** underwent chiral separation using 8% IPA in hexane on a 4.6 × 250 mm Daicel OD-H column at 1 mL min^{-1} using multiple injections, enantiomers eluting at 8.64 and 18.01 minutes for levorotary and dextrorotary enantiomers respectively. Two colourless oils were isolated (18 mg and 17 mg, 0.09 mmol).

$[\alpha]_D$ (25 °C): -82.0 ° (C = 0.05 M, CH_2Cl_2), +95.5 ° (C = 0.05 M, CH_2Cl_2).

5.2.4 – Synthesis of Target D

5.2.4.1 - 4-Phenylbut-3-yn-1-ol (209)



$C_{10}H_{10}O$ (146.07)

Procedure:[162] To a stirring solution of $Pd(PPh_3)_4$ (2.60 g, 2.25 mmol) in pyrrolidine (56 mL), bromobenzene (4.74 mL, 45.0 mmol) and 3-butyn-1-ol (3.56 mL, 47.0 mmol) were added at RT and under nitrogen. The reaction was then stirred at 80 °C for 4 hours. The reaction mixture was cooled to RT, poured into sat. $NH_4Cl_{(aq)}$ (200 mL) and extracted with Et_2O (3× 300 mL). The organic phases were combined, washed with sat. $NH_4Cl_{(aq)}$ (200 mL), water (200 mL), brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 50% Et_2O in hexane over silica followed by 30% EtOAc in hexane over silica to afford the title compound as a bright yellow-orange oil (5.84 g, 40.0 mmol, 89%).

GC (AP40): Rt 5.55 mins.

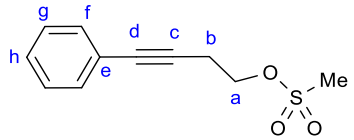
^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.45 – 7.38 (2 H, m, ArH), 7.31 – 7.26 (3 H, m, ArH), 3.80 (2 H, t, *J* 6.4 Hz, Ha), 2.68 (2 H, t, *J* 6.4 Hz, Hb), 2.28 (1 H, s, OH).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 131.74 (2 CH, Cf/g), 128.34 (2 CH, Cf/g), 128.01 (CH, Ch), 123.44 (C, Ce), 86.54 (C, Cc/d), 82.47 (C, Cc/d), 61.22 (CH_2, Ca), 23.85 (CH_2, Cb).

LRMS (EI): *m/z*: 146 ($[M]^{+\bullet}$, 67%), 128 ($[M\text{-}H_2O]^{+\bullet}$, 26%), 115 ($[M\text{-}CH_2OH]^{+\bullet}$, 100%), 105 (12%), 89 (25%), 77 (8%), 63 (23%), 51 (12%).

Characterisation data was consistent with that reported in the literature.[232]

5.2.4.2 - 4-Phenylbut-3-yn-1-yl methanesulfonate (216)



$C_{11}H_{12}O_3S$ (224.27)

Procedure:[233] To a stirring solution of 4-phenylbut-3-yn-1-ol **209** (5.66 g, 38.7 mmol) in CH_2Cl_2 (78 mL), freshly distilled triethylamine (8.10 mL, 58.1 mmol) was added at RT and under nitrogen. The reaction was cooled to 0 °C and mesyl chloride (3.09 mL, 39.9 mmol) was added dropwise over 1 minute. The reaction was stirred at 0 °C for 15 minutes before being poured into water (175 mL) and extracted with CH_2Cl_2 (3× 175 mL). The organic phases were combined, washed with 2 M $HCl_{(aq)}$ (175 mL), sat. $NaHCO_{3\,(aq)}$ (175 mL), brine (175 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the title compound as an orange oil (8.68 g, 38.7 mmol, 100%).

GC (AP40): Rt 7.83 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.43 – 7.37 (2 H, m, ArH), 7.33 – 7.27 (3 H, m, ArH), 4.38 (2 H, t, *J* 6.8 Hz, Ha), 3.06 (3 H, s, Me), 2.88 (2 H, t, *J* 6.8 Hz, Hb).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 131.72 (2 CH, Cf/g), 128.42 (2 CH, Cf/g), 128.34 (CH, Ch), 122.94 (C, Ce), 84.06 (C, Cc/d), 82.96 (C, Cc/d), 67.58 (CH_2, Ca), 37.78 (CH_3, Me), 20.79 (CH_2, Cb).

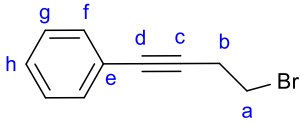
LRMS (CI) *m/z*: 242 ($[M+NH_4]^+$, 8%), 210 ($[M\text{-}Me\&OH]^{+\bullet}$, 2%), 164 (10%), 143 (10%), 128 ($[M\text{-}MeSO_3H]^{+\bullet}$, 100%), 115 ($[M\text{-}MeSO_3CH_2]^{+\bullet}$, 51%), 103 (55%), 91 (22%).

HRMS (EI): Found *m/z*: 224.0494 $[M]^{+\bullet}$. Calculated 224.0502 Da.

IR (ATR): ν_{max}/ cm^{-1} 3022 (=C-H), 2966w (C-H), 2938w (C-H), 2907w (C-H), 1490m (C-H), 1441w (C-H), 1416w (C-H), 1350vs (S=O), 1334s (C-O), 1169vs (S=O), 957s, 755s, 691s, 524s.

^{1}H-NMR was consistent with that reported in the literature.[233]

5.2.4.3 - 1-Bromo-4-phenylbutan-3-yne (208)



$C_{10}H_9Br$ (209.09)

Procedure:[234] To a stirring solution of LiBr (9.63 g, 111 mmol) in acetone (40 mL) 4-phenylbut-3-yn-1-yl methanesulfonate **216** (8.57 g, 38.2 mmol) was added in acetone (30 mL) under nitrogen and at 0 °C. The reaction was stirred at 0 °C for 10 minutes and subsequently for 144 hours at RT. The reaction mixture was poured into water (200 mL) and extracted with Et_2O (3× 250 mL). The organic phases were combined, washed with water (200 mL), brine (50 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 0-10% EtOAc in hexane over silica to afford the title compound as a colourless oil (7.24 g, 34.6 mmol, 91%).

GC (AP40): Rt 6.03 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.44 – 7.38 (2 H, m, ArH), 7.31 – 7.26 (3 H, m, ArH), 3.52 (2 H, t, *J* 7.3 Hz, Ha), 2.97 (2 H, t, *J* 7.4 Hz, Hb).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 131.80 (2 CH, Cf/g), 128.40 (2 CH, Cf/g), 128.23 (CH, Ch), 123.26 (C, Ce), 86.67 (C, Cc/d), 82.58 (C, Cc/d), 29.68 (CH_2, Ca), 24.03 (CH_2, Cb).

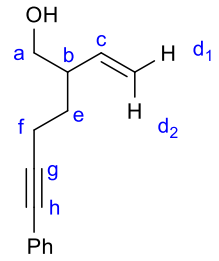
LRMS (EI): *m/z*: 208 ($[M]^{+\bullet}$, 96%), 128 ($[M\text{-}HBr]^{+\bullet}$, 94%), 115 ($[M\text{-}CH_2Br]^{+\bullet}$, 100%), 102 (64%), 89 (48%), 77 (63%), 63 (64%), 51 (55%).

HRMS (EI): Found *m/z*: 207.9872 $[M]^{+\bullet}$. Calculated 207.9882 Da.

IR (ATR): ν_{max}/ cm^{-1} 3077w (=C-H), 3054w (=C-H), 3032w (=C-H), 3019w (=C-H), 2969w (C-H), 2921w (C-H), 2890w (C-H), 1597m (Ar), 1570w (Ar), 1489s (Ar), 1440m (C-H), 753s, 689s, 528s.

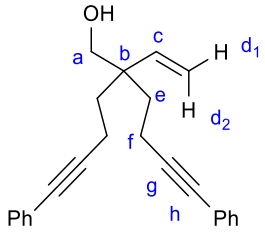
^{1}H-NMR was consistent with that reported in the literature.[234]

5.2.4.4 – *Rac*-6-phenyl-2-vinylhex-5-yn-1-ol (205) & 6-Phenyl-2-(4-phenylbut-3-yn-1-yl)-2-vinylhex-5-yn-1-ol (218)



$C_{14}H_{16}O$ (200.28)

205



$C_{24}H_{24}O$ (328.46)

218

Procedure:[155] To a stirring solution of *n*-BuLi (2.5 M, 3.90 mL, 9.75 mmol) in THF (3.75 mL), distilled diethylamine (1.06 mL, 10.3 mmol) was added dropwise over 3 minutes at -78 °C and subsequently stirred at 0 °C for 30 minutes. The reaction was re-cooled to -78 °C and crotonic acid (430 mg, 5.0 mmol) in THF (3.7 mL) was added dropwise over 15 minutes, the reaction was stirred at 0 °C for 40 minutes. The reaction was re-cooled to -78 °C, 1-bromo-4-phenylbutan-3-yne **208** (1.05 g, 5.0 mmol) in THF (10 mL) was added dropwise over 20 minutes and the reaction was stirred for 6 hours whilst allowing to warm slowly from -78 to – 50 °C, then maintaining -50 ^{o}C. The reaction was subsequently stirred at -20 ^{o}C for 15 hours. The reaction was quenched with water (10 mL), poured into water (80 mL) and extracted with Et_2O (3× 70 mL). The aqueous phase was acidified with conc. $HCl_{(aq)}$ at 0 $^\circ$C and subsequently extracted with EtOAc (3× 70 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The isolated oil was dissolved in THF (5 mL) and added dropwise over 4 minutes to a stirring suspension of $LiAlH_4$ (157 mg, 4.14 mmol) in THF (7 mL) under nitrogen. The reaction was stirred at RT for 1 hour. The reaction was quenched with dropwise addition of water (6 mL) before being poured into water (100 mL) and extracted with EtOAc (3× 150 mL). The organic phases were combined, washed with water (100 mL) and brine (2× 100 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 20% EtOAc

in hexane over silica to afford title compound **205** as a colourless oil (345 mg 1.65 mmol, 33%).

6-Phenyl-2-vinylhex-5-yn-1-ol **205**

GC (AP40): Rt 7.29 mins.

^{1}H-NMR: δ_H (400 MHz, $CDCl_3$) 7.41 – 7.33 (2 H, m, ArH), 7.31 – 7.23 (3 H, m, ArH), 5.62 (1 H, ddd, *J* 17.5, 9.7, 8.7 Hz, Hc), 5.22 (1 H, ddd, *J* 17.6, 1.8, 0.9 Hz, Hd_2), 5.22 (1 H, ddd, *J* 9.6, 1.8, 0.6 Hz, Hd_1), 3.63 (1 H, ddd, *J* 10.8, 7.0, 5.4 Hz, Ha), 3.51 (1 H, ddd, *J* 10.8, 7.5, 3.7 Hz, Ha), 2.55 – 2.42 (2 H, m, Hb & Hf), 2.38 (1 H, dt, *J* 16.9, 7.8 Hz, Hf), 1.76 (1 H, dtd, *J* 13.2, 8.0, 4.9 Hz, He), 1.56 (1 H, ddd, *J* 13.4, 9.4, 7.6, 5.8 Hz, He), 1.45 (1 H, dd, *J* 7.0, 4.5 Hz, OH).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 138.91 (CH, Cc), 131.68 (2 CH, *o*/*m*-Ph), 128.35 (2 CH, *o*/*m*-Ph), 127.75 (CH, *p*-Ph), 124.00 (C, *i*-Ph), 118.38 (CH_2, Cd), 89.78 (C, Cg/h), 81.14 (C, Cg/h), 65.56 (CH_2, Ca), 46.22 (CH, Cb), 29.79 (CH_2, Ce), 17.27 (CH_2, Cf).

LRMS (EI): *m/z*: 200 ($[M]^{+\bullet}$, 18%), 182 ($[M\text{-}H_2O]^{+\bullet}$, 13%), 169 ($[M\text{-}CH_2OH]^{+\bullet}$, 58%), 152 (25%), 141 (67%), 128 ($[C_6H_5C{\equiv}CC(H)CH_2]^{+\bullet}$, 55%), 115 ($[C_6H_5C{\equiv}CCH_2]^{+\bullet}$, 100%), 91 (72%).

HRMS (EI): Found *m/z*: 200.1198 $[M]^+$. Calculated 200.1196 Da.

IR (ATR): ν_{max}/ cm^{-1} 3359brm (OH), 3077w (=C-H), 3032vw (=C-H), 3020vw (=C-H), 2923m (C-H), 2871m (C-H), 2232w (C≡C), 1639w (C=C), 1598w (C=C), 1570w (Ar), 1489m (Ar), 1441m (Ar), 1421m (C-H), 1027m (C-O), 915m, 754s, 690s, 525m.

The reaction was repeated on a larger scale of 12.0 mmol using the same conditions described. A lower yield of alcohol **205** was obtained (colourless oil, 221 mg, 1.10 mmol, 9%) due to the formation of a larger quantity of double alkylated product **218** obtained as a colourless oil (53 mg, 0.16 mmol, 1%) allowing for its characterisation (listed below).

6-Phenyl-2-(4-phenylbut-3-yn-1-yl)-2-vinylhex-5-yn-1-ol **218**

^{1}H-NMR: δ_H (400 MHz, $CDCl_3$) 7.41 – 7.35 (4 H, m, ArH), 7.31 – 7.22 (6 H, m, ArH), 5.68 (1 H, dd, *J* 17.9, 11.1 Hz, Hc), 5.28 (1 H, dd, *J* 11.1, 0.9 Hz, Hd_1), 5.11 (1 H, dd, *J* 17.9, 0.9 Hz, Hd_2), 3.60 (2 H, d, *J* 3.5 Hz, Ha),

2.43 (4 H, dd, *J* 8.8, 6.9 Hz, Hf), 1.89 – 1.75 (4 H, m, He), 1.64 (1 H, s, OH).

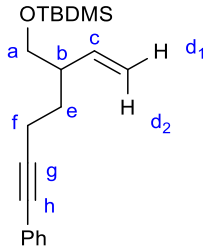
^{13}C-NMR: δ_C (101 MHz, $CDCl_3$) 142.27 (CH, Cc), 131.66 (4 CH, *o*/*m*-Ph), 128.36 (4 CH, *o*/*m*-Ph), 127.79, (2 CH, *p*-Ph) 123.85 (2 C, *i*-Ph), 116.05 (CH_2, Cd), 90.36 (2 C, Cg/h), 80.85 (2 C, Cg/h), 65.81 (CH_2, Ca), 44.81 (C, Cb), 32.86 (2 CH_2, Ce), 14.28 (2 CH_2, Cf).

LRMS (ESI$^+$): *m/z*: 329 ($[M+H]^+$, 100%).

HRMS (APPI): Found *m/z*: 328.15 $[M]^+$. Calculated 328.1822 Da.

IR (ATR): ν_{max}/ cm^{-1} 3448mbr (OH), 3081w (=C-H), 3058w (=C-H), 3033w (=C-H), 3020w (=C-H), 2998w (C-H), 2932m (C-H), 2871m (C-H), 2246w (C≡C), 1636w (C=C), 1598m (Ar), 1571w (Ar), 1489m (Ar), 1442m (C-H), 1006m (C-O), 906s, 755s, 728s, 690s.

5.2.4.5 – *Rac*-*tert*-butyldimethyl((6-phenyl-2-vinylhex-5-yn-1-yl)oxy)silane (204)



$C_{20}H_{30}OSi$ (314.54)

Procedure:[231] To a stirring solution of enyne **205** (345 mg, 1.72 mmol) in DMF (1.7 mL), 1H-imidazole (258 mg, 3.78 mmol) and TBDMSCl (428 mg, 2.84 mmol) were added and the reaction was stirred at RT overnight. The reaction mixture was poured into sat. $NaHCO_{3\,(aq)}$ (20 mL) and extracted with Et_2O (3× 15 mL). The organic phases were combined, washed with sat. $NaHCO_{3\,(aq)}$ (20 mL), brine (20 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 0-10% Et_2O in hexane over silica to afford the title compound as a colourless oil (512 mg, 1.63 mmol, 95%).

GC (AP40): Rt 8.41 mins.

^{1}H-NMR: δ_H (400 MHz, $CDCl_3$) 7.41 – 7.36 (2 H, m, ArH), 7.31 – 7.24 (3 H, m, ArH), 5.65 (1 H, ddd, *J* 17.2, 10.3, 8.6 Hz, Hc), 5.12 (1 H, ddd, *J* 17.2, 1.9, 0.9 Hz, Hd_2), 5.10 (1 H, ddd, *J* 10.3, 2.0, 0.7 Hz, Hd_1), 3.57 (2 H, ddd, *J* 10.3, 2.0, 0.7 Hz, Ha), 2.47 (1 H, ddd, *J* 16.9, 8.1, 5.6 Hz, Hf), 2.42 – 2.30 (2 H, m, Hf & Hb), 1.86 (1 H, dtd, *J* 13.1, 8.1, 4.7 Hz, He),

1.54 (1 H, dddd, *J* 13.4, 9.4, 7.6, 5.8 Hz, He), 0.90 (9 H, s, *t*Bu), 0.05 (6 H, s, $SiMe_2$).

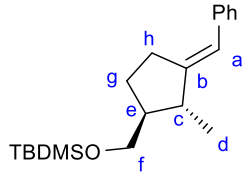
^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 139.37 (CH, Cc), 131.68 (2 CH, *o*/*m*-Ph), 128.31 (2 CH, *o*/*m*-Ph), 127.60 (CH, *p*-Ph), 124.24 (C, *i*-Ph), 116.52 (CH_2, Cd), 90.38 (C, Cg/h), 80.84 (C, Cg/h), 66.55 (CH_2, Ca), 45.91 (CH, Cb), 30.07 (CH_2, Ce), 26.08 (3 CH_3, *t*Bu), 18.49 (C, *t*Bu), 17.32 (CH_2, Cf), -5.17 (CH_3, SiMe), -5.21 (CH_3, SiMe).

LRMS (CI): *m/z*: 315 ($[M+H]^+$, 30%), 299 ($[M-CH_3]^{+\bullet}$, 5%), 257 ($[M-t\text{Bu}]^{+\bullet}$, 56%), 227 ($[M-t\text{Bu}\&2(CH_3)]^{+\bullet}$, 20%), 183 ($[M-OTBDMS]^{+\bullet}$, 100%), 169 (19%), 155 (17%), 141 (31%).

HRMS (EI): Found *m/z*: 314.2066 $[M]^+$. Calculated 314.2061 Da.

IR (ATR): ν_{max}/ cm^{-1} 3077w (=C-H), 2952s (C-H), 2927m (C-H), 2895m (C-H), 2855m (C-H), 1640w (C=C), 1598w (C=C), 1490m (Ar), 1471m (Ar), 1462m (Ar), 1441m (C-H), 1106s (C-O), 833s, 774s, 753s, 690s.

5.2.4.6 - *Rac*-(1*S*, 2*R*)-(*E*)-((3-benzylidene-2-methylcyclopentyl)methoxy)(*tert*-butyl)dimethylsilane (222-*anti*)



$C_{20}H_{32}OSi$ (316.56)

Anti

Procedure:[53] To a stirring solution of Cp_2ZrCl_2 (146 mg, 0.5 mmol) in THF (2.5 mL) was added *n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) dropwise over 2 minutes at -78 ^oC under nitrogen and stirred for 30 minutes. The enyne **204** (157 mg, 0.5 mmol) in THF (1 mL) was added dropwise at -78 °C. The reaction was allowed to warm to RT, stirred for 3.5 hours and then quenched with MeOH (5 mL) and sat. $NaHCO_{3\,(aq)}$ (5 mL) and stirred at RT for 16 hours. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined and washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 10% CH_2Cl_2 in hexane over silica to afford the title compound as a colourless oil (140 mg, 0.44 mmol, 88%, 6.5:1 **222-*anti*** to **222-*syn*** by ^{1}H-NMR).

(^{1}H-NMR of the crude mixture showed a 5.8:1 ratio between **222-*anti*** to **222-*syn***).

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.31 (4 H, d, *J* 4.4 Hz, ArH), 7.16 (1 H, tt, *J* 8.6, 4.5 Hz, ArH), 6.23 (1 H, q, *J* 2.4 Hz, Ha), 3.70 (1 H, dd, *J* 10.0, 5.1 Hz, Hf), 3.57 (1 H, dd, *J* 10.0, 6.4 Hz, Hf), 2.69 (1 H, ddt, *J* 17.2, 8.7, 2.7 Hz, Hh), 2.57 (1 H, dddt, *J* 17.3, 8.9, 8.7, 2.6 Hz, Hh), 2.37 (1 H, dqdd, *J* 9.0, 6.8, 2.0, 1.2 Hz, Hc), 1.95 (1 H, dddd, *J* 12.0, 8.5, 6.5, 3.3 Hz, Hg), 1.68 (1 H, ttd, *J* 9.1, 6.5, 6.4, 5.1 Hz, He), 1.50 (1 H, m, Hg), 1.20 (3 H, d, *J* 6.8 Hz, Hd), 0.91 (9 H, s, *t*Bu), 0.06 (6 H, s, $SiMe_2$).
[Visible peaks for **222-*syn*** diastereoisomer: δ_H ppm (400 MHz, $CDCl_3$) 3.63 (1 H, J 10.1, 6.7 Hz, Hf'), 3.45 (1 H, dd, J 10.1, 7.7 Hz, Hf'), 2.20 (1 H, dq, J 13.9, 6.9 Hz, He'), 1.09 (3 H, d, J 7.2 Hz, Hd')].

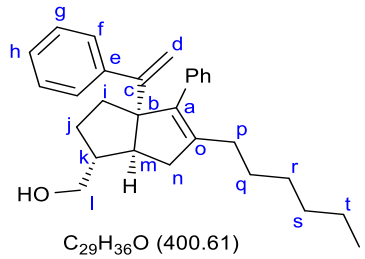
^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 151.88 (C, Cb), 138.99 (C, *i*-Ph), 128.31 (2 CH, *o*/*m*-Ph), 128.27 (2 CH, *o*/*m*-Ph), 125.80 (CH, *p*-Ph), 120.58 (CH, Ca), 65.48 (CH_2, Cf), 49.22 (CH, Ce), 42.95 (CH, Cc), 30.35 (CH_2, Ch), 28.44 (CH_2, Cg), 26.12 (3 CH_3, *t*Bu), 18.64 (CH_3, Cd), 18.52 (C, *t*Bu), -5.18 (CH_3, SiMe), -5.21 (CH_3, SiMe).
[Visible peaks for **222-*syn*** diastereoisomer: δ_C ppm (101 MHz, $CDCl_3$) 120.50 (CH, Ca'), 63.10 (CH_2, Ca'), 29.73 (CH_2, Ch'), 26.87 (CH_2, Cg'), 26.07 (3 CH_3, tBu'), 14.91 (CH_3, Cd')].

LRMS (CI): *m/z*: 317 ($[M+H]^+$, 10%), 301 ($[M-CH_3]^{+\bullet}$, 3%), 359 ($[M-tBu]^{+\bullet}$, 16%), 185 (M-OTBDMS]$^{+\bullet}$, 100%), 169 (52%), 155 (15%), 141 (19%), 129 (19%).

HRMS (APPI): Found *m/z*: 316.2217 $[M]^+$. Calculated 316.2217 Da.

IR (ATR): ν_{max}/ cm^{-1} 3085 (=C-H), 3056 (=C-H), 3024 (=C-H), 2954 (C-H), 2927 (C-H), 2884 (C-H), 2856 (C-H), 1653w (C=C), 1599w (C=C), 1496m (Ar), 1471m (Ar), 1462m (Ar), 1446m (C-H), 1105s (C-O) 833s, 773s, 693s.

5.2.4.7 - *Rac*-(*1R, 3R, 6S*)-1-(9-(1-phenylvinyl)-2-phenyl-3-hexyl-6-methylol-bicyclo[3.3.0]oct-2-ene (203-*exo*)



$C_{29}H_{36}O$ (400.61)

Exo

Procedure:[53, 223] To a stirring solution of Cp_2ZrCl_2 (300 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexane, 0.80 mL, 2.0 mmol) was added dropwise over 1.5 minutes at -78 °C under nitrogen and stirred for 30 minutes. Enyne **204** (315 mg, 1.0 mmol) in THF (3 mL) was added dropwise over 7 minutes at -78 °C, stirred for 20 minutes and subsequently stirred for 4 hours at RT. The reaction was re-cooled to -78 °C and 1,1-dibromoheptane **163** (284 mg, 1.1 mmol) in THF (1 mL) was added followed by LDA (1 M in THF, 1.10 mL, 1.1 mmol) dropwise over 1 minute and stirred for 15 minutes at -78 °C. Lithium phenylacetylide [*n*-BuLi (2.5 M in hexane, 1.20 mL, 3.0 mmol) was added dropwise over 3 minutes to phenylacetylene (0.33 mL, 3.0 mmol) in THF (3 mL) at 0 °C under nitrogen and stirred at 0 °C for 30 minutes] was added dropwise over 1.5 minutes at -78 °C and stirred for 1 hour, allowing to warm from -78 ^{o}C to -55 ^{o}C. MeOH (10 mL) followed by sat. $NaHCO_{3\,(aq)}$ (10 mL) were added at -55 ^{o}C under nitrogen and stirred at RT 16 hours. The reaction mixture was poured into water (80 mL) and extracted with Et_2O (3× 70 mL). The organic phases were combined, washed with water (2× 80 mL) and brine (80 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 0 – 10% CH_2Cl_2 in hexane over silica to afford a yellow oil. The isolated oil was dissolved in THF (2.5 mL) and TBAF (1 M in THF, 1.62 mL, 1.62 mmol) was added dropwise over 1 minute at RT and under nitrogen. The reaction was stirred at RT for 15 hours. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 30 mL). The organic phases were combined, washed with water (50 mL), brine (50 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 1% MeOH in CH_2Cl_2 over ISOLUTE®SiII pre-packed silica and subsequently by column chromatography using 20% hexane in CH_2Cl_2 over ISOLUTE®SiII pre-packed silica to afford the title compound as a colourless oil (239 mg, 0.60 mmol, 60%, 1:9 *endo*/*exo*).

Separation of **203-*endo*** and **203-*exo*** was carried out by HPLC using 0.5% IPA in hexane on a techsphere silica column (25 cm × 10 mm at 4 mL min^{-1}) using multiple injections to afford

the title compound as three colourless oils; pure **203-*exo*** (63 mg, 0.16 mmol, 16%), 16.7:1 *exo*/*endo* (83 mg, 0.21 mmol, 21%) and 1:1.3 *exo*/*endo* (17 mg, 0.04 mmol, 4%). Combined yield of 41% (compound ratios according to ^{1}H-NMR).

(^{1}H-NMR of the crude mixture showed a 9.4:1 ratio between **203-*exo*** and **203-*endo***).

The following characterisation was conducted on the pure sample of **203-*exo*** isolated.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.36 – 7.20 (10 H, m, ArH), 5.09 (1 H, d, *J* 1.6 Hz, Hd), 4.99 (1 H, d, *J* 1.6 Hz, Hd), 3.51 (1 H, dd, *J* 10.4, 6.6 Hz, Hl), 3.44 (1 H, dd, *J* 10.2, 8.1 Hz, Hl), 2.24 (1 H, dd, *J* 16.5, 7.8 Hz, Hn), 2.15 – 2.00 (4 H, m, Hm, Hn & Hp), 1.91 – 1.80 (2 H, m, Hk & Hj), 1.75 – 1.58 (2 H, m, Hj & Hi), 1.44 (1 H, m, Hi), 1.39 – 1.17 (9 H, m, Hq-t & OH), 0.86 (3 H, t, *J* 7.0 Hz, Me).

δ_H ppm (400 MHz, C_6D_6) 7.45 (2 H, dt, *J* 8.1, 1.6 Hz), 7.41 – 7.36 (2 H, m), 7.24 (2 H, t, *J* 7.6), 7.19 – 7.08 (4 H, m), 5.16 (1 H, d, *J* 1.7 Hz, Hd), 5.07 (1 H, d, *J* 1.7 Hz, Hd), 3.27 (1 H, dd, *J* 10.2, 6.4 Hz, Hl), 3.21 (1 H, dd, *J* 10.2, 7.6 Hz, Hl), 2.35 (1 H, dd, *J* 16.4, 7.9 Hz, Hn), 2.22 (1 H, dd, *J* 7.4, 4.5 Hz, Hm), 2.14 (2 H, dd, *J* 9.0, 6.6 Hz, Hp), 2.05 (1 H, d, *J* 16.5 Hz, Hn), 1.90 (1 H, m, Hj), 1.83 – 1.63 (3 H, m, Hk, Hj & Hi), 1.46 (1 H, m, Hi), 1.41 – 1.29 (2 H, m, Hq), 1.29 – 1.07 (6 H, m), 0.87 (3 H, t, *J* 7.1 Hz, Me), 0.64 (1 H, s, OH).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 155.13 (C), 143.98 (C), 141.98 (C), 139.34 (C), 137.90 (C), 129.65 (2 CH), 128.28 (2 CH), 127.86 (2 CH), 127.68 (2 CH), 126.72 (CH), 126.60 (CH), 114.34 (CH_2, Cd), 70.00 (C), 66.43 (CH_2, Cl), 51.86 (CH, Ck), 49.96 (CH, Cm), 42.39 (CH_2, Cn), 33.59 (CH_2, Cj), 31.84 (CH_2), 30.05 (CH_2, Cp), 29.58 (CH_2), 28.34 (CH_2, Ci), 28.02 (CH_2), 22.75 (CH_2), 14.23 (CH_3, Me).

δ_C ppm (101 MHz, C_6D_6) 155.75 (C), 144.43 (C), 142.03 (C), 139.99 (C), 138.33 (C), 129.94 (2 CH), 128.59 (2 CH), 128.35 (2 CH), 128.24 (2 CH), 127.96 (CH), 126.99 (CH), 114.39 (CH_2), 70.40 (C), 65.99 (CH_2, Cl), 52.18 (CH, Ck), 50.31 (CH, Cm), 42.66 (CH_2, Cn), 33.84 (CH_2, Cj), 32.05 (CH_2), 30.32 (CH_2, Cp), 29.83 (CH_2, Ci), 28.52 (CH_2, Cq), 28.32 (CH_2), 23.03 (CH_2), 14.34 (CH_3, Me).

LRMS (ESI$^+$): *m/z*: 401 ($[M+H]^+$, 100%).

HRMS (ESI$^+$): Found *m/z*: 401.2842 $[M+H]^+$. Calculated 401.2839 Da.

IR (ATR): ν_{max}/ cm^{-1} 3306brw (OH), 3078w (=C-H), 3051w (=C-H), 3017w (=C-H), 2923s (C-H), 2855s (C-H), 1597w (C=C), 1573w (Ar), 1489m (Ar), 1439m (C-H), 1029m (C-O), 902m, 764m, 699s.

The NMR of the 3:4 mixture of the *exo*/*endo* diastereoisomers revealed the following peaks for **203-*endo*** diastereoisomer.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 3.65 (2 H, d, *J* 7.1 Hz, Hl'), 2.56 (1 H, td, *J* 9.0, 2.0 Hz, Hm').

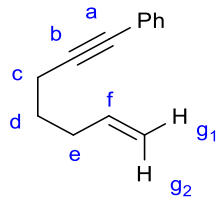
^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 115.18 (C), 144.28 (C), 143.23 (C), 139.19 (C), 137.58 (C), 129.77 (2 CH), 128.01 (2 CH), 127.77 (2 CH), 127.75 (2 CH), 126.74 (CH), 126.61 (CH), 115.12 (CH_2, Cd), 70.54 (C), 64.66 (CH_2, Cl), 46.64 (CH, Ck), 46.09 (CH, Cm), 35.29 (CH_2), 34.69 (CH_2), 30.01 (CH_2), 29.63 (CH_2), 28.86 (CH_2), 28.08 (CH_2).*

*Missing 2 CH_2 and 1 CH_3 as must appear at the same ppm as the *exo* diastereoisomer.

5.3 – Insertion of Benzyl Carbenoids into Unsaturated Zirconacycles

5.3.1 – Enynes

5.3.1.1 - Hept-6-en-1-yn-1-ylbenzene (134)



$C_{13}H_{14}$ (170.26)

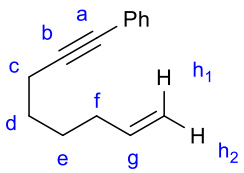
Procedure: [166, 167] To a stirring solution of phenylacetylene (3.29 mL, 30.0 mmol) in dry THF (88 mL), *n*-BuLi (2.5 M in hexanes, 12.0 mL, 30.0 mmol) was added dropwise over 5 minutes at -78 °C under nitrogen. The reaction mixture was allowed to warm to -20 °C and was stirred at this temperature for two hours. HMPA (5.22 mL, 30.0 mmol) was added dropwise over 2 minutes at -20 °C and the reaction mixture was subsequently stirred for 20 minutes. 5-Bromopent-1-ene (4.62 mL, 39.0 mmol) in THF (45 mL) was added dropwise over 9 minutes at -30 °C and the reaction was allowed to warm to RT and stirred overnight (17 hours). The reaction mixture was quenched with water (5 mL)

and stirred at RT for 2 hours. The reaction mixture was poured into water (300 mL) and extracted with Et_2O (3× 250 mL). The organic phases were combined, washed with water (300 mL) and brine (300 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 100% hexane over silica to afford the title compound as a colourless oil (4.46 g, 26.2 mmol, 87%).

GC (AP40):	Rt 5.78 mins.
^{1}H-NMR:	δ_H ppm (400 MHz, $CDCl_3$) 7.46 – 7.37 (2 H, m, ArH), 7.33 – 7.26 (3 H, m, ArH), 5.85 (1 H, ddt, *J* 17.1, 10.3, 6.7 Hz, Hf), 5.09 (1 H, ddd, *J* 17.1, 3.4, 1.6 Hz, Hg_2), 5.02 (1 H, ddt, *J* 10.2, 1.9, 1.1 Hz, Hg_1), 2.44 (2 H, t, *J* 7.1 Hz, Hc), 2.25 (2 H, brq, *J* 7.1 Hz, He), 1.72 (2 H, p, *J* 7.2 Hz, Hd).
^{13}C-NMR:	δ_C ppm (101 MHz, $CDCl_3$) 138.03 (CH, Cf), 131.68 (2 CH, *o*/*m*-Ph), 128.32 (2 CH, *o*/*m*-Ph), 127.65 (CH, *p*-Ph),), 124.16 (C, *i*-Ph), 115.34 (CH_2, Cd), 90.08 (C, Ca/b), 81.01 (C, Ca/b), 32.99 (CH_2, Cd/e), 28.07 (CH_2, Cd/e), 18.94 (CH_2, Cc).
LRMS (CI):	*m/z*: 188 ($[M+NH_4]^+$, 66%), 171 ($[M+H]^+$, 100%), 155 (33%), 142 (73%), 128 (28%), 115 ($[PhC{\equiv}CCH_2]^{+\bullet}$, 46%), 102 (6%), 91 (17%).

Characterisation data was consistent with that reported in the literature.[235]

5.3.1.2 - Oct-7-en-1-yn-1-ylbenzene (227)



$C_{14}H_{16}$ (184.28)

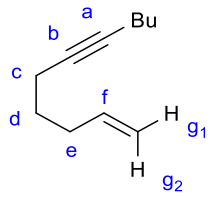
Procedure:[166, 167] To a stirring solution of phenyl acetylene (3.36 mL, 30.0 mmol) in dry THF (88 mL), *n*-BuLi (2.5 M in hexanes, 12.0 mL, 30.0 mmol) was added dropwise over 4 minutes at -78 °C under nitrogen. The reaction mixture was allowed to warm to -20 °C and was stirred at this temperature for two hours. HMPA (5.22 mL, 30.0 mmol) was added dropwise over 2 minutes at -20 °C and the reaction mixture was subsequently stirred for 20 minutes. 6-Bromohex-1-ene (5.32 mL, 39.0 mmol) in THF (44 mL) was added dropwise over 9 minutes at -30 °C and the reaction was allowed to warm to RT and stirred overnight (16 hours). The reaction mixture was quenched with water (5 mL) and concentrated *in vacuo* for THF removal. The resulting mixture was poured into water

(300 mL) and extracted with Et_2O (3× 250 mL). The organic phases were combined, washed with water (300 mL) and brine (300 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 1% Et_2O in hexane over silica followed by Kugelrohr distillation at 131 °C, 0.1 mbar to afford the title compound as a colourless oil (4.91 g, 26.7 mmol, 89%).

GC (AP40):	Rt 6.29 mins.
^{1}H-NMR:	δ_H ppm (400 MHz, $CDCl_3$) 7.45 – 7.36 (2 H, m, ArH), 7.33 – 7.27 (3 H, m, ArH), 5.85 (1 H, ddt, *J* 17.0, 10.3, 6.7 Hz, Hg), 5.06 (1 H, dq, *J* 17.1, 1.6 Hz, Hh_1), 4.99 (1 H, brd, *J* 10.2 Hz, Hh_2), 2.44 (2 H, t, *J* 6.8 Hz, Hc), 2.13 (2 H, brq, *J* 7.1 Hz, Hf), 1.72 – 1.54 (4 H, m, Hd & He).
^{13}C-NMR:	δ_C ppm (101 MHz, $CDCl_3$) 138.78 (CH, Cg), 131.68 (2 CH, *o*/*m*-Ph), 128.31 (2 CH, *o*/*m*-Ph), 127.62 (CH, *p*-Ph), 124.19 (C, *i*-Ph), 114.73 (CH_2, Ch), 90.31 (C, Ca/b), 80.84 (C, Ca/b), 33.42 (CH_2), 28.33 (CH_2), 28.26 (CH_2), 19.41 (CH_2, Cc).
LRMS (CI):	*m/z*: 202 ($[M+NH_4]^+$, 85%), 185 $(M+H]^+$, 100%), 169 (27%), 156 (26%), 143 ($[M-CH_2CHCH_2]^{+\bullet}$, 77%), 128 (28%), 115 ($[PhC{\equiv}CCH_2]^{+\bullet}$, 49%), 104 (9%).

Characterisation data was consistent with that reported in the literature.[236]

5.3.1.3 - Undec-1-en-6-yne (228)



$C_{11}H_{18}$ (150.27)

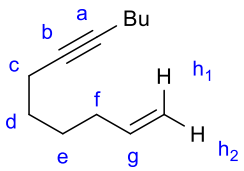
Procedure:[166, 167] To a stirring solution of hex-1-yne (3.45 mL, 30.0 mmol) in dry THF (88 mL), *n*-BuLi (2.5 M in hexanes, 12.0 mL, 30.0 mmol) was added dropwise over 4 minutes at -78 ℃ under nitrogen. The reaction mixture was allowed to warm to -20 ^oC and was stirred at this temperature for two hours. HMPA (5.22 mL, 30.0 mmol) was added dropwise over 2 minutes at -20 ^oC and the reaction mixture was subsequently stirred for 20 minutes. 5-Bromopent-1-ene (3.32 mL, 28.0 mmol) in THF (44 mL) was added dropwise over 9 minutes at -30 ^oC and the reaction was allowed to warm to RT and stirred overnight (17 hours). The reaction mixture was quenched with water (10 mL) and stirred at

RT for 2 hours. The reaction mixture was poured into water (300 mL) and extracted with Et_2O (3× 250 mL). The organic phases were combined, washed with water (300 mL) and brine (300 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 100% hexane over silica to afford the title compound as a colourless oil (3.23 g, 21.5 mmol, 72%).

GC (AP40):	Rt 4.06 mins.
^{1}H-NMR:	δ_H ppm (400 MHz, $CDCl_3$) 5.80 (1 H, ddt, *J* 17.0, 10.3, 6.7 Hz, Hf), 5.03 (1 H, dq, *J* 17.1, 1.8 Hz, Hg_2), 4.97 (1 H, ddt, *J* 10.2, 2.1, 1.1 Hz, Hg_1), 2.20 – 2.09 (6 H, m), 1.57 (2 H, quin, *J* 7.2 Hz), 1.52 – 1.30 (4 H, m), 0.90 (3 H, t, *J* 7.2 Hz, Me).
^{13}C-NMR:	δ_C ppm (101 MHz, $CDCl_3$) 138.29 (CH, Cf), 115.05 (CH_2, Cg), 80.68 (C, Ca/b), 79.87 (C, Ca/b), 32.97 (CH_2), 31.40 (CH_2), 28.51 (CH_2), 22.08 (CH_2), 18.58 (CH_2), 18.33 (CH_2), 13.76 (CH_3, Me).
LRMS (CI):	*m/z*: 151 ($[M+H]^+$, 100%), 135 ($[M-CH_3]^{+\bullet}$, 21%), 121 ($[M-CH_2CH_3]^{+\bullet}$, 18%), 108 (52%), 93 ($[M-Bu]^{+\bullet}$, 54%), 81 (13%), 67 (6%), 58 (12%).

Characterisation data was consistent with that reported in the literature.[237]

5.3.1.4 - Dodec-1-en-7-yne (229)



$C_{12}H_{20}$ (164.29)

Procedure:[166, 167] To a stirring solution of hex-1-yne (3.45 mL, 30.0 mmol) in dry THF (88 mL), *n*-BuLi (2.5 M in hexanes, 12.0 mL, 30.0 mmol) was added dropwise over 4 minutes at -78 ℃ under nitrogen. The reaction mixture was allowed to warm to -20 °C and was stirred at this temperature for two hours. HMPA (5.22 mL, 30.0 mmol) was added dropwise over 2 minutes at -20 °C and the reaction mixture was subsequently stirred for 20 minutes. 6-Bromohex-1-ene (2.41 mL, 18.0 mmol) in THF (20 mL) was added dropwise over 4 minutes at -30 °C and the reaction was allowed to warm to RT and stirred for 19 hours before being quenched with water (5 mL). The reaction mixture was poured into water (150 mL) and extracted with Et_2O (3× 150 mL). The organic phases were combined, washed with water (150 mL) and brine (150 mL), dried over $MgSO_4$, filtered

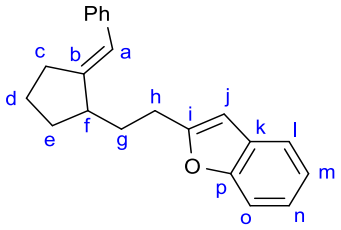
concentrated *in vacuo* and purified by column chromatography using 100% hexane over silica to afford the title compound as a colourless oil (2.91 g, 17.7 mmol, 98%).

GC (AP40):	Rt 4.63 mins.
^{1}H-NMR:	δ_H ppm (400 MHz, $CDCl_3$) 5.81 (1 H, ddt, *J* 17.0, 10.3, 6.7 Hz, Hg), 5.01 (1 H, dq, *J* 17.1, 1.8 Hz, Hh_1), 4.94 (1 H, ddt, *J* 10.2, 2.2, 1.2 Hz, Hh_2), 2.20 – 2.10 (4 H, m), 2.10 – 2.01 (2 H, m), 1.52 – 1.33 (8 H, m), 0.90 (3 H, t, *J* 7.2 Hz, Me).
^{13}C-NMR:	δ_C ppm (101 MHz, $CDCl_3$) 138.94 (CH, Cg), 114.56 (CH_2, Ch), 80.48 (C, Ca/b), 80.09 (C, Ca/b), 33.43 (CH_2), 31.41 (CH_2), 28.74 (CH_2), 28.20 (CH_2), 22.08 (CH_2), 18.76 (CH_2), 18.59 (CH_2), 13.77 (CH_3, Me).
LRMS (CI):	*m/z:* 165 ($[M+H]^+$, 42%), 149 ($[M\text{-}CH_3]^{+\bullet}$, 31%), 135 ($[M\text{-}CH_2CH_3]^{+\bullet}$, 53%), 122 (64%), 107 $(M\text{-}Bu]^{+\bullet}$, 100%), 93 (62%), 81 (44%), 67 (17%).

Characterisation data was consistent with that reported in the literature.[237]

5.3.2 – (*E*)-Alkenes

5.3.2.1 - (*E*)-2-(2-(2-Benzylidenecyclopentyl)ethyl)benzofuran (239)



$C_{22}H_{22}O$ (302.42)

Procedure:[2] To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M, 0.80 mL, 2.0 mmol) was added dropwise over 1.5 minutes at -78 °C under nitrogen and stirred at -78 °C for 30 minutes. Enyne **134** (170 mg, 1.0 mmol) in THF (2 mL) was added dropwise over 1.5 minutes at -78 °C, the reaction was allowed to warm to RT and stirred for 2 hours. The reaction was re-cooled to -78 °C and 2-chloromethylbenzofuran **236** (167 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by a dropwise addition of LDA (1 M, 1.0 mL, 1.0 mmol) over 2 minutes. The reaction was stirred at -78 °C for 30 minutes before being quenched with 2 M $HCl_{(aq)}$ (4 mL) at -50 °C and stirred at RT overnight. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined, washed with water

(2× 50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* and purified by column chromatography using 1% Et_2O in hexane over silica to afford the title compound as a pale yellow oil (242 mg, 0.80 mmol, 80%).

GC (AP40): Rt 10.92 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.50 (1 H, d+fs, *J* 7.1 Hz, ArH), 7.44 (1 H, d+fs, *J* 7.0 Hz, ArH), 7.33 (4 H, d, *J* 4.2 Hz, ArH), 7.25 – 7.15 (3 H, m, ArH), 6.44 (1 H, s, Hj), 6.33 (1 H, q, *J* 2.2 Hz, Ha), 2.99 – 2.79 (2 H, m, Hh), 2.75 – 2.52 (3 H, m, Hg & $H_{aliphatic}$), 2.18 (1 H, m), 2.08 – 1.74 (3 H, m), 1.67 (1 H, m), 1.42 (1 H, m).

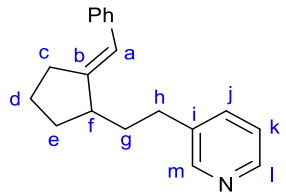
^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 159.66 (C, Cp), 154.80 (C, Ci), 149.86 (C, Cb), 138.84 (C), 129.12 (C), 128.33 (4 CH, *o*- & *m*-Ph), 125.96 (CH), 123.25 (CH), 122.55 (CH), 121.31 (CH, Ca), 120.33 (CH), 110.87 (CH), 102.03 (CH, Cj), 45.83 (CH, Cf), 32.80 (CH_2), 31.76 (CH_2), 31.62 (CH_2), 26.86 (CH_2, Ch), 25.01 (CH_2).

LRMS (EI): *m/z*: 302 ($[M]^{+\bullet}$, 100%), 221 (15%), 211 (52%), 195 (28%), 181 (17%), 170 (89%), 155 (53%), 144 (81%).

HRMS (APPI): Found *m/z*: 302.1662 $[M]^+$. Calculated 302.1665 Da.

IR (ATR): ν_{max}/ cm^{-1} 3117w, 3106w (=C-H), 3085w (=C-H), 3065w (=C-H), 3050w (=C-H), 3018w (=C-H), 2995w (C-H), 2966m (C-H), 2946m (C-H), 2937m (C-H), 2921m (C-H), 2909m (C-H), 2853m (C-H), 1645m (C=C), 1599m (C=C), 1587m (Ar), 1489m (Ar), 1454s (Ar), 1444m (Ar), 1424m (C-H), 1252s (C-O), 790s, 750s, 740s, 696s.

5.3.2.2 - (*E*)-3-(2-(2-Benzylidenecyclopentyl)ethyl)pyridine (240)



$C_{19}H_{21}N$ (263.38)

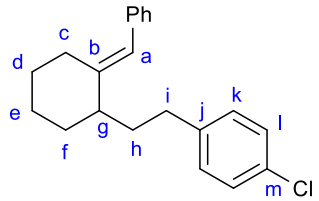
Procedure:[2] To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred at -78 °C for 15 minutes. Enyne **134** (170 mg, 1.0 mmol) in THF (3 mL) was added dropwise at -78 °C, the reaction was allowed to warm to RT and stirred for 2 hours. [3-(Chloromethyl)pyridine hydrochloride (328 mg, 2.0 mmol) was washed with sat. $NaHCO_{3\,(aq)}$ (10 mL) and extracted with Et_2O (2× 10 mL). The organic

phases were combined, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* at 0 °C to afford 3-(chloromethyl)pyridine as a pale yellow oil (222 mg, 1.74 mmol).] The reaction was re-cooled to -78 °C and 3-(chloromethyl)pyridine (222 mg, 1.74 mmol) in THF (1 mL) was added dropwise followed by a dropwise addition of LDA (1M, 1.0 mL, 1.0 mmol) over 5 minutes. The reaction was stirred at -78 °C for 30 minutes before MeOH (5 mL) was added at -60 °C and the reaction stirred at RT for 16 hours. The reaction mixture was poured into 2 M $NaOH_{(aq)}$ (100 mL) and extracted with Et_2O (2× 100 mL). The organic phases were combined and washed a further time with 2 M $NaOH_{(aq)}$ (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 80% Et_2O in hexane over silica to afford the title compound as an orange oil (188 mg, 0.71 mmol, 71%).

GC (AP239):	Rt 3.56 mins.
^{1}H-NMR:	δ_H ppm (400 MHz, $CDCl_3$) 8.50 (1 H, s, Hm), 8.45 (1 H, d, *J* 4.1 Hz, Hl), 7.54 (1 H, dt, *J* 7.8, 1.9 Hz, Hj), 7.38 – 7.28 (4 H, m, ArH), 7.22 (1 H, dd, *J* 7.8, 4.8 Hz, Hk), 7.17 (1 H, m, *p*-Ph), 6.27 (1 H, q, *J* 2.3 Hz, Ha), 2.86 – 2.49 (5 H, m, Hg & $H_{aliphatic}$), 2.09 – 1.82 (3 H, m), 1.75 – 1.59 (2 H, m), 1.46 – 1.35 (1 H, m).
^{13}C-NMR:	δ_C ppm (101 MHz, $CDCl_3$) 150.11 (CH, Cm), 149.91 (C, Cb), 147.46 (CH, Cl), 138.76 (C), 137.93 (C), 135.86 (CH, Cj), 128.31 (2 CH, *o*-/*m*-Ph), 128.28 (2 CH, *o*-/*m*-Ph), 125.96 (CH, *p*-Ph), 123.44 (CH, Ck), 121.18 (CH, Ca), 45.83 (CH, Cf), 36.44 (CH_2), 31.83 (CH_2), 31.65 (CH_2), 31.29 (CH_2), 25.02 (CH_2).
LRMS (ESI$^+$):	*m/z*: 264 ($[M+H]^+$, 100%).
HRMS (ESI$^+$):	Found *m/z*: 264.1752 $[M+H]^+$. Calculated 264.1747 Da.
IR (ATR):	ν_{max}/ cm^{-1} 3082w (=C-H), 3051w (=C-H), 3023w (=C-H), 2993w (C-H), 2941m (C-H), 2858m (C-H), 1652 (C=C), 1596m (C=C), 1489m (Ar), 1478m (Ar), 1446m (Ar), 1421m (C-H), 749s, 713s, 694s.

Characterisation data was consistent with that reported in S. Fillery Thesis.[1]

5.3.2.3 - (*E*)-1-(2-(2-Benzylidenecyclohexyl)ethyl)-4-chlorobenzene (245)



$C_{21}H_{23}Cl$ (310.87)

Procedure:[2] To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexane, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred at -78 °C for 30 minutes. Enyne **227** (184 mg, 1.0 mmol) in THF (2 mL) was added dropwise at -78 °C, the reaction was allowed to warm to RT and stirred for 3 hours. The reaction was re-cooled to -90 °C and 4-chlorobenzyl chloride (161 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by the dropwise addition of LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise to *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C over 1 minute and stirred for 15 minutes] over 2 minutes. The reaction was stirred for 5 minutes before being quenched with MeOH (2 mL) at -90 °C, then it was allowed to warm to RT and stirred for 16 hours. 2 M $HCl_{(aq)}$ (2 mL) was added and the reaction was stirred for 1 hour at RT. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined, washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified twice by column chromatography using 100% hexane over silica to afford the title compound as a colourless oil (283 mg, 0.91 mmol, 91%).

GC (AP40): Rt 10.24 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.35 (2 H, t, *J* 7.7 Hz, ArH), 7.28 (2 H, d, *J* 8.2 Hz, ArH), 7.26 – 7.20 (3 H, m, ArH), 7.17 (2 H, d, *J* 8.2 Hz), 6.28 (1 H, s, Ha), 2.65 (2 H, t, *J* 8.0 Hz, Hi), 2.50 – 2.20 (3 H, m, Hg & $H_{aliphatic}$), 2.06 (1 H, dtt, *J* 13.6, 8.0, 7.9 Hz, Hc), 1.85 (1 H, m), 1.80 – 1.45 (6 H, m).

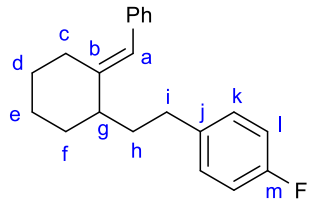
^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 145.45 (C, Ca), 141.39 (C), 138.51 (C), 131.47 (C), 129.91 (2 CH, , *o/m*-Ar), 129.11 (2 CH, *o/m*-Ar), 128.52 (2 CH, *o/m*-Ar), 128.16 (2 CH, *o/m*-Ph), 126.04 (CH), 122.17 (CH, Ca), 44.58 (CH, Cg), 34.06 (CH_2), 33.84 (CH_2), 33.47 (CH_2), 28.39 (CH_2), 27.21 (CH_2), 23.35 (CH_2).

LRMS (EI): *m/z*: 310 ($[M]^{+\bullet}$, 31%), 185 ($[M\text{-}CH_2C_6H_4Cl]^{+\bullet}$, 23%), 171 ([M-(CH2)2C6H4Cl]$^{+\bullet}$, 80%), 141 (27%), 129 (62%), 115 (53%), 103 (30%), 91 ($[M\text{-}C_{14}H_{17}Cl]^{+\bullet}$, 100%).

HRMS (EI): Found *m/z*: 310.1481 $[M]^{+\bullet}$. Calculated 310.1483 Da.

IR (ATR): ν_{max}/ cm^{-1} 3078w (=C-H), 3054w (=C-H), 3022w (=C-H), 2924m (=C-H), 2852m (=C-H), 1647m (C=C), 1598m (C=C), 1575w (Ar), 1490s (Ar), 1444m (Ar), 1406m (C-H), 807s, 729s, 698s.

5.3.2.4 - (*E*)-1-(2-(2-Benzylidenecyclohexyl)ethyl)-4-fluorobenzene (246)



$C_{21}H_{23}F$ (294.41)

Procedure:[2] To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexane, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred at -78 °C for 30 minutes. Enyne **227** (184 mg, 1.0 mmol) in THF (2 mL) was added dropwise at -78 °C, the reaction was allowed to warm to RT and stirred for 3 hours. The reaction was re-cooled to -90 °C and 4-fluorobenzyl chloride (145 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by the dropwise addition of LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise to *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C over 1 minute and stirred for 15 minutes] over 2 minutes. The reaction was stirred for 5 minutes before the reaction was quenched with MeOH (2 mL) at -90 °C, then it was allowed to warm to RT and stirred for 17 hours. 2 M $HCl_{(aq)}$ (2 mL) was added and the reaction was stirred for 1 hour at RT. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined, washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 3% CH_2Cl_2 in hexane over silica to afford the title compound as a colourless oil (243 mg, 0.83 mmol, 83%).

GC (AP40): Rt 9.37 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.34 (2 H, t, *J* 7.4 Hz, ArH), 7.23 (3 H, d, *J* 7.8 Hz, ArH), 7.18 (2 H, dd, *J* 8.1, 6.0 Hz, ArH), 7.00 (2 H, t, *J* 8.7 Hz, ArH), 6.28 (1 H, s, Ha), 2.65 (2 H, t, *J* 8.0 Hz, Hi), 2.47 – 2.19 (3 H, m, Hg & $H_{aliphatic}$), 2.05 (1 H, m), 1.86 (1 H, td, *J* 10.5, 4.8 Hz), 1.80 – 1.44 (6 H, m).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 161.32 (d, *J* 243.0 Hz, C, Cm), 145.56 (C, Ca), 138.55 (d, *J* 3.4 Hz, C, Cj),* 129.84 (d, *J* 7.7 Hz, 2 CH, Ck), 129.13

(2 CH, *o*-/*m*-Ph), 128.17 (2 CH, *o*-/*m*-Ph), 126.02 (CH, *p*-Ph), 122.10 (CH, Ca), 115.14 (d, *J* 21.0 Hz, 2 CH, Cl), 44.61 (CH, Cg), 34.31 (CH_2), 33.86 (CH_2), 33.31 (CH_2), 28.42 (CH_2), 27.24 (CH_2), 23.38 (CH_2).

*Cb quaternary carbon likely hidden under this peak.

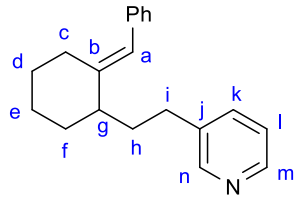
^{19}F-NMR: δ_F ppm (376 MHz, $CDCl_3$) -118.20.

LRMS (EI): *m/z*: 294 ($[M]^{+\bullet}$, 48%), 185 ($[M\text{-}CH_2C_6H_4F]^{+\bullet}$, 22%), 172 (100%), 141 (27%), 129 (47%), 115 (38%), 109 (51%), 91 (59%).

HRMS (EI): Found *m/z*: 294.1788 $[M]^{+\bullet}$. Calculated 294.1778 Da.

IR (ATR): ν_{max}/ cm^{-1} 3078w (=C-H), 3052w (=C-H), 3036w (=C-H), 3022w (=C-H), 2924m (C-H), 2853m (C-H), 1647w (C=C), 1599m (C=C), 1508s (Ar), 1444m (Ar), 1219s (C-F), 823s, 730m, 698s.

5.3.2.5 - (*E*)-3-(2-(2-Benzylidenecyclohexyl)ethyl)pyridine (247)



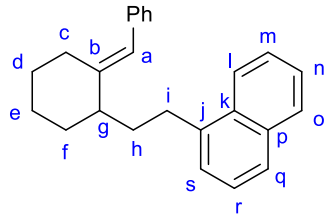
$C_{20}H_{23}N$ (277.41)

Procedure:[2] To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexane, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred at -78 °C for 30 minutes. Enyne **227** (184 mg, 1.0 mmol) in THF (2 mL) was added dropwise at -78 °C, the reaction was allowed to warm to RT and stirred for 3 hours. [3-(Chloromethyl)pyridine hydrochloride (328 mg, 2.0 mmol) was washed with sat. $NaHCO_{3\,(aq)}$ (10 mL) and extracted with Et_2O (2× 5 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* at 0 °C to afford 3-(chloromethyl)pyridine as a pale yellow oil (217 mg, 1.7 mmol).] The reaction was re-cooled to -90 °C and 3-(chloromethyl)pyridine (217 mg, 1.7 mmol) in THF (1 mL) was added dropwise followed by the dropwise addition of LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise to *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C over 1 minute and stirred for 15 minutes] over 2 minutes. The reaction was stirred for 5 minutes before being quenched with MeOH (2 mL) at -90 °C, then it was allowed to warm to RT and stirred for 24 hours. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined, washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by

column chromatography using 20% EtOAc in hexane over silica to afford the title compound as a colourless oil (237 mg, 0.85 mmol, 85%).

GC (AP40):	Rt 9.85 mins.
^{1}H-NMR:	δ_H (400 MHz, $CDCl_3$) 8.48 (1 H, d, *J* 1.5 Hz, Hn), 8.44 (1 H, dd, *J* 4.7, 1.2 Hz, Hm), 7.52 (1 H, ddd, *J* 7.8, 2.2, 1.7 Hz, Hk), 7.35 – 7.27 (2 H, m, ArH), 7.24 – 7.13 (4 H, m, ArH), 6.25 (1 H, s, Ha), 2.65 (2 H, t, *J* 8.0 Hz, Hi), 2.41 (1 H, m), 2.36 – 2.21 (2 H, m, Hg & $H_{aliphatic}$), 2.05 (1 H, m), 1.84 (1 H, m), 1.78 – 1.42 (6 H, m).
^{13}C-NMR:	δ_C ppm (101 MHz, $CDCl_3$) 150.17 (CH, Cn), 147.41 (CH, Cm), 145.24 (C, Cb), 138.41 (C), 138.10 (C), 135.96 (CH, Ck), 129.12 (2 CH, *o*-/*m*-Ph), 128.19 (2 CH, *o*-/*m*-Ph), 126.09 (CH, *p*-Ph/Cl), 123.42 (CH, *p*-Ph/Cl), 122.32 (CH, Ca), 44.59 (CH, Cg), 33.82 (CH_2), 33.79 (CH_2), 31.24 (CH_2), 28.37 (CH_2), 27.18 (CH_2), 23.31 (CH_2).
LRMS (ESI$^+$):	*m/z*: 278 ($[M+H]^+$, 100%).
HRMS (ESI$^+$):	Found *m/z*: 278.1909 $[M+H]^+$. Calculated 278.1903 Da.
IR (ATR):	ν_{max}/ cm^{-1} 3079w (=C-H), 3051w (=C-H), 3023w (=C-H), 2992w (C-H), 2923m (C-H), 2852m (C-H), 1647w (C=C), 1598w (C=C), 1574m (Ar), 1478m (Ar), 1444m (Ar), 1421m (C-H), 729s, 713s, 698s.

5.3.2.6 - (*E*)-1-(2-(2-Benzylidenecyclohexyl)ethyl)naphthalene (248)



$C_{25}H_{26}$ (326.48)

Procedure:[2] To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexane, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred at -78 °C for 30 minutes. Enyne **227** (184 mg, 1.0 mmol) in THF (2 mL) was added dropwise at -78 °C under nitrogen, the reaction was allowed to warm to RT and stirred for 3 hours. The reaction was re-cooled to -90 °C and 1-naphthylmethyl chloride (177 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by the dropwise addition of LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise to *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C over 1 minute and stirred for 15 minutes] over 2 minutes. The reaction was stirred for 10 minutes before being quenched with MeOH (2 mL) at -90 °C, then it was allowed to warm to RT and stirred for

17 hours. 2 M $HCl_{(aq)}$ (2 mL) was added and stirred for 1 hour at RT. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined, washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 2.5% CH_2Cl_2 in hexane over silica and heated in Kugelrohr distillation equipment at 140 °C under 1.0 mbar (for unreacted 1-naphthylmethyl chloride removal) to afford the title compound as a colourless oil (222 mg, 0.68 mmol, 68%).

GC (AP40): Rt 12.33 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 8.06 (1 H, d, *J* 8.2 Hz, ArH), 7.86 (1 H, d, *J* 7.7 Hz, ArH), 7.72 (1 H, d, *J* 7.8 Hz, ArH), 7.57 – 7.45 (2 H, m, ArH), 7.45 – 7.29 (4 H, m, ArH), 7.25 – 7.13 (3 H, m, ArH), 6.35 (1 H, s, Ha), 3.11 (2 H, t, *J* 8.2 Hz, Hi), 2.53 – 2.29 (3 H, m, Hg + $H_{aliphatic}$), 2.17 (1 H, dtt, *J* 13.7, 8.0 7.9 Hz), 1.98 – 1.79 (2 H, m), 1.77 – 1.43 (5 H, m).

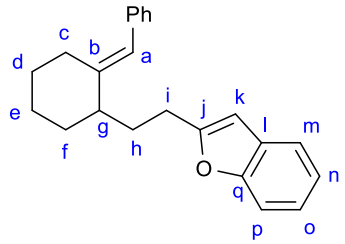
^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 145.70 (C, Cb), 139.29 (C), 138.63 (C), 134.07 (C), 132.03 (C), 129.17 (2 CH, *o*-/*m*-Ph), 128.94 (CH), 128.19 (2 CH, *o*-/*m*-Ph), 126.61 (CH), 126.02 (CH), 126.01 (CH), 125.88 (CH), 125.76 (CH), 125.55 (CH), 123.96 (CH), 122.27 (CH, Ca), 45.40 (CH, Cg), 34.04 (CH_2), 33.82 (CH_2), 31.45 (CH_2), 28.45 (CH_2), 27.32 (CH_2), 23.43 (CH_2).

LRMS (EI): *m/z*: 326 ($[M]^{+\bullet}$, 61%), 235 (30%), 207 (28%), 185 ($[M\text{-}CH_2Np]^{+\bullet}$, 37%), 171 ($[M\text{-}(CH_2)_2Np]^{+\bullet}$, 43%), 154 (99%), 141 ($[NpCH_2]^{+\bullet}$, 100%), 129 (82%).

HRMS (APPI): Found *m/z*: 326.2023 $[M]^+$. Calculated 326.2029 Da.

IR (ATR): ν_{max}/ cm^{-1} 3055w (=C-H), 3021w (=C-H), 2923m (C-H), 2851m (C-H), 1646w (C=C), 1597s (C=C), 1510m (Ar), 1493m (Ar), 1444m (Ar), 795s, 775s, 730s, 697s.

5.3.2.7 - (*E*)-2-(2-(2-benzylidenecyclohexyl)ethyl)benzofuran (249a)



$C_{23}H_{24}O$ (316.44)

Procedure:[2] To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexane, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and the reaction was stirred at -78 °C for 30 minutes. Enyne **227** (184 mg, 1.0 mmol) in THF (2 mL) was added dropwise at -78 °C , the reaction was allowed to warm to RT and stirred for 3 hours. The reaction was re-cooled to -90 °C and 2-(chloromethyl)benzofuran (167 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by the dropwise addition of LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise to *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C over 1 minute and stirred for 15 minutes] over 2 minutes. The reaction was stirred for 5 minutes before the reaction was quenched with 2 M HCl in Et_2O (2 mL) at -90 °C. The reaction was allowed to warm to RT and stirred for 16 hours. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined, washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 5% CH_2Cl_2 in hexane over silica afford the title compound as a colourless oil (266 mg, 0.84 mmol, 84%).

GC (AP240): Rt 6.56 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.49 (1 H, d+fs, *J* 6.6 Hz, ArH), 7.43 (1 H, d+fs, *J* 7.7 Hz, ArH), 7.32 (2 H, dd*, *J* 8.0, 7.0 Hz, ArH), 7.25 – 7.14 (5 H, m, ArH), 6.41 (1 H, d, *J* 0.8 Hz, Hk), 6.29 (1 H, s, Ha), 2.82 (2 H, t, *J* 7.8 Hz, Hi), 2.43 (1 H, dt, *J* 14.1, 5.2 Hz), 2.38 – 2.27 (2 H, m, Hg & $H_{aliphatic}$), 2.19 (1 H, m, Hh), 1.92 – 1.80 (2 H, m, Hd), 1.80 – 1.43 (5 H, m).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 159.82 (C, Cq), 154.80 (C, Cj), 145.10 (C, Cb), 138.49 (C), 129.16 (2 CH, *o*-/*m*-Ph)*, 128.17 (2 CH, *o*-/*m*-Ph), 126.07 (CH), 123.21 (CH), 122.53 (CH), 122.45 (CH, Ca), 120.31 (CH), 110.86 (CH, Cp), 102.04 (CH, Ck), 44.53 (CH, Cg), 33.81 (CH_2), 30.20 (CH_2), 28.36 (CH_2), 27.11 (CH_2), 26.83 (CH_2, Ci), 23.29 (CH_2).

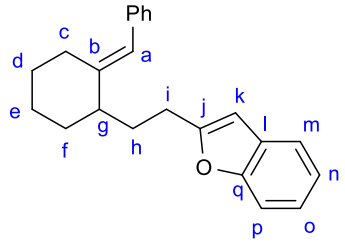
*Cb quaternary carbon missing, likely hidden under this peak.

LRMS (EI): *m/z*: 316 ($[M]^{+\bullet}$, 98%), 225 (57%), 209 (59%), 184 (79%), 171 ($[M-(CH_2)_2C_8H_5O]^{+\bullet}$, 14%), 155 (31%), 144 (100%), 131 ($[CH_2C_8H_5O]^{+\bullet}$, 86%).

HRMS (APPI): Found *m/z*: 316.1816 $[M]^+$. Calculated 316.1822 Da.

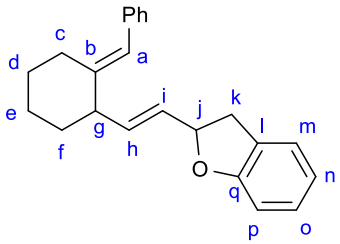
IR (ATR): ν_{max}/ cm^{-1} 3078w (=C-H), 3054w (=C-H), 3021w (=C-H), 2924m (C-H), 2852m (C-H), 1647w (C=C), 1599m (C=C), 1587 (Ar), 1494 (Ar), 1454s (Ar), 1251s (C-O), 749s, 731s, 698s,

5.3.2.8 - (*E*)-2-(2-(2-Benzylidenecyclohexyl)ethyl)benzofuran (249a) & 2-((*E*)-2-(2-((*E*)-Benzylidene)cyclohexyl)vinyl)-2,3-dihydrobenzofuran (249b)



$C_{23}H_{24}O$ (316.44)

249a



$C_{23}H_{24}O$ (316.44)

249b

Procedure:[2] To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexane, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred at -78 °C for 30 minutes. Enyne **227** (184 mg, 1.0 mmol) in THF (2 mL) was added dropwise at -78 °C, the reaction was then allowed to warm to RT and stirred for 3 hours. The reaction was re-cooled to -90 °C and 2-(chloromethyl)benzofuran (167 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by the dropwise addition of LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise to *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C over 1 minute and stirred for 15 minutes] over 2 minutes. The reaction was stirred for 5 minutes before the reaction was quenched with MeOH (2 mL) at -90 °C. The reaction was allowed to warm to RT and stirred for 16 hours. 2 M $HCl_{(aq)}$ (2 mL) was added and the reaction was stirred for 1 hour at RT. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined, washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 0.5% Et_2O in hexane over silica followed by 5-30% CH_2Cl_2 in hexane over silica afford two colourless oils **249a** (187 mg, 0.59 mmol, 59%) and **249b** (93 mg, 0.29 mmol, 29%). Combined yield of both products was 88%.

(^{1}H-NMR of the crude mixture showed a 1:1.5 ratio between **249b** and **249a** respectively).

249a

GC (AP40):	Rt 6.56 mins.
^{1}H-NMR:	δ_H (400 MHz, $CDCl_3$) 7.50 (1 H, d+fs, *J* 6.9 Hz ArH), 7.44 (1 H, d+fs, *J* 7.8 Hz, ArH), 7.36 – 7.29 (2 H, m, ArH), 7.25 – 7.14 (5 H, m, ArH), 6.42 (1 H, d, *J* 0.9 Hz, Hk), 6.30 (1 H, s, Ha), 2.83 (2 H, t, *J* 7.8 Hz, Hi), 2.44 (1 H, dt, *J* 14.1, 5.2 Hz), 2.38 – 2.27 (2 H, m, Hg & $H_{aliphatic}$), 2.21 (1 H, m, Hh), 1.93 – 1.81 (2 H, m, Hd), 1.80 – 1.42 (5 H, m).
^{13}C-NMR:	δ_C ppm (101 MHz, $CDCl_3$) 159.81 (C, Cq), 154.79 (C, Cj), 145.08 (C, Cb), 138.47 (C), 129.15 (2 CH, *o*-/*m*-Ph)*, 128.17 (2 CH, *o*-/*m*-Ph), 126.06 (CH), 123.20 (CH), 122.53 (CH), 122.44 (CH, Ca), 120.31 (CH), 110.85 (CH, Cp), 102.04 (CH, Ck), 44.52 (CH, Cg), 33.80 (CH_2), 30.18 (CH_2), 28.35 (CH_2), 27.10 (CH_2), 26.82 (CH_2, Ci), 23.28 (CH_2). *Quaternary carbon missing, likely hidden under this peak.
LRMS (EI):	*m/z*: 316 ($[M]^{+\bullet}$, 63%), 225 (12%), 209 (12%), 184 (42%), 171 ($[M-(CH_2)_2C_8H_5O]^{+\bullet}$, 13%), 155 (10%), 144 ($[M-C_7H_{10}Ph-H]^{+\bullet}$, 100%), 131 ($[M-CH_2C_7H_{10}Ph]^{+\bullet}$, 62%).

Characterisation data was consistent with that reported in 5.3.2.7.

249b

GC (AP240):	6.65 mins.
^{1}H-NMR:	δ_H ppm (400 MHz, $CDCl_3$) 7.35 – 7.27 (2 H, m, ArH), 7.23 – 7.08 (5 H, m, ArH), 6.84 (1 H, td, *J* 7.4, 0.9 Hz, ArH), 6.80 (1 H, d, *J* 8.0 Hz, ArH), 6.21 (1 H, s, Ha), 6.01 (1 H, ddd, *J* 15.5, 7.2, 0.7 Hz, Hh), 5.76 (1 H, ddd, *J* 15.5, 7.6, 1.1 Hz, Hi), 5.25 (1 H, qd, *J* 8.1, 0.4 Hz, Hj), 3.38 (1 H, dd, *J* 15.5, 9.1 Hz, Hk), 3.03 (1 H, dd, *J* 15.5, 8.2 Hz, Hk), 2.94 (1 H, m, Hg), 2.64 (1 H, ddd, *J* 13.6, 6.5, 3.8 Hz, Hc), 2.14 (1 H, ddd, *J* 13.5, 9.3, 4.0 Hz, Hc), 1.90 (1 H, m), 1.78 (1 H, m), 1.73 – 1.38 (4 H, m).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 159.57 (C, Cq), 144.74 (C, Cb), 138.42 (C, *i*-Ph), 136.68 (CH, Ch), 129.90 (CH, Ci), 129.12 (2 CH, *o*-/*m*-Ph), 128.17 (CH), 128.15 (2 CH, *o*-/*m*-Ph), 127.01 (C), 126.12 (CH), 124.98 (CH), 122.63 (CH, Ca), 120.49 (CH), 109.53 (CH, Cp), 83.98 (CH, Cj), 47.50 (CH, Cg), 36.49 (CH_2, Ck), 34.19 (CH_2), 28.55 (CH_2, Cc), 27.91 (CH_2), 24.76 (CH_2).

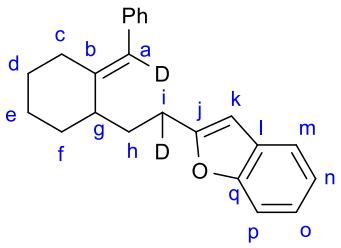
LRMS (EI): *m/z*: 316 ($[M]^{+\bullet}$, 25%), 225 (26%), 209 (100%), 197 (50%), 181 (21%), 167 (91%), 153 (27%), 141 (62%), 128 (40%).

HRMS (APPI): Found *m/z*: 316.1816 $[M]^+$. Calculated 316.1822 Da.

IR (ATR): ν_{max}/ cm^{-1} 3079w (=C-H), 3051w (=C-H), 3022w (=C-H), 2926m (C-H), 2853m (C-H), 1648w (C=C), 1479s (Ar), 1460m (Ar), 1444m (Ar), 1227s (C-O), 906s, 728s, 699s.

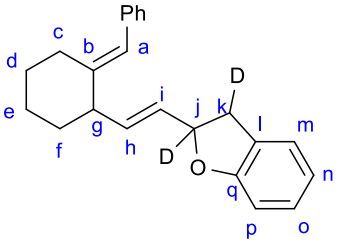
(Relative stereochemistry of compound **249b** was undetermined and assumed to be racemic).

5.3.2.9 - (*E*)-2-(2-(2-(Phenylmethylene-*d*)cyclohexyl)ethyl-1-*d*)benzofuran (258a), 2-((*E*)-2-(2-((*E*)-Benzylidene)cyclohexyl)vinyl)-2,3-dihydrobenzofuran-2,3-d_2 (258b) & 2-(2-(2-((*E*)-Benzylidene)cyclohexyl)ethylidene)-2,3-dihydrobenzofuran-3-*d* (258c)



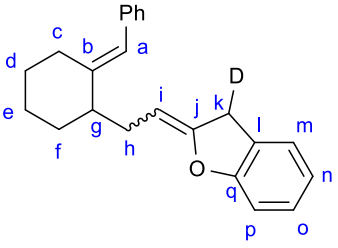
$C_{23}H_{22}D_2O$ (318.46)

258a



$C_{23}H_{22}D_2O$ (318.46)

258b



$C_{23}H_{23}DO$ (317.45)

258c

Procedure:[2] To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexane, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred at -78 °C for 30 minutes. Enyne **227** (184 mg, 1.0 mmol) in THF (2 mL) was added dropwise at -78 °C, the reaction was allowed to warm to RT and stirred for 3 hours. The reaction was re-cooled to -90 °C and 2-(chloromethyl)benzofuran (167 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by the dropwise addition of LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise to *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C over 1 minute and stirred for 15 minutes] over 2 minutes. The reaction was stirred for 5 minutes at before the reaction was quenched with MeOD (1.5 mL)

at -90 °C. The reaction was allowed to warm to RT and stirred for 16 hours. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined, washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 5-25% CH_2Cl_2 in hexane over silica afford a three colourless oils; **258a** (140 mg, 0.44 mmol, 44%), **258b** (99 mg, 0.31 mmol, 31%), **258c** (46 mg, estimated 0.14 mmol, estimated 14%).

(^{1}H-NMR of the crude mixture showed 2.4:1.4:1 ratio between **258a**, **258b** and **258c** respectively).

258a

GC (AP240):	Rt 6.59 mins.
^{1}H-NMR:	δ_H ppm (400 MHz, $CDCl_3$) 7.51 (1 H, d+fs, *J* 6.8 Hz, ArH), 7.45 (1 H, d+fs, *J* 7.2 Hz, ArH), 7.39 – 7.30 (2 H, m, ArH), 7.29 – 7.15 (5 H, m, ArH), 6.43 (1 H, s, Hk), 6.31 (0.3 H, s, Ha), 2.82 (1.1 H, m, Hi), 2.45 (1 H, dt, *J* 14.1, 5.2 Hz), 2.41 – 2.27 (2 H, m, Hg & $H_{aliphatic}$), 2.20 (1 H, m, Hh), 1.95 – 1.81 (2 H, m, Hd), 1.81 – 1.43 (5 H, m).
^{13}C-NMR:	δ_C (101 MHz, $CDCl_3$) 159.77 (C, Cq), 154.80 (C, Cj), 144.98 (C, Cb), 138.39 (C), 129.14 (2 CH, *o*-/*m*-Ph)*, 128.16 (2 CH, *o*-/*m*-Ph), 126.05 (CH), 123.19 (CH), 122.52 (CH), 122.43w (CH, Ca), 122.08 (t, *J* 23.3 Hz, CD, Ca), 120.30 (CH), 110.85 (CH, Cp), 102.04 (CH, Ck), 44.44 (CH, Cg), 33.80 (CH_2), 30.10 (CH_2), 28.34 (CH_2), 27.10 (CH_2), 26.80w (CH_2, Ci), 26.48 (t, *J* 19.5 Hz, CHD, Ci), 23.31 (CH_2). *Quaternary carbon missing, likely hidden under this peak.
LRMS (EI):	*m/z*: 318 ($[M]^{+\bullet}$, 63%), 226 (18%), 211 (20%), 185 (51%), 172 ($[M-CH_2CHDC_8H_5O]^{+\bullet}$, 13%), 156 (14%), 145 (100%), 132 ($[CHDC_8H_5O]^{+\bullet}$, 84%).
HRMS (APPI):	Found *m/z*: 318.1935 $[M]^+$. Calculated 318.1947 Da.
IR (ATR):	ν_{max}/ cm^{-1} 3102w (=C-H), 3078w (=C-H), 3054w (=C-H), 3033w (=C-H), 3020w (=C-H), 2925m (C-H), 2852m (C-H), 1638w (C=C), 1598m (Ar), 1586m (C=C), 1492m (Ar), 1454s (Ar), 1252s (C-O), 907s, 730s, 698s.

258b

GC (AP240): 6.69 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.36 – 7.28 (2 H, m, ArH), 7.24 – 7.07 (5 H, m, ArH), 6.85 (1 H, t, *J* 7.4 Hz, ArH), 6.81 (1 H, d, *J* 8.0 Hz, ArH), 6.22 (1 H, s, Ha), 6.01 (1 H, ddd, *J* 15.5, 7.2, 1.0 Hz, Hh), 5.77 (1 H, dd, *J* 15.5, 5.5 Hz, Hi), 5.25 (0.3 H, t, *J* 7.8 Hz, Hj), 3.36 (0.1 H, s, Hk), 3.01 (1 H, s, Hk), 2.94 (1 H, m, Hg), 2.65 (1 H, ddd, *J* 13.1, 5.7, 4.0 Hz, Hc), 2.14 (1 H, ddd, *J* 13.4, 9.3, 4.0 Hz, Hc), 1.91 (1 H, m), 1.79 (1 H, m), 1.71 – 1.41 (4 H, m).

^{13}C-NMR: δ_C (101 MHz, $CDCl_3$) 159.59 (C, Cq), 144.73 (C, Cb), 138.41 (C, *i*-Ph), 136.68 (CH, Ch), 129.83 (CH, Ci), 129.11 (2 CH, *o*-/*m*-Ph), 128.17 (CH), 128.15 (2 CH, *o*-/*m*-Ph), 126.95 (C), 126.12 (CH), 125.00 (CH), 122.61 (CH, Ca), 120.48 (CH), 109.52 (CH, Cp), 83.92w (CH, Cj), 83.52 (t, *J* 20.7 Hz, CD, Cj), 47.50 (CH, Cg), 36.36w (CH_2, Ck), 36.05 (t, *J* 20.7 Hz, CHD, Ck), 34.18 (CH_2), 28.55 (CH_2, Cc), 27.90 (CH_2), 24.76 (CH_2).

LRMS (EI): *m/z*: 318 ($[M]^{+\bullet}$, 13%), 281 (10%), 253 (9%), 227 (14%), 207 (98%), 197 ($[M\text{-}C_8H_5D_2O]^{+\bullet}$, 50%), 168 (71%), 141 (44%), 129 (45%), 115 (45%), 91 (100%).

HRMS (APPI): Found *m/z*: 318.1945 $[M]^+$. Calculated 318.1947 Da.

IR (ATR): ν_{max}/ cm^{-1} 3078w (=C-H), 3050w (=C-H), 3022w (=C-H), 2925m (C-H), 2852m (C-H), 1648w (C=C), 1596s (C=C), 1476s (Ar), 1459s (Ar), 1444s (Ar), 1239s (C-O), 910s, 747s, 731s, 698s.

258c

GC (AP240): 6.60 mins.

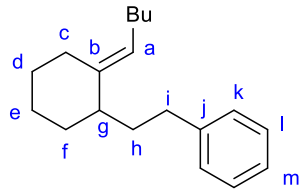
^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.30 (2 H, t, *J* 7.4 Hz, ArH), 7.23 – 7.09 (5 H, m, ArH), 6.91 (1 H, t, *J* 7.4 Hz, ArH), 6.86 (1 H, d, *J* 8.0 Hz, ArH), 6.25 (1 H, s, Ha), 5.20 (1 H, m, Hi), 3.84 (1 H, s, Hk), 2.55 – 2.31 (2 H, m), 2.31 – 2.19 (2 H, m), 2.08 (1 H, m), 1.87 (1 H, m), 1.74 (1 H, m), 1.62 – 1.35 (4 H, m).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 158.54 (C, Cq), 154.58 (C, Cj), 145.78 (C, Cb), 138.62 (C), 129.16 (2 CH, *o*-/*m*-Ph), 128.23 (CH), 128.15 (2 CH,

o-/*m*-Ph), 126.00 (CH), 125.54 (C), 124.86 (CH), 121.53 (CH), 121.45 (CH), 109.37 (CH, Cp), 99.79 (CH, Ci), 45.21 (CH, Cg), 33.34 (CH_2), 30.81 (t, *J* 20.4 Hz, CHD, Ck), 30.39w (CH_2, Ck), 29.86 (CH_2), 28.42 (CH_2), 28.12 (CH_2), 24.22 (CH_2).

LRMS (EI): *m/z*: 317 ($[M]^{+\bullet}$, 100%), 226 (34%), 210 (34%), 185 ($[M-CHC_8H_5DO]^{+\bullet}$, 70%), 171 ($[M-CH_2CHC_8H_5DO]^{+\bullet}$, 26%), 156 (18%), 145 (80%), 131 (70%).

5.3.2.10 - (*E*)-(2-(2-Pentylidenecyclohexyl)ethyl)benzene (263)



$C_{19}H_{28}$ (256.43)

Procedure:[2] To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexane, 0.80 mL, 2.0 mmol) dropwise over 2 minutes at -78 °C under nitrogen and stirred at -78 °C for 30 minutes. Enyne **229** (164 mg, 1.0 mmol) in THF (2 mL) was added dropwise at -78 °C, the reaction was allowed to warm to RT and stirred for 3 hours. The reaction was re-cooled to -90 °C and benzyl chloride (127 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by the dropwise addition of LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise to *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C over 1 minute and stirred for 15 minutes] over 2 minutes and stirred at -90 °C for 5 minutes. MeOH (2 mL) was added at -90 °C and the reaction stirred at RT for 16 hours. 2 M $HCl_{(aq)}$ (2 mL) was added and the reaction stirred at RT for 1 hour. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined, washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 100% hexane over silica to afford the title compound as a colourless oil (165 mg, 0.65 mmol, 65%).

GC (AP40): Rt 8.10 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.30 – 7.24 (2 H, m, ArH), 7.22 – 7.13 (3 H, m, ArH), 5.10 (1 H, t, *J* 7.2 Hz, Ha), 2.55 (2 H, t, *J* 8.1 Hz, Hi), 2.16 – 1.97 (5 H, m), 1.90 (1 H, m), 1.76 – 1.55 (4 H, m), 1.52 – 1.36 (3 H, m), 1.36 – 1.26 (4 H, m), 0.94 – 0.85 (3 H, m).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 143.40 (C, Cb), 141.56 (C), 128.57 (2 CH, *o*-/*m*-Ph), 128.39 (2 CH, *o*-/*m*-Ph), 125.66 (CH, *p*-Ph), 121.51 (CH, Ca), 44.42 (CH, Cg), 34.22 (2 CH_2), 34.07 (CH_2), 32.67 (CH_2), 28.39 (CH_2), 26.94 (CH_2), 26.58 (CH_2), 23.79 (CH_2), 22.48 (CH_2), 14.18 (CH_3, Me).

LRMS (EI): *m/z*: 256 ($[M]^{+\bullet}$, 20%), 165 (10%), 152 (99%), 124 (21%), 117 (28%), 109 (73%), 104 (66%), 91 ($[C_7H_7]^{+\bullet}$, 100%).

HRMS (EI): Found *m/z*: 256.2178 $[M]^{+\bullet}$. Calculated 256.2186 Da.

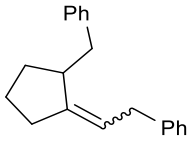
IR (ATR): ν_{max}/ cm^{-1} 3085w (=C-H), 3062w (=C-H), 3026w (=C-H), 2954m (C-H), 2922m (C-H), 2853m (C-H), 1604w (C=C), 1496m (Ar), 1453m (Ar), 746s, 697s.

Characterisation data was consistent with that reported in L. Norman Thesis.[2]

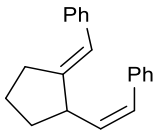
5.3.3 – Zirconocene Trap Testing

5.3.3.1 – Five Parallel Zirconocene Trap Tests

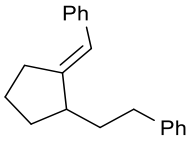
To a stirring solution of Cp_2ZrCl_2 (876 mg, 3.0 mmol) in THF (15 mL) was added *n*-BuLi (2.5 M in hexane, 1.24 mL, 6.0 mmol) dropwise over 6 minutes at -78 °C under nitrogen. The reaction was stirred at -78 °C for 30 minutes before enyne **134** (511 mg, 3.0 mmol) in THF (6 mL) was added dropwise at -78 °C under nitrogen. The reaction was allowed to warm to RT and stirred for 3 hours. The reaction vessel was re-cooled to -90 °C and benzyl chloride (380 mg, 3.0 mmol) in THF (3 mL) was added dropwise followed by the dropwise addition of LDA [n-BuLi (2.5M in hexanes, 1.20 mL, 3.0 mmol) was added dropwise to *i*-Pr_2NH (0.51 mL, 3.6 mmol) in THF (3 mL) at 0 °C over 3 minutes and stirred for 15 minutes] over 5 minutes. The reaction was stirred from -90 to -70 °C over 30 minutes. The reaction mixture (at -70 °C) was transferred and equally split into five separate Schlenk tubes (at 0 °C) by cannula under nitrogen, all of which contained the designated zirconocene trap being tested. The 5 reactions were allowed to warm to RT and stirred for 65 hours. Each reaction mixture was quenched with 2 M $HCl_{aq)}$ (1 mL) and stirred at RT for 1 hour. Each reaction mixture was worked up separately; poured into water (30 mL) and extracted with Et_2O (3× 30 mL). The organic phases were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the respective crude oils.



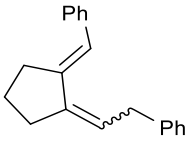
266b
$C_{20}H_{22}$ (262.40)



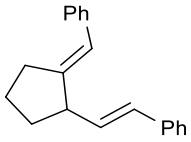
137-*cis*
$C_{20}H_{20}$ (260.38)



266
$C_{20}H_{22}$ (262.40)



137b
$C_{20}H_{20}$ (260.38)

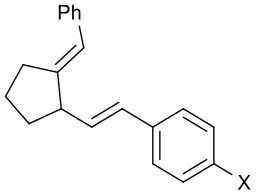


137-*trans*
$C_{20}H_{20}$ (260.38)

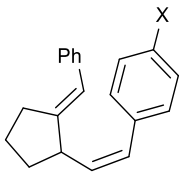
	266b	**137-*cis***	**266**	**137b**	**137-*trans***
GC (AP40) Rt (mins)	8.93	9.16	9.26	9.44	9.46

5.3.2.1 – Benzyl Chloride Zirconocene Trap on Different Aryls

To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (15 mL) was added *n*-BuLi (2.5 M in hexane, 0.80 mL, 2.0 mmol) dropwise over 2 minutes at -78 °C under nitrogen. The reaction was stirred at -78 °C for 30 minutes before enyne **134** (170 mg, 1.0 mmol) in THF (6 mL) was added dropwise at -78 °C under nitrogen. The reaction was allowed to warm to RT and stirred for 3 hours. The reaction vessel was re-cooled to -78 °C and *p*-X-benzyl chloride (2.0 mmol) in THF (1 mL) was added dropwise followed by the dropwise addition of LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise to *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C over 1 minutes and stirred for 15 minutes] over 2 minutes. The reaction was stirred from -78 to -60 °C over 30 minutes. The reaction was allowed to warm to RT and stirred for 65 hours. Each reaction mixture was quenched with 2 M $HCl_{aq)}$ (1 mL) and stirred at RT for 1 hour. Each reaction mixture was poured into water (30 mL) and extracted with Et_2O (3× 30 mL). The organic phases were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the respective crude oils.



274-*trans*
$C_{20}H_{20}$ (260.38)

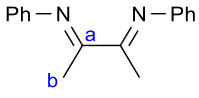


274-*cis*
$C_{20}H_{20}$ (260.38)

	GC (AP40) Rt (mins)		^{1}H-NMR Peaks δ_H ppm (400 MHz, $CDCl_3$)	
X	**274-*cis***	**274-*trans***	**274-*cis***	**274-*trans***
H	**9.16**	**9.46**	6.64 (1 H, d, *J* 11.5 Hz), 5.58 (1 H, dd, *J* 11.4, 9.8 Hz).	6.47 (1 H, d, *J* 15.7 Hz), 6.15 (1 H, dd, *J* 15.7, 8.5 Hz)
Cl	**9.96**	**10.42**	6.58 (1 H, d, *J* 11.4 Hz), 5.60 (1 H, dd, *J* 11.4, 9.8 Hz).	6.42 (1 H, d, *J* 15.7 Hz), 6.13 (1 H, dd, *J* 15.7, 8.4 Hz),
OMe	**10.20**	**10.69**	6.58 (1 H, d, *J* 11.4 Hz), 5.49 (1 H, dd, *J* 11.4, 9.6 Hz)	6.41 (1 H, d, *J* 15.7 Hz), 6.00 (1 H, dd, *J* 15.7, 8.4 Hz)

Ratios stated in Section 3.3.1 between **274-*trans*** and **274-*cis*** compounds were from the GC peaks and alkene ^{1}H-NMR peaks shown. ^{1}H-NMR of the alkene protons were consistent with those reported by L. Norman.[2]

5.3.1.3 - *N*^{2}, *N*^{3}-diphenylbutane-2,3-diimine (279)



$C_{16}H_{16}N_2$ (236.32) Procedure: To a stirring solution of 2,3-dibutanedione (0.88 mL, 10.0 mmol) in EtOH (50 mL), aniline (1.22 mL, 13.4 mmol) was added and 5 drops of formic acid at RT. The reaction was stirred at RT for 16 hours. The reaction mixture was cooled to 0 °C for 30 minutes, filtered, washed with cold MeOH (5 mL) and hexane (5 mL), dried under high vacuum to afford a yellow crystalline solid (851 mg, 3.6 mmol, 36%).

GC (AP40): Rt 8.12 mins

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.41 – 7.32 (4 H, m), 7.15 – 7.04 (2 H, m), 6.84 – 6.75 (4 H, m), 2.15 (6 H, s, Hb).

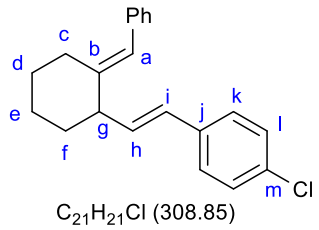
^{13}C-NMR: δ_C ppm (100.5 MHz, $CDCl_3$) 168.4 (C, Ca), 151.1 (C, *i*-Ph), 129.1 (4 CH, *o*/*m*-Ph), 124.0 (2 CH, *p*-Ph), 118.9 (4 CH, *o*/*m*-Ph), 15.6 (2 CH_3, Cb).

LRMS (EI): *m/z*: 236 ($[M]^{+\bullet}$, 57%), 194 (4%), 180 (3%), 143 (5%), 118 (100%), 103 (7%), 91 (7%), 77 (73%).

Characterisation data was consistent with that reported in the literature.[238]

5.3.4 – (*E*, *E*)-/ (*E*, *Z*)-Dienes

5.3.4.1 - 1-((*E*)-2-(2-((*E*)-Benzylidene)cyclohexyl)vinyl)-4-chlorobenzene (281)



$C_{21}H_{21}Cl$ (308.85)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexane, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred at -78 °C for 30 minutes. Enyne **227** (184 mg, 1.0 mmol) in THF (2 mL) was added dropwise at -78 °C, the reaction was allowed to warm to RT and stirred for 3 hours. The reaction was re-cooled to -90 °C and 4-chlorobenzyl chloride (161 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by the dropwise addition of LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise to *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C over 1 minute and stirred for 15 minutes] over 2 minutes. The reaction was stirred from -90 to -70 °C over 30 minutes. Anhydrous $CHCl_3$ (0.16 mL, 2.0 mmol) was added at -70 °C, the reaction was allowed to warm to RT and stirred for 62 hours. The reaction was quenched with 2 M $HCl_{(aq)}$ (2 mL) and stirred for 1 hour at RT. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined, washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 100% hexane over silica to afford the title compound as a colourless oil (266 mg, 0.86 mmol, 86%, *trans*-diene only).

(GC analysis of the crude mixture showed a 1:20.5 peak ratio between *cis*-diene and *trans*-dienes **281** respectively).

GC (AP40): Rt 10.64 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.36 – 7.26 (6 H, m, ArH), 7.23 – 7.14 (3 H, m, ArH), 6.42 (1 H, d, *J* 16.0 Hz, Hi), 6.37 (1 H, dd, *J* 16.2, 5.4 Hz, Hh), 6.25 (1 H, s, Ha), 3.04 (1 H, dt, *J* 8.6, 4.5 Hz, Hg), 2.69 (1 H, ddd, *J* 13.6, 6.0, 4.1 Hz, Hc), 2.16 (1 H, ddd, *J* 13.7, 9.6, 4.0 Hz, Hc), 1.94 (1 H, m), 1.84(1 H, m), 1.73 – 1.42 (4 H, m).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 145.05 (C, Cb), 138.43 (C), 136.42 (C), 133.96 (CH, Ci/h), 132.73 (C), 129.13 (CH, Ch/i), 129.12 (2 CH), 128.79 (2 CH), 128.17 (2 CH), 127.46 (2 CH), 126.15 (CH, *p*-Ph),

122.80 (CH, Ca), 48.25 (CH, Cg), 34.48 (CH_2), 28.70 (CH_2, Cc), 27.92 (CH_2), 24.93 (CH_2).

LRMS (EI): *m/z*: 308 ($[M]^+$, 70%), 265 (38%), 215 (45%), 183 (92%), 175 (34%), 165 (35%),153 (44%), 141 (100%).

HRMS (APPI): Found *m/z*: 308.1323 $[M]^+$. Calculated 308.1326 Da.

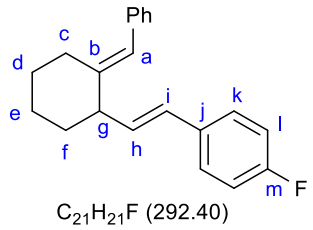
IR (ATR): ν_{max}/ cm^{-1} 3078w (=C-H), 3052w (=C-H), 3023w (=C-H), 2927m (C-H), 2853m (C-H), 1647w (C=C), 1597w (C=C), 1490s, (Ar) 1445m (Ar), 1404w (C-H), 906s, 730s, 698s.

^{1}H-NMR of the crude mixture revealed the following peaks for the *cis*-diene isomer of **281**.

GC (AP40): Rt 9.98 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 6.46 (1 H, d, *J* 11.6 Hz, Hi'), 6.30 (1 H, s, Ha'), 5.69 (1 H, dd, *J* 11.6, 9.6 Hz, Hh').

5.3.4.2 - 1-((*E*)-2-(2-((*E*)-Benzylidene)cyclohexyl)vinyl)-4-fluorobenzene (282)



$C_{21}H_{21}F$ (292.40)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexane, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred at -78 °C for 30 minutes. Enyne **227** (184 mg, 1.0 mmol) in THF (2 mL) was added dropwise at -78 °C, the reaction was allowed to warm to RT and stirred for 3 hours. The reaction was re-cooled to -90 °C and 4-fluorobenzyl chloride (145 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by the dropwise addition of LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise to *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C over 1 minute and stirred for 15 minutes] over 2 minutes. The reaction was stirred from -90 to -70 °C over 30 minutes. Anhydrous $CHCl_3$ (0.16 mL, 2.0 mmol) was added at -70 °C, the reaction was allowed to warm to RT and stirred for 17 hours. The reaction was quenched with 2 M $HCl_{(aq)}$ (2 mL) and stirred for 1 hour at RT. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined, washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 0 – 0.5% Et_2O in hexane over silica followed by 3% CH_2Cl_2 in hexane

over silica to afford the title compound as a colourless oil (245 mg, 0.84 mmol, 84%, *trans*-diene only).

(GC analysis of the crude mixture showed a 1:19.1 peak ratio between *cis*-diene *and trans*-diene **282** respectively).

GC (AP40): Rt 9.62 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.39 (2 H, dd, *J* 8.6, 5.6 Hz, ArH), 7.33 (2 H, t, *J* 7.7 Hz, ArH), 7.25 – 7.18 (3 H, m, ArH), 7.03 (2 H, t, *J* 8.7 Hz, ArH), 6.45 (1 H, d, *J* 16.0 Hz, Hi), 6.34 (1 H, dd, *J* 16.2, 7.2 Hz, Hh), 6.30 (1 H, s, Ha), 3.06 (1 H, m, Hg), 2.73 (1 H, ddd, *J* 13.6, 6.0, 4.1 Hz, Hc), 2.19 (1 H, ddd, *J* 13.6, 9.6, 4.0 Hz, Hc), 1.96 (1 H, m), 1.85 (1 H, m), 1.77 – 1.47 (4 H, m).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 162.16 (d, *J* 245.9 Hz, C, Cm), 145.17 (C, Cb), 138.47 (C, *i*-Ph), 134.07 (d, *J* 3.3 Hz, C, Cj), 132.94 (CH, Ci/h), 132.92 (CH, Ch/i), 129.12 (2 CH, *o*-/*m*-Ph), 128.15 (2 CH, *o*-/*m*-Ph), 127.71 (d, *J* 7.9 Hz, 2 CH, Cl), 126.11 (CH, *p*-Ph), 122.71 (CH, Ca), 115.50 (d, *J* 21.5 Hz, 2 CH, Ck), 48.22 (CH, Cg), 34.55 (CH_2), 28.72 (CH_2, Cc), 27.93 (CH_2), 24.96 (CH_2).

^{19}F-NMR: δ_F ppm (376 MHz, $CDCl_3$) -115.64.

LRMS (EI): *m/z*: 292 ($[M]^{+\bullet}$, 100%), 263 (19%), 249 (62%), 233 (33%), 201 (44%), 183 (74%), 159 (52%), 141 (87%).

HRMS (EI): Found *m/z*: 292.1631 $[M]^{+\bullet}$. Calculated 292.1622 Da.

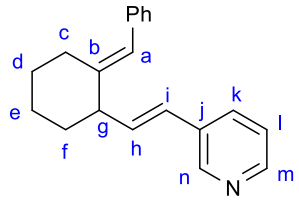
IR (ATR): ν_{max}/ cm^{-1} 3077w (=C-H), 3051w (=C-H), 3021w (=C-H), 2925m (C-H), 2852m (C-H), 1646w (C=C), 1599m (C=C), 1507s (Ar), 1444m (Ar), 1412w (C-H), 1225s (C-F), 846m, 808m, 734m, 698s.

^{1}H-NMR of the crude mixture revealed the following peaks for the *cis*-diene isomer of **282**.

GC (AP40): Rt 9.18 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 6.55 (1 H, d, *J* 11.7 Hz, Hi'), 6.39 (1 H, s, Ha'), 5.72 (1 H, dd, *J* 11.6, 9.6 Hz, Hh').

5.3.4.3 - 3-((*E*)-2-(2-((*E*)-Benzylidene)cyclohexyl)vinyl)pyridine (283)



$C_{20}H_{21}N$ (275.40)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexane, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred at -78 °C for 30 minutes. Enyne **227** (184 mg, 1.0 mmol) in THF (2 mL) was added dropwise at -78 °C and the reaction was allowed to warm to RT and stirred for 2 hours. [3-(Chloromethyl)pyridine hydrochloride (328 mg, 2.0 mmol) was washed with sat. $NaHCO_{3\,(aq)}$ (10 mL) and extracted with Et_2O (2× 5 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* at 0 °C to afford 3-(chloromethyl)pyridine as a pale yellow oil (236 mg, 1.85 mmol).] The reaction was re-cooled to -90 °C and 3-(chloromethyl)pyridine (236 mg, 1.85 mmol) in THF (1 mL) was added dropwise followed by the dropwise addition of LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise to *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C over 1 minute and stirred for 15 minutes] over 2 minutes. The reaction was stirred from -90 to -70 °C over 30 minutes. Anhydrous $CHCl_3$ (0.24 mL, 3.0 mmol) was added at -70 °C and the reaction was stirred at RT for 24 hours. The reaction was quenched with MeOH (2 mL) and stirred for 1 hour at RT. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined, washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 20% EtOAc in hexane over silica followed by 5% EtOAc in CH_2Cl_2 over silica to afford the title compound as an orange oil (168 mg, 0.61 mmol, 61%, *trans*-diene only).

(GC analysis of the crude mixture showed a 1:20.6 peak ratio ratio between *cis*-diene and *trans*-diene **283**).

GC (AP40): Rt 10.18 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 8.62 (1 H, s, Hn), 8.45 (1 H, d, *J* 4.0 Hz, Hm), 7.73 (1 H, dt, *J* 7.9, 1.9 Hz, Hk), 7.31 (2 H, dd*, *J* 8.0, 7.0 Hz, ArH), 7.24 (1 H, dd, *J* 8.0, 4.9 Hz, Hl), 7.22 – 7.16 (3 H, m, ArH), 6.50 (1 H, dd, *J* 16.1, 6.2 Hz, Hh), 6.44 (1 H, d, *J* 16.1 Hz, Hi), 6.26 (1 H, s, Ha), 3.08 (1 H, m, Hg), 2.69 (1 H, ddd, *J* 13.7, 6.4, 3.9 Hz, Hc), 2.18

(1 H, dddd, *J* 13.7, 9.6, 4.0, 0.9 Hz, Hc), 1.95 (1 H, m), 1.92 (1 H, m), 1.77 – 1.44 (4 H, m).

*Doublet with second order effects.

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 148.30 (2 CH, Cm & Cn), 144.80 (C, Cb), 138.31 (C), 135.67 (CH, Ci/h), 133.44 (C), 132.69 (CH, Ck), 129.10 (2 CH, *o*-/*m*-Ph), 128.18 (2 CH, *o*-/*m*-Ph), 126.83 (CH, Ch/i), 126.20 (CH, *p*-Ph), 123.54 (CH, Cl), 122.93 (CH, Ca), 48.35 (CH, Cg), 34.37 (CH_2), 28.68 (CH_2, Cc), 27.87 (CH_2), 24.89 (CH_2).

LRMS (ESI$^+$): *m/z*: 276 ($[M+H]^+$, 100%).

HRMS (ESI$^+$): Found *m/z*: 276.1753 $[M+H]^+$. Calculated 276.1747 Da.

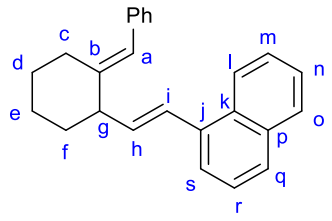
IR (ATR): ν_{max}/ cm^{-1} 3079w (=C-H), 3053w (=C-H), 3024w (=C-H), 2926m (C-H), 2853m (C-H), 1647w (C=C), 1598w (C=C), 1569w (Ar), 1481w (Ar), 1444m (Ar), 1415m (C-H), 907s, 728s, 698s.

^{1}H-NMR of the crude mixture revealed the following peaks for the *cis*-diene isomer of **283**.

GC (AP40): Rt 9.76 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 6.54 (1 H, d, *J* 11.7 Hz, Hi'), 6.37 (1 H, s, Ha'), 5.89 (1 H, dd, *J* 11.6, 9.7 Hz, Hh').

5.3.4.4 - 1-((*E*)-2-(2-((*E*)-Benzylidene)cyclohexyl)vinyl)naphthalene (284)



$C_{25}H_{24}$ (324.47)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexane, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred at -78 °C for 30 minutes. Enyne **227** (184 mg, 1.0 mmol) in THF (2 mL) was added dropwise at -78 °C and the reaction was allowed to warm to RT and stirred for 3 hours. The reaction was re-cooled to -90 °C and 1-(chloromethyl)naphthalene (177 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by the dropwise addition of LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise to *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C over 1 minute and stirred for 15 minutes] over 2 minutes. The reaction was stirred from -90 to -70 °C over

30 minutes. Anhydrous $CHCl_3$ (0.24 mL, 3.0 mmol) was added at -70 °C and the reaction was allowed to warm to RT and stirred for 16 hours before being quenched with 2 M $HCl_{(aq)}$ (2 mL) and stirred for 1 hour at RT. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined, washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 0.5% Et_2O in hexane over silica, heated in Kugelrohr distillation equipment at 130 °C under 0.1 mbar pressure (for 1-(chloromethyl)naphthalene removal) and further purified using 2.5% CH_2Cl_2 in hexane over silica to afford the title compound as two colourless oils (182 mg, 0.56 mmol, 56%, *trans*-diene only) and 1:15.4 *cis*/*trans*-diene (53 mg, 0.16 mmol, 16%), combined yield of 72%.

(GC analysis of the crude mixture showed a 1:34.3 peak ratio ratio between *cis*-diene and *trans*-diene **284** respectively).

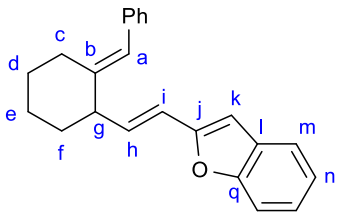
GC (AP40):	Rt 12.98 mins.
^{1}H-NMR:	δ_H ppm (400 MHz, $CDCl_3$) 8.16 (1 H, m, ArH), 7.86 (1H, m *J* 7.0, 2.5 Hz, ArH), 7.77 (1 H, d, *J* 8.2 Hz, ArH), 7.65 (1 H, d, *J* 7.1 Hz, ArH), 7.54 – 7.47 (2 H, m, ArH), 7.47 (1 H, dd, *J* 15.6, 7.5 Hz, Hh), 7.36 – 7.28 (2 H, m, ArH), 7.25 – 7.15 (4 H, m, ArH), 6.43 (1 H, dd, *J* 15.7, 7.3 Hz, Hi), 6.39 (1 H, s, Ha), 3.21 (1 H, m, Hg), 2.77 (1 H, ddd, *J* 13.6, 6.0, 4.1 Hz, Hc), 2.22 (1 H, dddd, *J* 13.7, 9.6, 4.0, 0.9 Hz, Hc), 2.04 (1 H, m), 1.88 (1 H, m), 1.80 – 1.54 (4 H, m).
^{13}C-NMR:	δ_C ppm (101 MHz, $CDCl_3$) 145.31 (C, Cb), 138.56 (C), 136.62 (CH, Ci), 135.84 (C), 133.79 (C), 131.38 (C), 129.17 (2 CH), 128.63 (CH), 128.17 (2 CH), 127.58 (2 CH), 126.11 (CH), 126.02 (CH), 125.82 (2 CH), 124.13 (CH), 123.80 (CH), 122.86 (CH, Ca), 48.61 (CH, Cg), 34.65 (CH_2), 28.78 (CH_2, Cc), 27.99 (CH_2), 25.02 (CH_2).
LRMS (EI):	*m/z*: 324 ($[M]^{+\bullet}$, 58%), 281 (19%), 265 (21%), 252 (16%), 233 (45%), 207 (32%), 196 (100%), 191 (79%).
HRMS (APPI):	Found *m/z*: 324.1868 $[M]^+$. Calculated 324.1873 Da.
IR (ATR):	ν_{max}/ cm^{-1} 3076w (=C-H), 3056w (=C-H), 3021w (=C-H), 2924m (C-H), 2852m (C-H), 1692w (C=C), 1645w (C=C), 1598w (C=C), 1591w (Ar), 1507w (Ar), 1493w (Ar), 1443m (Ar), 906s, 773s, 727s, 698s.

^{1}H-NMR of the 1:15.1 mixture of *cis*/*trans* dienes revealed the following peaks for the *cis*-diene isomer of **284**.

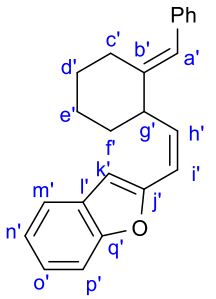
GC (AP40): Rt 11.47 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 6.07 (dd, *J* 11.4, 9.8 Hz, Hh').

5.3.4.5 - 2-(2-(2-((*E*)-Benzylidene)cyclohexyl)vinyl)benzofuran (285)



$C_{23}H_{22}O$ (314.43)
trans



$C_{23}H_{22}O$ (314.43)
cis

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexane, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred at -78 °C for 30 minutes. Enyne **227** (184 mg, 1.0 mmol) in THF (2 mL) was added dropwise at -78 °C under nitrogen and the reaction was allowed to warm to RT and stirred for 3 hours. The reaction was re-cooled to -90 °C and 2-(chloromethyl)benzofuran (167 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by the dropwise addition of LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise to *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C over 1 minute and stirred for 15 minutes] over 2 minutes. The reaction was stirred for 30 minutes at low temperature (-90 to -70 °C). Anhydrous $CHCl_3$ (0.24, 3.0 mmol) was added at -70 °C, the reaction was then allowed to warm to RT and stirred for 65 hours. The reaction was quenched with 2 M $HCl_{(aq)}$ (2 mL) and stirred for 1 hour at RT. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined, washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 5% CH_2Cl_2 in hexane over silica afford a colourless oil (127 mg, 0.40 mmol, 40%, 1:1.2 *cis*:*trans* by ^{1}H-NMR).

(^{1}H-NMR of the crude mixture showed a 1:2.3 ratio between *cis*:*trans*-dienes **285**).

GC (AP40): Rt 10.99 mins (*cis*), 11.81 mins (*trans*).

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.54 (1 H, ddd, *J* 7.5, 1.4, 0.6 Hz, ArH'), 7.51 (1 H, ddd, *J* 7.5, 1.4, 0.6 Hz, ArH), 7.47 (1 H, q, *J* 0.8 Hz, ArH'), 7.45 (1 H, q, *J* 3.6 Hz, ArH), 7.35 – 7.26 (4.2 H, m, ArH & ArH'), 7.26 – 7.16 (7.7 H, m, ArH & ArH'), 6.69 (1 H, dd, *J* 15.9, 7.3 Hz, Hh), 6.63 (1 H, s, Hk'), 6.53 (1 H, s, Hk), 6.47 (1 H, d, *J* 11.9 Hz, Hi'), 6.42 (1 H, dd, *J* 15.9, 1.2 Hz, Hi), 6.36 (1 H, s, Ha'), 6.33 (1 H, s, Ha), 5.95 (1 H, dd, *J* 11.9, 9.5 Hz, Hh'), 3.82 (1 H, td, *J* 9.5, 4.3 Hz, Hg'), 3.11 (1 H, td, *J* 7.8, 4.5 Hz, Hg), 2.92 (1 H, dt, *J* 13.2, 3.9 Hz, Hc'), 2.69 (1 H, ddd, *J* 13.6, 6.7, 3.8 Hz, Hc), 2.24 (1 H, ddd, *J* 13.7, 9.6, 4.0 Hz, Hc), 2.14 (1 H, m, Hc'), 2.06 – 1.93 (1.8 H, m), 1.93 – 1.77 (2.7 H, m), 1.77 – 1.45 (6.8 H, m).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 155.25 (C, Cq/j), 154.81 (C, Cj/q), 154.76 (C, Cq/j'), 154.62 (C, Cj/q'), 144.56 (C, Cb), 143.67 (C, Cb'), 138.58 (C'), 138.39 (C), 136.93 (CH, Ch'), 135.81 (CH, Ch), 129.26 (C), 129.14 (2 CH, *o*-/*m*-Ph), 128.93 (C'), 128.16 (2 CH & 2 CH', *o*-/*m*-Ph), 128.13 (2 CH, *o*-/*m*-Ph'), 126.16 (CH), 126.08 (CH'), 124.35 (CH'), 124.27 (CH), 123.19 (CH), 122.88 (CH'), 122.84 (CH, Ca), 121.95 (CH'), 120.91 (CH, Ca'), 120.81 (CH), 119.09 (CH, Ci), 118.01 (CH, Ci'), 111.16 (CH, Cp'), 110.96 (CH, Cp), 105.70 (CH, Ck'), 103.45 (CH, Ck), 48.23 (CH, Cg), 45.09 (CH, Cg'), 35.40 (CH_2'), 34.25 (CH_2), 29.12 (CH_2'), 28.51 (CH_2), 27.90 (CH_2), 27.86 (CH_2'), 25.45 (CH_2'), 24.73 (CH_2).

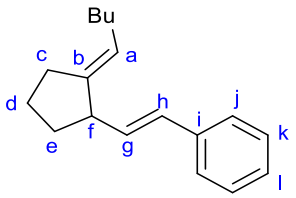
LRMS (EI): 22.49 mins (*cis*): *m/z*: 314 ($[M]^{+\bullet}$, 52%), 271 (12%), 223 (37%), 207 (100%), 191 (24%), 181 (44%), 165 (27%), 141 (41%).
23.18 mins (*trans*): *m/z*: 314 ($[M]^{+\bullet}$, 55%), 271 (11%), 223 (39%), 207 (100%), 191 (25%), 181 (42%), 165 (25%), 141 (41%).

HRMS (APPI): Found *m/z*: 314.1659 $[M]^+$. Calculated 314.1665 Da.

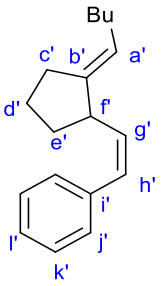
IR (ATR): ν_{max}/ cm^{-1} 3078w (=C-H), 3056w (=C-H), 3022w (=C-H), 2925w (C-H), 2852w (C-H), 1693w (C=C), 1648w (C=C), 1598w (C=C), 1555w (Ar), 1493w (Ar), 1451m (Ar), 906s, 728s, 698s.

(Note: NMR assignment of *cis*/*trans* peaks was aided by the NMR of a sample with a 1:2.4 *cis*/*trans* ratio which had previously been obtained but was not pure).

5.3.4.6 - (2-((*E*)-2-Pentylidenecyclopentyl)vinyl)benzene (286)



$C_{18}H_{24}$ (240.39)



$C_{18}H_{24}$ (240.39)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexane, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred at -78 °C for 30 minutes. Enyne **228** (150 mg, 1.0 mmol) in THF (2 mL) was added dropwise at -78 °C and the reaction was allowed to warm to RT and stirred for 3 hours. The reaction was re-cooled to -90 °C and benzyl chloride (127 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by the dropwise addition of LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise to *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C over 1 minute and stirred for 15 minutes] over 2 minutes. The reaction was stirred from -90 to -70 °C over 30 minutes. Anhydrous $CHCl_3$ (0.16 mL, 2.0 mmol) was added at -70 °C, the reaction was allowed to warm to RT and stirred for 17 hours. The reaction was quenched with 2 M $HCl_{(aq)}$ (2 mL) and stirred for 1 hour at RT. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined, washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 100% hexane over silica and Kugelrohr distilled at 180 °C and 0.1 mbar to afford the title compound as a colourless-pale yellow oil (174 mg, 0.72 mmol, 72%, 1:2.4 *cis*:*trans* by ^{1}H-NMR).

GC (AP40): Rt 7.65 mins (*cis*), 7.96 (*trans*).

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.42 (2.0 H, d+fs, *J* 8.1 Hz, ArH & ArH'), 7.40 – 7.30 (3.5 H, m, ArH & ArH'), 7.28 – 7.19 (1.6 H, m, ArH), 6.58 (0.4 H, d, *J* 11.5 Hz, Hh'), 6.42 (1 H, d, *J* 15.7 Hz, Hh), 6.10 (1 H, dd, *J* 15.7, 8.4 Hz, Hg), 5.51 (0.41 H, dd, *J* 11.4, 9.8 Hz, Hg'), 5.27 (0.3 H, tq, *J* 7.2, 2.4 Hz, Ha'), 5.22 (1 H, tq, *J* 7.2, 2.4 Hz, Ha), 3.52 (0.45 H, q, *J* 8.8 Hz, Hf'), 3.13 (1 H, q, *J* 8.2 Hz, Hf), 2.46 – 2.36 (1.4 H, m), 2.36 – 2.23 (1.5 H, m), 2.11 – 1.94 (4.2 H, m), 1.94 – 1.77 (1.5 H, m), 1.73 – 1.27 (9.3 H, m), 1.01 – 0.85 (4.5 H, m, Me & Me').

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 144.98 (C, Cb), 144.92 (C, Cb'), 137.99 (C), 137.86 (C'), 135.71 (CH, Cg'), 133.94 (CH, Cg), 129.90 (CH, Ch), 129.18 (CH, Ch'), 128.59 (2 CH, *o*-/*m*-Ph), 128.47 (2 CH, *o*-/*m*-Ph'), 128.29 (2 CH, *o*-/*m*-Ph'), 126.93 (CH, *p*-Ph), 126.73 (CH, *p*-Ph'), 126.17 (2 CH, *o*-/*m*-Ph), 122.80 (CH, Ca), 122.31 (CH, Ca'), 49.14 (CH, Cf), 44.47 (CH, Cf'), 35.20 (CH_2'), 34.55 (CH_2), 31.95 (CH_2)*, 29.48 (CH_2), 29.42 (CH_2'), 29.06 (CH_2), 28.93 (CH_2'), 24.81 (CH_2), 24.79 (CH_2'), 22.59 (CH_2), 22.57 (CH_2'), 14.20 (CH_3, Me'), 14.19 (CH_3, Me).

**Cis* CH_2' peak likely hidden underneath.

LRMS (EI): 8.20 mins (*cis*): *m/z*: 240 ($[M]^{+\bullet}$, 72%), 197 (20%), 183 (98%), 169 (66%), 155 (52%), 149 (37%), 141 (91%), 91 ($[C_7H_7]^{+\bullet}$, 100%).

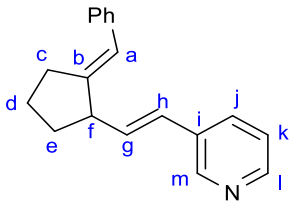
8.41 mins (*trans*): *m/z*: 240 ($[M]^{+\bullet}$, 94%), 197 (34%), 183 (100%), 169 (66%), 155 (58%), 149 (58%), 141 (94%), 128 (54%).

HRMS (EI): Found *m/z*: 240.1872 $[M]^{+\bullet}$. Calculated 240.1873 Da.

IR (ATR): ν_{max}/ cm^{-1} 3103w (=C-H), 3081w (=C-H), 3059w (=C-H), 3006w (=C-H), 2953m (C-H), 2925m (C-H), 2869m (C-H), 2857m (C-H), 1646w (C=C), 1600w (C=C), 1494m (Ar), 1447m (Ar), 962s, 743s, 691s.

Characterisation data was consistent with that reported in L. Norman thesis.[2]

5.3.4.7 - 3-(2-(2-((*E*)-Benzylidene)cyclopentyl)vinyl)pyridine (287)



$C_{19}H_{19}N$ (261.37)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexane, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred at -78 °C for 30 minutes . Enyne **134** (170 mg, 1.0 mmol) in THF (2 mL) was added dropwise at -78 °C and the reaction was allowed to warm to RT and stirred for 2 hours. [3-(Chloromethyl)pyridine hydrochloride (410 mg, 2.5 mmol) was washed with sat. $NaHCO_{3\,(aq)}$ (10 mL) and extracted with Et_2O (2× 5 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* at 0 °C to afford 3-(chloromethyl)pyridine as a pale yellow oil (255 mg, 2.0 mmol).] The reaction was re-cooled

to -90 °C and 3-(chloromethyl)pyridine (255 mg, 2.0 mmol) in THF (1 mL) was added dropwise followed by the dropwise addition of LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise to *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C over 1 minute and stirred for 15 minutes] over 2 minutes. The reaction was stirred for 30 minutes at low temperature (-90 to -70 °C). Anhydrous chloroform (0.24 mL, 3.0 mmol) was added at -70 °C, the reaction was then allowed to warm to RT and stirred for 24 hours. The reaction was quenched with MeOH (2 mL) and stirred for 1 hour at RT. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined, washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 20-30% EtOAc in hexane over silica to afford the title compound as an orange oil (165 mg, 0.63 mmol, 63%, 1:8.6 *cis:trans* by ^{1}H-NMR).

(^{1}H-NMR of the crude mixture showed a ratio of 1:6.5 *cis*-diene *and trans*-diene **287**).

GC (AP239): Rt 3.87 mins (*cis*), 4.19 (*trans*).

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 8.62 (1 H, d, *J* 1.9 Hz, Hm), 8.45 (1 H, dd, *J* 4.8, 1.5 Hz, Hl), 7.73 (1 H, dt, *J* 8.0, 1.9 Hz, Hj), 7.35 – 7.30 (4 H, m, ArH), 7.24 (1 H, m, Hk), 7.18 (1 H, m, ArH), 6.46 (1 H, d, *J* 15.8 Hz, Hh), 6.24 (1 H, dd, *J* 15.8, 8.4 Hz, Hg), 6.24 (1 H, d, *J* 2.5 Hz, Ha), 3.37 (1 H, q, *J* 8.5 Hz, Hf), 2.77 (1 H, m), 2.64 (1 H, dddt, *J* 17.3, 8.7, 8.9, 2.6 Hz), 2.02 (2 H, m), 1.74 (1 H, m), 1.54 (1 H, m).
[Visible peaks for **287-*cis***: 8.48 (1 H, dd, *J* 4.8, 1.5 Hz, Hl'), 7.67 (1 H, dt, *J* 7.7, 1.8, Hj'), 6.59 (1 H, d, *J* 11.5 Hz, Hh'), 5.73 (1 H, dd, *J* 11.4, 9.8 Hz, Hg'), 3.69 – 3.57 (1 H, m, Hf'), 1.48 (1 H, m).]

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 148.27 (C, Cb), 148.14 (CH, Cm/l), 148.10 (CH, Cl/m), 138.51 (C), 135.80 (CH, Cj), 133.36 (C), 132.83 (CH, *p*-Ph), 128.39 (2 CH, *o*-/*m*-Ph), 128.25 (2 CH, *o*-/*m*-Ph), 127.04 (CH, Ch), 126.23 (CH, Ck), 123.59 (CH, Cg/a), 123.26 (CH, Ca/g), 51.13 (CH, Cf), 33.66 (CH_2), 31.72 (CH_2), 25.63 (CH_2).
[Visible peaks for **287-*cis***: 149.60 (CH, Cl/m'), 147.95 (CH, Cm/l'), 138.44 (C'), 137.32 (CH, Cj'), 135.63 (CH, *p*-Ph), 133.31 (C'), 128.33 (2 CH, *o*-/*m*-Ph'), 126.34 (CH, Ck'), 123.38 (CH, Cg/a'), 122.64 (CH, Ca/g'), 46.35 (CH, Cf'), 34.19 (CH_2'), 31.40 (CH_2'), 25.48 (CH_2').]

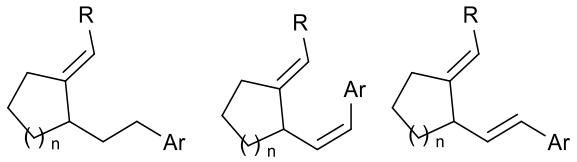
LRMS (ESI$^+$): *m/z*: 262 $(M+H)^{+\bullet}$, 100%).

HRMS (ESI$^+$): Found *m/z*: 262.1593 $[M+H]^+$. Calculated 262.1590 Da.

IR (ATR): ν_{max}/ cm^{-1} 3082w (=C-H), 3050w (=C-H), 3023w (=C-H), 3023w (=C-H), 2953m (C-H), 2865m (C-H), 1700vw (C=C), 1647m (C=C), 1597w (C=C), 1568m (Ar), 1481m (Ar), 1446m (Ar), 1415m (C-H), 966m, 707s, 695s.

5.3.5 – Kinetics Experiments

To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexane, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred at -78 °C for 30 minutes. Enyne (1.0 mmol) in THF (2 mL) was added dropwise at -78 °C, the reaction was allowed to warm to RT and stirred for 3 hours. The reaction was re-cooled to -90 °C and benzyl chloride (1.0 mmol) in THF (1 mL) was added dropwise followed by the dropwise addition of LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise to *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C over 1 minute and stirred for 15 minutes] over 2 minutes. The reaction was stirred from -90 to -70 °C over 30 minutes. Anhydrous $CHCl_3$ (0.16 mL, 2.0 mmol) was added at -70 °C, the reaction was allowed to warm to RT and stirred for 24 hours. Sampling was begun immediately upon removal of the cooling bath and conducted every 15 minutes with T0 taken at -78 °C. Samples of 0.1 mL were removed from the reaction, dispensed into 0.5 mL HCl or sat. $NaHCO_{3\,(aq)}$ and extracted with 0.5 mL Et_2O. The organic phase was subsequently submitted for GC analysis. Monitoring was conducted for the synthesis of diene **286** (R = Bu, n=1, Ar = Ph) and diene **287** (R = Ph, n=1, Ar = 3-pyridine).



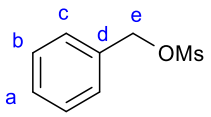
133 **132-*cis*** **132-trans**

				GC Rt (mins)		
R	n	Ar	GC Programme	**133-*cis***	**132**	**133**-*trans*
Ph	1	3-Pyridine	AP239	3.56	3.87	4.19
Bu	1	Ph	AP40	7.65	7.76	7.96

5.4 – Insertion of Benzyl Chlorides into Zirconocene η^2-Alkene Complexes

5.4.1 – Benzyl Mesylate/Tosylate, Benzyl Chlorides and Precursors

5.4.1.1 - Benzyl Mesylate (338)

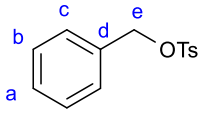


$C_8H_{10}O_3S$ (186.23) Procedure:[185] To a stirring solution of benzyl alcohol (4.37 g, 40.0 mmol) in CH_2Cl_2 (100 mL), mesyl chloride (4.32 mL, 56.0 mmol) was added dropwise over 12 minutes at -30 °C followed by freshly distilled Et_3N (11.16 mL, 80.0 mmol) dropwise over 20 minutes. The reaction was stirred for 30 minutes at -30 °C. The reaction mixture was poured into water (200 mL) and extracted with Et_2O (3× 200 mL). The organic phases were combined and washed with 2 M $HCl_{(aq)}$ (200 mL), brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the title compound as a yellow oil (7.15 g, 38.4 mmol, 96%).

GC (AP40):	Rt 6.05 mins
^{1}H-NMR:	δ_H ppm (400 MHz, $CDCl_3$) 7.45 – 7.39 (5 H, m, ArH), 5.25 (2 H, s, He), 2.91 (3 H, s, Me).
^{13}C-NMR:	δ_C ppm (101 MHz, $CDCl_3$) 133.50 (C, Cd), 129.51 (CH, Ca), 129.02 (2 CH, Cb/c), 128.97 (2 CH, Cb/c), 71.66 (CH_2, Ce), 38.44 (CH_3, Me).
LRMS (EI):	*m/z*: 186 ($[M]^{+\bullet}$, 10%), 126 (11%), 107 ($[M\text{-}SO_2Me]^{+\bullet}$, 71%), 91 ($[C_7H_7]^{+\bullet}$, 100%), 79 (54%), 77 (61%), 65 (60%), 51 (37%).

Characterisation data was consistent with that reported in the literature.[185, 239]

5.4.1.2 - Benzyl Tosylate (339)



$C_{14}H_{14}O_3S$ (262.32) Procedure:[186] To a stirring solution of benzyl alcohol (649 mg, 6.0 mmol), DMAP (183 mg, 1.5 mmol) and Et_3N (1.32 mL, 9.48 mmol) in CH_2Cl_2 (30 mL), tosyl chloride (1.72 g, 9.0 mmol) in CH_2Cl_2 (30 mL) was added dropwise over 15 mins at 0 °C. The reaction was stirred for 1 hour at 0 °C before it was poured into water (50 mL) and

extracted with CH_2Cl_2 (2× 50 mL). The organic phases were combined and washed with sat. $NaHCO_{3\,(aq)}$ (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography twice using 20% Et_2O in hexane over silica to afford the title compound as a pale yellow-white solid (232 mg, 1.0 mmol, 17%).

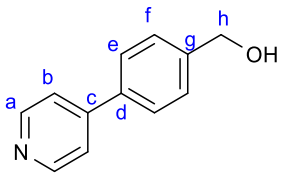
GC (AP40): Rt 8.78 mins

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.80 (2 H, d*, *J* 8.3 Hz, ArH), 7.38 – 7.28 (5 H, m, ArH), 7.28 – 7.22 (2 H, m, ArH), 5.06 (2 H, s, He), 2.45 (3 H, s, Me).

* Doublet with second order effects.

^{1}H-NMR was consistent with that reported in the literature.[186]

5.4.1.3 - (4-(Pyridin-4-yl)phenyl)methanol (320)



$C_{12}H_{11}NO$ (185.23)

Procedure:[182] To a stirring solution of 4-(hydroxymethyl) phenylboronic acid (1.52 g, 10.0 mmol), 4-bromopyridine hydrochloride (2.14 g, 11.0 mmol) and $Pd(PPh_3)_4$ (578 mg, 0.50 mmol) in DME (60 mL), 1 M $Na_2CO_{3\,(aq)}$ (25.0 mL, 25.0 mmol) was added at RT and under nitrogen. The reaction was refluxed at 100 °C for 15 hours. The reaction mixture was allowed to cool to RT and concentrated *in vacuo*. The reaction mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (2× 400 mL). The organic phases were combined and washed with water (100 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography twice using 3% MeOH in CH_2Cl_2 over silica to afford the title compound as a pale yellow solid (1.70 g, 9.18 mmol, 92%).

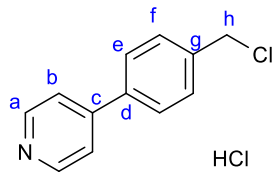
^{1}H-NMR: δ_H ppm (400 MHz, DMSO) 8.62 (2 H, d*, *J* 4.5 Hz, Ha), 7.77 (2 H, d, *J* 8.3 Hz, He), 7.70 (2 H, d*, *J* 4.5 Hz, Hb), 7.46 (2 H, d, *J* 8.2 Hz, Hf), 5.27 (1 H, t, *J* 5.7 Hz, OH), 4.56 (2 H, d, *J* 5.7 Hz, Hh).

*Doublets with second order effects.

^{13}C-NMR:	δ_C ppm (101 MHz, DMSO) 150.20 (2 CH, Ca), 146.85 (C, Cc), 143.87 (C, Cd/g), 135.40 (C, Cg/d), 127.11 (2 CH), 126.51 (2 CH), 121.02 (2 CH), 62.46 (CH_2, Ch).
LRMS (ESI$^+$):	*m/z:* 186 ($[M+H]^+$, 100%).
HRMS (ESI$^+$):	Found *m/z*: 186.0914 $[M+H]^+$. Calculated 186.0913 Da.
IR (ATR):	ν_{max}/ cm^{-1} 3162brm (OH), 3032m (=C-H), 2903m (=C-H), 2865m (C-H), 2823m (C-H), 2708m (C-H), 1594s (Ar), 1540m (Ar), 1488m (Ar), 1457m (Ar), 1400s (C-H), 1057s (C-O), 999s, 798s, 719s.
Mp:	177.6 °C.

^{1}H-NMR was consistent with that reported in the literature.[240]

5.4.1.4 - 4-(4-(Chloromethyl)phenyl)pyridine Hydrochloride (321)



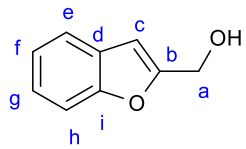
$C_{12}H_{11}Cl_2N$ (240.13)
$C_{12}H_{10}ClN$ (203.67)

Procedure:[183] To a stirring solution of (4-(pyridin-4-yl)phenyl)methanol **320** (558 mg, 3.0 mmol) in $CHCl_3$, thionyl chloride (0.88 mL, 12.0 mmol) was added dropwise at RT under nitrogen and stirred at RT for 46 hours. The reaction mixture was concentrated *in vacuo* to afford the title compound as an off-white solid (748 mg, 3.1 mmol, quant.).

^{1}H-NMR:	δ_H ppm (400 MHz, DMSO) 8.92 (2 H, d*, *J* 6.6 Hz, Ha), 8.29 (2 H, d*, *J* 6.4 Hz, Hb), 8.02 (2 H, d*, *J* 8.3 Hz, He), 7.68 (2 H, d*, *J* 8.2 Hz, Hf), 4.87 (2 H, s, Hh). *Doublets with second order effects.
^{13}C-NMR:	δ_C ppm (101 MHz, DMSO) 154.37 (C, Cc), 142.59 (2 CH, Ca), 141.14 (C, Cd/g), 134.32 (C, Cg/d), 129.92 (2 CH) 128.33 (2 CH), 123.76 (2 CH), 45.27 (CH_2, Ch).
LRMS (ESI$^+$):	*m/z*: 204 ($[M-HCl+H]^+$, 100%).
HRMS (ESI$^+$):	Found *m/z*: 204.0572 $[M-HCl+H]^+$. Calculated 204.0575 Da.
IR (ATR):	ν_{max}/ cm^{-1} 3174 (=C-H), 3122 (=C-H), 3061 (=C-H), 3037 (=C-H), 2960brm (N-H), 2864 (C-H), 1630s (Ar), 1608m (Ar), 1589s (Ar),

1571m (Ar), 1525m (Ar), 1483s (Ar), 1407m (Ar), 794s, 742s, 722s, 683s.

5.4.1.5 - Benzofuran-2-ylmethanol (235)



$C_9H_8O_2$ (148.16)

Procedure:[168, 169] To a stirring solution of 2,3-benzofuran (4.40 mL, 40.0 mmol) in THF (80 mL), *n*-BuLi (2.5 M in hexanes, 16.8 mL, 42.0 mmol) was added dropwise over 5 minutes at -78 °C under nitrogen and stirred at this temperature for 15 minutes. DMF (9.29 mL, 3.0 mmol) was added at -78 °C the reaction was then allowed to stir at RT for 30 minutes. The reaction was quenched with H_2O (5 mL), poured into water (300 mL) and extracted with EtOAc (3× 250 mL). The organic phases were combined, washed with water (2× 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude benzofuran-2-carbaldehyde (5.85 g, 40.0 mmol) was dissolved in MeOH (24 mL) and $NaBH_4$ (2.72 mg, 48.0 mmol) in MeOH (48 mL) was added dropwise at 0 °C. The reaction was stirred at 0 °C for 30 minutes before quenching with water (16 mL). The reaction mixture was concentrated *in vacuo*, purified by column chromatography using 20% EtOAc in hexane over silica and subsequently by Kugelrohr distillation at 121 °C and 0.1 mbar to afford the title compound as a colourless oil (3.20 mg, 21.5 mmol, 54%).

GC (AP40): Rt 5.50 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.42 (1 H, ddd, *J* 7.5, 1.4, 0.6 Hz, ArH), 7.34 (1 H, ddd, *J* 8.2, 1.7, 0.9 Hz, ArH), 7.15 (1 H, m, ArH), 7.10 (1 H, td, *J* 7.5, 1.1 Hz, ArH), 6.51 (1 H, d, *J* 0.8 Hz, Hc), 4.63 (2 H, d, *J* 3.6 Hz, Ha), 2.24 (1 H, br s, OH).

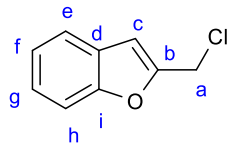
^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 156.55 (C, Ci/b), 155.18 (C, Cb/i), 128.25 (C), 124.47 (CH), 122.92 (CH), 121.23 (CH), 111.34 (CH, Ch), 104.22 (CH, Cb), 58.18 (CH_2, Ca).

LRMS (EI): *m/z*: 148 ($[M]^{+\bullet}$, 79%), 131 ($[M\text{-}OH]^{+\bullet}$, 100%), 119 (12%), 103 (20%), 91 (46%), 77 (22%), 63 (47%), 51 (29%).

HRMS (EI): Found *m/z*: 148.0518 [M]+•. Calculated 148.0519 Da.

IR (ATR): ν_{max}/ cm^{-1} 3316br (OH), 3085w (=C-H), 3056w (=C-H), 2925w (C-H), 2868w (C-H), 1604w (Ar), 1586w (Ar), 1452s (Ar), 1253s (C-O), 1006s (C-O), 806s, 739s.

5.4.1.6 - 2-(Chloromethyl)benzofuran (236)



C_9H_7ClO (166.60)

Procedure:[170] To a stirring solution of benzofuran-2-ylmethanol **235** (1.48 g, 10.0 mmol) in THF (7.4 mL) and DMF (2.1 mL), thionyl chloride (1.02 mL, 14.0 mmol) was added dropswise over 1.5 minutes at RT under nitrogen. The reaction was stirred at RT for 1 hour before being poured into water (150 mL) and extracted with EtOAc (3× 100 mL). The organic phases were combined, washed with water (2× 150 mL) and brine (150 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 10% CH_2Cl_2 in hexane over silica to afford the title compound as a white solid (1.48 g, 8.88 mmol, 89%).

GC (AP40): Rt 5.42 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.54 (1 H, ddd, *J* 7.7, 1.3, 0.7 Hz, ArH), 7.48 (1 H, ddd, *J* 7.7, 1.7, 0.8 Hz, ArH), 7.30 (1 H, ddd, *J* 8.3, 7.3, 1.4 Hz, ArH), 7.22 (1 H, m, ArH), 6.73 (1 H, d, *J* 0.6 Hz, Hb), 4.69 (2 H, d, *J* 0.4 Hz, Ha).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 155.48 (C, Ci/b), 152.65 (C, Cb/i), 128.03 (C), 125.20 (CH), 123.22 (CH), 121.47 (CH), 111.55 (CH, Ch), 106.34 (CH, Cc), 37.91 (CH_2, Ca).

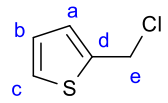
LRMS (EI): *m/z*: 166 ($[M]^{+\bullet}$, 12%), 131 ($[M\text{-}Cl]^{+\bullet}$, 100%), 103 (9%), 84 (4%), 77 (16%), 66 (6%), 63 (11%), 51 (20%).

HRMS (APPI): Found *m/z*: 166.0179 $[M]^+$. Calculated 166.0180 Da.

IR (ATR): ν_{max}/ cm^{-1} 3103 (=C-H), 3069 (=C-H), 3058 (=C-H), 3046 (=C-H), 3026 (C-H), 1597w (Ar), 1584w (Ar), 1450m (Ar), 1424m (Ar), 1282s (C-O), 953s, 815s, 739s, 709s, 690s.

Mp: 34.5 °C (Lit. 35-36 °C (hexane).[241]

5.4.1.7 - 2-(Chloromethyl)thiophene (327)

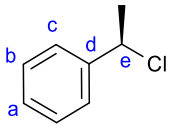


C_5H_5ClS (132.61) Procedure:[184] To a stirring solution of 2-thiophene methanol (2.33 g, 20.4 mmol) in dry CH_2Cl_2 (10 mL), thionyl chloride (2.19 mL, 30.0 mmol) was added dropwise over 6 minutes at 0 °C and stirred for 30 minutes. The reaction was then stirred at RT for 30 minutes and then quenched with water (2 mL). The reaction mixture was subsequently poured into water (50 mL) and extracted with EtOAc (3× 50 mL). The organic phases were combined and washed with brine (50 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and Kugelrohr distilled at 100 °C, 13.0 mbar to afford the title compound as a colourless oil (1.55 g, 11.7 mmol, 57%).

GC (AP40):	Rt 6.35 mins.
^{1}H-NMR:	δ_H ppm (400 MHz, $CDCl_3$) 7.32 (1 H, dd, *J* 5.1, 1.2 Hz, Hc), 7.09 (1 H, ddt, *J* 3.5, 1.3, 0.7 Hz, Ha), 6.96 (1 H, dd, *J* 5.1, 3.5 Hz, Hb), 4.82 (2 H, d, *J* 0.5 Hz, He).
^{13}C-NMR:	δ_C ppm (101 MHz, $CDCl_3$) 140.27 (C, Cd), 127.82 (CH), 127.07 (CH), 127.05 (CH), 40.52 (CH_2, Ce).
LRMS (EI):	*m/z*: 132 ($[M]^{+\bullet}$, 25%), 97 ($[M\text{-}Cl]^{+\bullet}$, 100%), 84 (6%), 69 (15%), 63 (8%), 58 (8%), 53 (14%), 45 (22%).

Characterisation data was consistent with that reported in the literature.[184, 242]

5.4.1.8 - (*R*)-(1-Chloroethyl)benzene (326-*R*)



C_8H_9Cl (140.61)
(*R*)

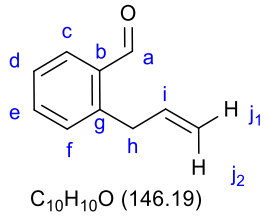
Procedure:[206] To a stirring solution of (*S*)-(−)-1-phenylethanol (1.22 g, 10.0 mmol) and 1-formylpyrrolidine (0.19 mL, 2.0 mmol) in MTBE (10 mL), benzoyl chloride (1.74 mL, 15.0 mmol) was added dropwise over 25 mins at 0 °C. The reaction was stirred at RT for 24 hours before re-treatment with 1-formylpyrrolidine (0.10 mL, 1.0 mmol) and benzoyl chloride (0.87 mL, 7.5 mmol) at RT, and stirred for a further 24 hours. The reaction was subsequently treated with ethanolamine (2.40 mL), diluted in Et_2O (30 mL), treated with sat. $NaHCO_{3\,(aq)}$ (10 mL) and stirred for 15 minutes at RT. The phases were separated and

the aqueous extracted further with Et_2O (2× 30 mL). The organic phases were combined, washed with sat. $NaHCO_{3\,(aq)}$ (2× 10 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 0.5% Et_2O in hexane over silica to afford the title compound as a colourless oil (744 mg, 5.50 mmol, 55%).

GC (AP40):	Rt 3.75 mins.
(BP70):	Rt 21.14 mins (>95% *R*-enantiomer). (*S*/*R* mixture 20.69/21.02 mins).
^{1}H-NMR:	δ_H ppm (400 MHz, $CDCl_3$) 7.46 – 7.41 (2 H, m, ArH), 7.41 – 7.34 (2 H, m, ArH), 7.31 (1 H, m, ArH), 5.11 (1 H, q, *J* 6.8 Hz, He), 1.86 (3 H, d, *J* 6.8 Hz, Me).
^{13}C-NMR:	δ_C ppm (101 MHz, $CDCl_3$) 142.94 (C, Cd), 128.77 (2 CH, *o*-/*m*-Ph), 128.39 (CH, *p*-Ph), 126.63 (2 CH, *o*-/*m*-Ph), 58.92 (CH, Ce), 26.65 (CH_3, Me).
LRMS (EI):	*m/z*: 140 ($[M]^{+\bullet}$, 17%), 125 (10%), 105 ($[M\text{-}Cl]^{+\bullet}$, 100%), 103 (57%), 91 (9%), 78 (64%), 63 (20%), 51 (52%).

Enantiopurity was determined upon comparison of **326-*R*** with racemic **326** by chiral GC. Characterisation data was consistent with that reported in the literature.[206]

5.4.1.9 - 2-Allylbenzaldehyde (378)



$C_{10}H_{10}O$ (146.19)

Procedure:[201] To a stirring solution of 2-formylphenylboronic acid (3.0 g, 20.0 mmol) and $PdCl_2(PPh_3)_4$ (421 mg, 0.6 mmol) in THF (100 mL), degassed allyl bromide (2.60 mL, 30.0 mmol) was added followed by degassed 1 M $Na_2CO_{3\,(aq)}$ (40 mL, 40 mmol) at RT under nitrogen. The reaction was then heated to 85 °C and refluxed for 5 hours. The reaction mixture was cooled to RT, poured into water (200 mL) and extracted with CH_2Cl_2 (3× 150 mL). The organic phases were combined and washed with brine (200 mL), dried over $MgSO_4$ filtered and concentrated *in vacuo*. The crude compound was purified by column chromatography using 2% EtOAc in hexane over silica followed by Kugelrohr distillation at 51 °C, 0.01 mbar to afford the title compound as a colourless oil (1.44 g, 9.86 mmol, 49%).

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 10.26 (1 H, s, Ha), 7.85 (1 H, dd, *J* 7.7, 1.4 Hz, Hc), 7.53 (1 H, td, *J* 7.5, 1.5 Hz, Hd), 7.40 (1 H, td, *J* 7.5, 0.9 Hz, He), 7.30 (1 H, d, *J* 7.6 Hz, Hf), 6.04 (1 H, ddt, *J* 16.9, 10.3, 6.2 Hz, Hi), 5.09 (1 H, dq, *J* 10.1, 1.5 Hz, Hj_1), 4.99 (1 H, dq, *J* 17.1, 1.7 Hz, Hj_2), 3.82 (2 H, dt, *J* 6.2, 1.7 Hz, Hh).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 192.48 (C, Ca), 142.42 (C), 137.08 (CH, Ci), 134.11 (CH), 134.01 (CH), 131.74 (CH), 131.21 (CH), 127.06 (CH), 116.56 (CH_2, Cj), 36.66 (CH_2, Ch).

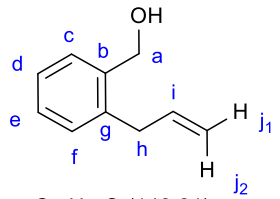
LRMS (CI): *m/z:* 164 ($[M+NH_4]^+$, 58%), 417 ($[M+H]^+$, 100%), 131 (70%), 118 (38%), 115 (21%), 106 (8%), 91 (14%), 63 (5%).

HRMS (EI): Found *m/z*: 146.0717 $[M]^{+\bullet}$. Calculated 146.0726 Da.

IR (ATR): ν_{max}/ cm^{-1} 3076 (=C-H), 3007 (=C-H), 2979 (C-H), 2916 (C-H), 2858 (C-H), 2736 (CHO), 1692 (C=O),1636m (C=C), 1598s (C=C), 1574m (Ar), 1485m (Ar), 1452m (Ar), 1208s, 915s, 751s.

^{1}H- and ^{13}C-NMR was consistent with that reported in the literature.[243]

5.4.1.10 - (2-Allylphenyl)methanol (379)



$C_{10}H_{12}O$ (148.21)

Procedure:[202] To a stirring solution of 2-allylbenzaldehyde **378** (1.10 g, 7.50 mmol) in dry EtOH (11 mL), $NaBH_4$ (425 mg, 11.2 mmol) was added at 0 °C. The reaction was allowed to warm to RT and stirred for 2 hours. The reaction was quenched with water (5 mL) at 0 °C, poured into water (40 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The organic phases were combined, washed with brine (40 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 20% EtOAc in hexane over silica to afford the title compound as a colourless oil (994 mg, 6.71 mmol, 89% estimated yield as compound shows a 20:1 product to (2-propylphenyl)methanol by ^{1}H-NMR).

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.39 (1 H, m, ArH), 7.29 – 7.18 (3 H, m, ArH), 6.01 (1 H, ddt, *J* 16.9, 10.3, 6.3 Hz, Hg), 5.08 (1 H, dq, *J* 10.1,

1.6 Hz, Hh), 5.01 (1 H, dq, *J* 17.1, 1.7 Hz, Hi), 4.70 (2 H, s, Ha), 3.48 (2 H, dt, *J* 6.2, 1.4 Hz, Hf), 1.77 (1 H, s, OH).

[Visible peaks for (2-propylphenyl)methanol: 2.70 – 2.61 (2 H, m), 1.00 (3 H, t, *J* 7.3 Hz).]

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 138.78 (C), 137.94 (C), 137.59 (CH, Ci), 130.03 (CH), 128.47 (CH), 128.19 (CH), 126.80 (CH), 116.00 (CH_2, Cj), 63.29 (CH_2, Ca), 36.89 (CH_2, Ch).

[Visible peaks for (2-propylphenyl)methanol: 129.56 (CH), 127.97 (CH), 126.21 (CH), 63.17 (CH_2), 34.48 (CH_2), 24.48 (CH_2), 14.28 (CH_3).]

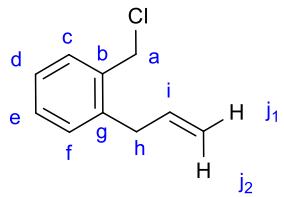
LRMS (CI): *m/z:* 166 ($[M+NH_4]^{+\bullet}$, 18%), 148 ($[M+NH_4-H_2O]^+$, 100%), 132 (83%), 117 ($[M-CH_2OH]^+$, 44%), 115 (29%), 105 (15%), 91 (20%), 78 (5%).

HRMS (EI): Found *m/z*: 148.0863 $[M]^{+\bullet}$. Calculated 148.0883 Da.

IR (ATR): ν_{max}/ cm^{-1} 3322br (OH), 3075m (=C-H), 30221m (=C-H), 2977m (C-H), 2887m (C-H), 1637m (C=C), 1604w (C=C), 1489m (Ar), 1453m (Ar), 1407m (C-H), 1038m (C-O), 994s, 913s, 748s.

^{1}H- and ^{13}C-NMR was consistent with that reported in the literature.[244]

5.4.1.11 - 1-Allyl-2-(chloromethyl)benzene (373)



$C_{10}H_{11}Cl$ (166.65)

Procedure:[203] To a stirring solution of (2-allylphenyl)methanol **379** (919 mg, 6.20 mmol) in CH_2Cl_2 (14 mL), thionyl chloride (1.0 mL, 13.6 mmol) was added dropwise over 5 minutes at 0 °C and subsequently stirred at RT for 2 hours. The reaction was quenched with 2 M $NaOH_{(aq)}$ (2 mL) at 0 °C and stirred for 20 minutes. The reaction mixture was poured into water (40 mL) and extracted with CH_2Cl_2 (3× 40 mL). The organic phases were combined, washed with brine (40 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 100% hexane over silica to afford the title compound as a colourless oil (904 mg, 5.09 mmol, 82% estimated yield as compound is 17.6:1 product to 1-(chloromethyl)-2-propylbenzene by ^{1}H-NMR).

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.41 - 7.22 (4 H, m, ArH), 6.04 (1 H, ddt, *J* 16.9, 10.3, 6.3 Hz, Hi), 5.13 (1 H, dq, *J* 10.1, 1.6 Hz, Hj_1), 5.06 (1 H, dq, *J* 17.1, 1.7 Hz, Hj_2), 4.66 (2 H, s, Ha), 3.57 (2 H, dt, *J* 6.3, 1.5 Hz, Hh).

[Visible peaks for 1-(chloromethyl)-2-propylbenzene: 2.79 – 2.71 (2 H, m), 1.78 – 1.66 (2 H, m), 1.05 (3 H, t, 7.3 Hz).]

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 138.85 (C), 136.77 (CH, Ci), 135.69 (C), 130.41 (CH), 130.34 (CH), 129.23 (CH), 127.00 (CH), 116.33 (CH_2, Cj), 44.36 (CH_2, Ca), 36.81 (CH_2, Ch).

[Visible peaks for 1-(chloromethyl)-2-propylbenzene: 129.88 (CH), 129.01 (CH), 126.45 (CH), 34.48 (CH_2), 24.43 (CH_2), 14.31 (CH_3).

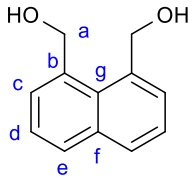
LRMS (EI): *m/z*: 166 ($[M]^{+\bullet}$, 39%), 129 (91%), 115 (100%), 102 (38%), 91 (65%), 77 (51%), 63 (51%), 51 (44%).

HRMS (APPI): Found *m/z*: 166.0543 $[M]^+$. Calculated 166.0544 Da.

IR (ATR): ν_{max}/ cm^{-1} 3077w (=C-H), 3023w (=C-H), 3006w (=C-H), 2976w (C-H), 2916w (C-H), 2873w (C-H), 2850w (C-H), 1637m (C=C), 1604w (C=C), 1490m (Ar), 1455m (Ar), 1436m (C-H), 914s, 764s, 730s, 669s.

^{1}H-NMR was consistent with that reported in the literature.[203]

5.4.1.12 - Naphthalene-1,8-diyldimethanol (386)



$C_{12}H_{12}O_2$ (188.23) Procedure:[204] To a stirring suspension of $LiAlH_4$ (911 mg, 24.0 mmol) in THF (72 mL), $ZnCl_2$ (1.5 M in THF, 8.0 mL, 12.0 mmol) was added at RT followed by naphthalic anhydride (3.96 g, 20.0 mmol). The reaction mixture was stirred at RT for 24 hours and then refluxed at 85 °C for a further 24 hours. The reaction mixture was allowed to cool to RT, quenched with water (10 mL) at 0 °C and acidified to pH 5 with 2 M $HCl_{(aq)}$. The mixture was poured into water (50 mL) and extracted with EtOAc (6× 50 mL). The organic phases were combined and washed with brine (50 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo*, washed with hexane and EtOAc to afford the title compound as a pale beige solid (2.94 g, 15.6 mmol, 78%).

^{1}H-NMR: δ_H ppm (400 MHz, DMSO) 7.86 (2 H, dd, *J* 8.2, 1.3 Hz, He), 7.63 (2 H, dd, *J* 7.1, 1.2 Hz, Hc), 7.46 (2 H, dd, *J* 8.0, 7.1 Hz, Hd), 5.28 (2 H, t, *J* 5.5 Hz, OH), 5.09 (4 H, d, *J* 5.5 Hz, Ha).

^{13}C-NMR: δ_C ppm (101 MHz, DMSO) 138.52 (2 C) , 135.07 (C), 130.04 (C), 129.00 (2 CH), 128.07 (2 CH), 124.88 (2 CH), 63.64 (2 CH_2, Ca).

LRMS (ESI$^+$): *m/z*: 211 ($[M+Na]^+$, 29%), 171 ($[M-OH]^+$, 100%).

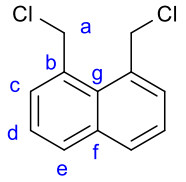
HRMS (EI): Found *m/z*: 188.0829 $[M]^{+\bullet}$. Calculated 188.0832 Da.

IR (ATR): ν_{max}/ cm^{-1} 3335br (OH), 3230br (OH), 3051m (=C-H), 3007m (=C-H), 2955m (C-H), 2936m (C-H), 2891w (C-H), 1601m (Ar), 1509m (Ar), 1451m (Ar), 1426m (C-H), 1010s (C-O), 996s, 824s, 766s.

Mp: 149.7 °C (Lit 161-162 °C (benzene).)[204]

^{1}H-NMR and ^{13}C-NMR was consistent with that reported in the literature.[204]

5.4.1.13 - 1,8-Bis(chloromethyl)naphthalene (383)



$C_{12}H_{10}Cl_2$ (225.11) Procedure:[205] To stirring conc. HCl (22.7 mL, 264.5 mmol) at 0 °C, conc. H_2SO_4 (11.3 mL, 212.0 mmol) was added dropwise. Diol **386** was subsequently added at RT and the reaction was stirred overnight (48 hours). The reaction mixture was poured into water (100 mL) and extracted with Et_2O (3× 100 mL). The organic phases were combined and washed with brine (100 mL), sat. $NaHCO_{3\ (aq)}$ (100 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 100% hexane over silica to afford the title compound as a crystalline white solid (1.74 g, 7.64 mmol, 51%).

GC (AP40): Rt 7.86 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.92 (2 H, dd, *J* 8.3, 1.3 Hz, He), 7.62 (2 H, dd, *J* 7.1, 1.4 Hz, Hc), 7.48 (2 H, dd, *J* 8.1, 7.1 Hz, Hd), 5.33 (4 H, s, Ha).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 136.2 (C), 133.1 (2 C), 132.98 (2 CH), 132.0 (2 CH), 129.6 (C), 125.8 (2 CH), 48.52 (2 CH_2, Ca).

LRMS (EI): *m/z*: 224 ($[M]^+$, 77%), 189 ($[M-Cl]^+$, 100%), 152 (99%), 139 (32%), 127 (28%), 115 (16%), 102 (13%), 94 (21%).

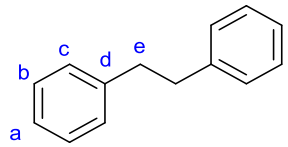
HRMS (APPI): Found *m/z*: 224.0254 $[M]^+$. Calculated 224.0154 Da.

IR (ATR): ν_{max}/ cm^{-1} 3059w (=C-H), 3037w (=C-H), 2988w (C-H), 2904w (C-H), 1600m (Ar), 1511m (Ar), 1478m (Ar), 1447m (Ar), 768s, 675s, 583s.

Mp: 92.5 °C. (Lit. 90.5 – 91 °C (hexane)).[245]

5.4.2 – Diarylethanes (and Methylaryls)

5.4.2.1 1,2-Diphenylethane (289)



$C_{14}H_{14}$ (182.27)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. Benzyl chloride (127 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C, the reaction was then allowed to warm to RT and subsequently stirred for 24 hours at RT. The reaction was quenched with 2 M $HCl_{(aq)}$ (4 mL) at RT and stirred for 1 hour. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined and washed with water (50 mL), brine (50 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 100% hexane over silica to afford the title compound as a white solid (26 mg, 0.14 mmol, 14%).

GC (AP40): Rt 6.24 mins.

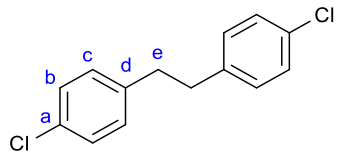
^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.36 – 7.28 (4 H, m, ArH), 7.25 – 7.18 (6 H, m, ArH), 2.96 (4 H, s, He).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 141.93 (2 C, Cd), 128.59 (4 CH, Cb/c), 128.47 (4 CH, Cb/c), 126.05 (2 CH, Ca), 38.08 (2 CH_2, Ce).

LRMS (EI): *m/z*: 182 ($[M]^{+\bullet}$, 51%), 165 (7%), 104 (8%), 91 ($[C_7H_7]^{+\bullet}$, 100%), 77 (16%), 65 (43%).

Characterisation data was consistent with that reported in the literature.[246, 247]

5.4.2.2 - 1,2-Bis(4-chlorophenyl)ethane (310)



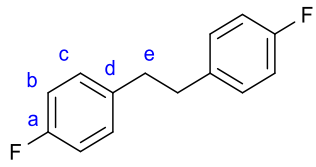
$C_{14}H_{12}Cl_2$ (251.15)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. 4-Chlorolbenzyl chloride (161 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C, the reaction was then allowed to warm to RT and subsequently stirred for 24 hours at RT. The reaction was quenched with 2 M $HCl_{(aq)}$ (4 mL) at RT and stirred for 1 hour. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined and washed with water (50 mL), brine (50 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 100% hexane over silica to afford the title compound as a white solid (48 mg, 0.19 mmol, 19%).

GC (AP40):	Rt 8.11 mins
^{1}H-NMR:	δ_H ppm (400 MHz, $CDCl_3$) 7.23 (4 H, d*, *J* 8.5 Hz, ArH), 7.05 (4 H, d*, *J* 8.4 Hz, ArH), 2.86 (4 H, s, He). *Doublets with second order effects.
^{13}C-NMR:	δ_C ppm (101 MHz, $CDCl_3$) 139.61 (2 C, Ca/d), 131.79 (2 C, Ca/d), 129.84 (4 CH, Cb/c), 128.46 (4 CH, Cb/c), 37.03 (2 CH_2, Ce).
LRMS (EI):	*m/z*: 250 ($[M]^{+\bullet}$, 9%), 178 (2%), 125 ($[C_7H_6Cl]^{+\bullet}$, 100%), 99 (4%), 89 (12%).

Characterisation data was consistent with that reported in the literature.[247]

5.4.2.3 - 1,2-Bis(4-fluorophenyl)ethane (311)



$C_{14}H_{12}F_2$ (218.25)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. 4-Fluorobenzyl chloride (145 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C, the reaction was then allowed to warm

to RT and subsequently stirred for 24 hours at RT. The reaction was quenched with 2 M $HCl_{(aq)}$ (4 mL) and stirred for an hour at RT. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined, washed with water (50 mL), brine (50 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 100% hexane over silica to afford the title compound as a white solid (26 mg, 0.12 mmol, 12%).

GC (AP40): Rt 6.30 mins.

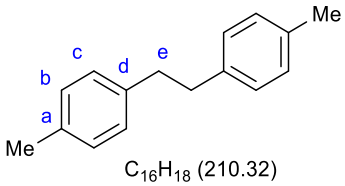
^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.07 (4 H, dd*, *J* 8.6, 5.5 Hz, ArH), 6.95 (4 H, t*, *J* 8.7 Hz, ArH), 2.86 (4 H, s, He).
*Multiplets with second order effects.

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 161.50 (d, *J* 243.5 Hz, 2 C, Ca), 137.10 (d, *J* 3.2 Hz, 2 C, Cd), 129.97 (d, *J* 7.8 Hz, 4 CH, Cc), 115.21 (d, *J* 21.1 Hz, 4 CH, Cb), 37.29 (s, 2 CH_2, Ce).

LRMS (EI): *m/z*: 218 ($[M]^{+\bullet}$, 57%), 201 (10%), 109 ($[C_7H_6F]^{+\bullet}$, 100%), 101 (18%), 89 (15%), 83 (58%).

Characterisation data was consistent with that reported in the literature.[246, 247]

5.4.2.4 - 1,2-Bis(4-methylphenyl)ethane (312)



$C_{16}H_{18}$ (210.32)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. 4-Methylbenzyl chloride (141 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C, the reaction was then allowed to warm to RT and subsequently stirred for 24 hours at RT. The reaction was quenched with 2 M $HCl_{(aq)}$ (4 mL) and stirred for an hour at RT. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined, washed with water (50 mL), brine (50 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 100% hexane over silica to afford the title compound as a white solid (39 mg, 0.19 mmol, 19%).

GC (AP40): Rt 7.17 mins.

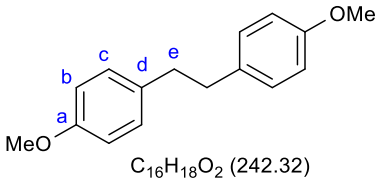
^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.09 (8 H, s, ArH), 2.86 (4 H, s, He), 2.33 (6 H, s, Me).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 139.02 (2 C), 135.44 (2 C), 129.15 (4 CH), 128.44 (4 CH), 37.79 (2 CH_2), 21.16 (2 CH_3).

LRMS (EI): *m/z*: 210 ($[M]^{+\bullet}$, 68%), 178 (17%), 105 ($[C_8H_9]^{+\bullet}$, 100%), 91 (20%), 77 (60%).

Characterisation data was consistent with that reported in the literature.[246, 247]

5.4.2.5 - 1,2-Bis(4-methoxyphenyl)ethane (313)



$C_{16}H_{18}O_2$ (242.32)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. 4-Methoxybenzyl chloride (157 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C, the reaction was then allowed to warm to RT and subsequently stirred for 24 hours at RT. The reaction was quenched with 2 M $HCl_{(aq)}$ (4 mL) and stirred for an hour at RT. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined, washed with water (50 mL), brine (50 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 0-5% Et_2O in hexane over silica to afford the title compound as a white solid (53 mg, 0.22 mmol, 22%).

GC (AP40): Rt 8.45 mins.

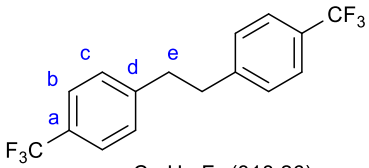
^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.08 (4 H, d*, *J* 8.6 Hz, ArH), 6.82 (4 H, d*, *J* 8.6 Hz, ArH), 3.79 (6 H, s, OMe), 2.83 (4 H, s, He).
*Doublets with second order effects.

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 157.94 (2 C, Ca), 134.12 (2 C, Cd), 129.51 (4 CH, Cb/c), 113.85 (4 CH, Cb/c), 55.40 (2 CH_3, OMe), 37.42 (2 CH_2, Ce).

LRMS (EI): *m/z*: 242 ($[M]^{+\bullet}$, 58 %), 165 (11%), 121 ($[C_8H_9O]^{+\bullet}$, 100%), 106 (11%), 91 (45%), 78 (51%).

Characterisation data was consistent with that reported in the literature.[247]

5.4.2.6 - 1,2-Bis(4-(trifluoromethyl)phenyl)ethane (314)



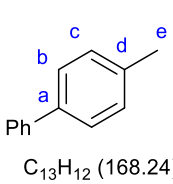
$C_{16}H_{12}F_6$ (318.26)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. 4-trifluoromethylbenzyl chloride (195 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C, the reaction was then allowed to warm to RT and subsequently stirred for 24 hours at RT. The reaction was quenched with 2 M $HCl_{(aq)}$ (4 mL) and stirred for an hour at RT. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined, washed with water (50 mL), brine (50 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo*, purified by column chromatography using 100% hexane over silica to afford the title compound as a white solid (26 mg, 0.08 mmol, 8%).

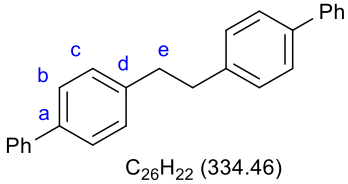
GC(AP40):	Rt 6.36 mins.
^{1}H-NMR:	δ_H ppm (400 MHz, $CDCl_3$) 7.54 (4 H, d, *J* 8.0 Hz, ArH), 7.25 (4 H, d, *J* 7.9 Hz, ArH), 3.00 (4 H, s, He).
^{13}C-NMR:	δ_C ppm (101 MHz, $CDCl_3$) 145.17 (q, *J* 1.2 Hz, 2 C, Cd), 128.92 (4 CH, Cc), 128.75 (q, *J* 32.3 Hz, 2 C, Ca), 125.52 (q, *J* 3.8 Hz, 4 CH, Cb), 124.43 (q, *J* 271.8 Hz, 2 CF_3), 37.37 (s, 2 CH_2, Ce).
LRMS (EI):	*m/z*: 318 ($[M]^{+\bullet}$, 23%), 299 ($[M\text{-}F]^{+\bullet}$, 19%), 159 ($[C_8H_6F_3]^{+\bullet}$, 100%), 151 (12%), 140 (20%), 119 (32%), 109 (57%).

Characterisation data was consistent with that reported in the literature.[248]

5.4.2.7 - 4-Methyl-1,1'-biphenyl (308) and 1,2-Di([1,1'-biphenyl]-4-yl)ethane (315)



$C_{13}H_{12}$ (168.24)



$C_{26}H_{22}$ (334.46)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. 4-Phenylbenzyl chloride (203 mg, 1.0 mmol) in THF (2

mL) was added at -78 °C, the reaction was then allowed to warm to RT and subsequently stirred for 2 hours at RT. The reaction was quenched with 2 M $HCl_{(aq)}$ (4 mL) and stirred for an hour at RT. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined, washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 0-5% Et_2O in hexane over silica to afford two white solids, 4-methyl-1,1'-biphenyl (**308**, 82 mg, 0.49 mmol, 50%) and 1,2-di([1,1'-biphenyl]-4-yl)ethane (**315**, 54 mg, 0.16 mmol, 16%).

4-Methyl-1,1'-biphenyl **308**

GC (AP40):	Rt 6.10 mins.
^{1}H-NMR:	δ_H ppm (400 MHz, $CDCl_3$) 7.61 (2 H, dd*, *J* 8.2, 1.1 Hz, Hb), 7.53 (2 H, d*, *J* 8.2 Hz, Ha), 7.46 (2 H, t*, *J* 7.6 Hz, *m*-Ph), 7.36 (1 H, t*, *J* 7.4 Hz, *p*-Ph), 7.29 (2 H, d, *J* 7.9, *o*-Ph), 2.43 (3 H, s, He). *Multiplets with second order effects.
^{13}C-NMR:	δ_C ppm (101 MHz, $CDCl_3$) 141.32 (C), 138.52 (C), 137.17 (C), 129.62 (2 CH), 128.85 (2 CH), 127.14 (2 CH), 127.12 (2 CH), 127.11 (CH, *p*-Ph), 21.24 (CH_3, Ce).
LRMS (EI):	*m/z*: 168 ($[M]^{+\bullet}$, 100%), 152 ($[M\text{-}CH_4]^{+\bullet}$, 71%), 139 (24%), 128 (20%), 115 (57%), 102 (16%), 91 (24%), 84 (56%).

Characterisation data was consistent with that reported in the literature.[249]

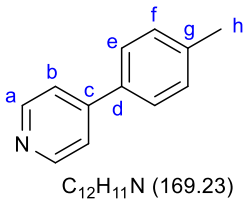
1,2-di([1,1'-biphenyl]-4-yl)ethane **315**

GC (AP40L):	Rt 15.14mins.
^{1}H-NMR:	δ_H ppm (400 MHz, $CDCl_3$) 7.60 (4 H, dd*, *J* 8.3, 1.3 Hz, ArH), 7.54 (4 H, d*, *J* 8.2 Hz, ArH), 7.44 (4 H, t*, *J* 7.6 Hz, *m*-Ph), 7.33 (2 H, t*, *J* 7.4 Hz, *p*-Ph), 7.30 (4 H, d*, *J* 8.2 Hz, ArH), 3.01 (4 H, s, He). *Multiplets with second order effects.
^{13}C-NMR:	δ_C ppm (101 MHz, $CDCl_3$) 141.21 (2 C), 141.01 (2 C), 139.08 (2 C), 129.04 (4 CH), 128.88 (4 CH), 127.25 (4 CH), 127.20 (2 CH, *p*-Ph), 127.15 (4 CH), 37.66 (2 CH_2, Ce).

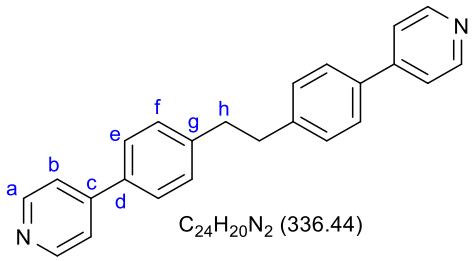
LRMS (EI): *m/z*: 334 ($[M]^{+\bullet}$, 24%), 207 (14%), 167 ($[C_7H_6Ph]^{+\bullet}$, 100%) 152 (32%), 128 (6%), 115 (6%).

Characterisation data was consistent with that reported in the literature. [250, 251]

5.4.2.8 - 4-(*p*-Tolyl)pyridine (309) and 1,2-Bis(4-(pyridin-4-yl)phenyl)ethane (316)



$C_{12}H_{11}N$ (169.23)



$C_{24}H_{20}N_2$ (336.44)

Procedure: 4-(4-(Chloromethyl)phenyl)pyridine hydrochloride **321** (288 mg, 1.2 mmol) was washed with sat $NaHCO_{3\,(aq)}$ (10 mL) and extracted with Et_2O (2× 10 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 4-(4-(chloromethyl)phenyl)pyridine (214 mg, 1.05 mmol). To a stirring solution of Cp_2ZrCl_2 (307 mg, 1.05 mmol) in THF (5.25 mL), *n*-BuLi (2.5 M in hexanes, 0.84 mL, 2.1 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. 4-(4-(Chloromethyl)phenyl)pyridine (214 mg, 1.05 mmol) in THF (2.1 mL) was added to the reaction dropwise and the reaction was stirred at RT for 24 hours. The reaction was quenched with deionised water (4 mL) at RT for 1 hour. The reaction mixture was poured into water (50 mL) and extracted with EtOAc (4× 50 mL). The organic phases were combined, washed with water (50 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 40% EtOAc, 1% Et_3N in hexane over silica to afford an off-white solid (**309**, 105 mg, 0.62 mmol, 62%) and subsequently 4% MeOH, 1% Et_3N in CH_2Cl_2 over silica to afford a pale yellow solid (**316**, 64 mg, 0.19 mmol, 20%).

4-(*p*-Tolyl)pyridine **309**

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 8.63 (2 H, dd, *J* 4.5, 1.6 Hz, Ha), 7.55 (2 H, d*, *J* 8.2 Hz, He), 7.49 (2 H, dd, *J* 4.5, 1.7 Hz, Hb), 7.29 (2 H, d, *J* 7.9 Hz, Hf), 2.42 (3 H, s, Hh).
*Doublet with second order effects.

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 150.35 (2 CH, Ca), 148.38 (C, Cc), 139.34 (C), 135.35 (C), 139.98 (2 CH), 126.96 (2 CH), 121.54 (2 CH), 21.36 (CH_3, Ch).

LRMS (ESI$^+$): *m/z*: 170 ($[M+H]^+$, 100%).

Characterisation data was consistent with that reported in the literature.[252]

1,2-Bis(4-(pyridin-4-yl)phenyl)ethane **316**

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 8.65 (4 H, br s, Ha), 7.58 (4 H, d*, *J* 8.3 Hz, He), 7.50 (4 H, dd, *J* 4.5, 1.3 Hz, Hb), 7.31 (4 H, d*, *J* 8.2 Hz, Hf), 3.03 (4 H, s, Hh).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 150.32 (4 CH, Ca), 148.23 (2 C, Cc), 142.75 (2 C), 135.97 (2 C), 129.42 (4 CH), 127.11 (4 CH), 121.57 (4 CH), 37.47 (2 CH_2, Ch).

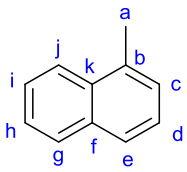
LRMS (ESI$^+$): *m/z*: 337 ($[M+H]^+$, 40%), 169 ($[M-C_{12}H_{10}N+H]^+$, 100%).

HRMS (ESI$^+$): Found *m/z*: 337.1698 $[M+H]^+$. Calculated 337.1699 Da.

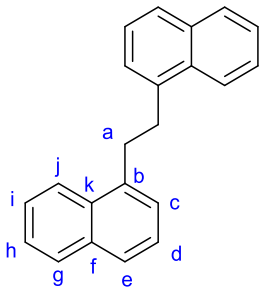
IR (ATR): ν_{max}/ cm^{-1} 3079 (=C-H), 3038 (=C-H), 3020 (=C-H), 2944 (C-H), 2922 (C-H), 2856 (C-H), 1591m (Ar), 1540m (Ar), 1486m (Ar), 1455m, 810s (Ar), 729m, 708m.

Mp: 241.2 °C.

5.4.2.9 - 1-Methylnaphthalene (292) and 1,2-Di(naphthalen-1-yl)ethane (291)



$C_{11}H_{10}$ (142.20)



$C_{22}H_{18}$ (282.39)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. 1-Naphthylmethyl chloride (177 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C and then allowed to warm to RT, stirring for 2 hours at RT. The

reaction was quenched with 2 M $HCl_{(aq)}$ (4 mL) and stirred for 1 hour at RT. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined, washed with 2 M $HCl_{(aq)}$ (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 100% hexane over silica to afford a colourless oil (methylnaphthalene **292**, 52 mg, 0.37 mmol, 37%) and a white solid (naphthalene dimer **291**, 44 mg, 0.16 mmol, 16%).

1-Methylnaphthalene **292**

GC (AP40):	Rt 5.18 mins.
^{1}H-NMR:	δ_H ppm (400 MHz, $CDCl_3$) 8.02 (1 H, dd, *J* 8.3, 1.2 Hz), 7.86 (1 H, dd, *J* 7.6, 1.7 Hz), 7.73 (1 H, d, *J* 8.1 Hz), 7.58 – 7.46 (2 H, m), 7.39 (1 H, dd, *J* 7.6, 7.0 Hz), 7.34 (1 H, d, *J* 6.9 Hz), 2.72 (3 H, s, Ha).
^{13}C-NMR:	δ_C (101 MHz, $CDCl_3$) 134.40 (C), 133.70 (C), 132.76 (C), 128.66 (CH), 126.69 (CH), 126.51 (CH), 125.84 (CH), 125.71 (CH), 125.67 (CH), 124.25 (CH), 19.51 (CH_3, Ca).
LRMS (EI):	*m/z*: 142 ($[M]^{+\bullet}$, 94%), 141 ($[M\text{-}H]^{+\bullet}$, 100%), 126 (18%), 115 (82%), 102 (17%), 89 (59%), 75 (34%), 71 (87%).

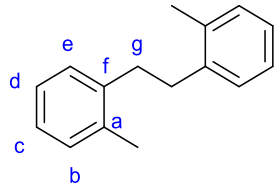
Characterisation data was consistent with that reported in the literature.[253]

1,2-Di(naphthalen-1-yl)ethane **291**

GC (AP40):	Rt 10.88 mins.
^{1}H-NMR:	δ_H ppm (400 MHz, $CDCl_3$) 8.14 (2 H, d, *J* 8.4 Hz), 7.90 (2 H, dd, *J* 7.7, 1.8 Hz), 7.76 (2 H, d, *J* 8.1 Hz), 7.58 – 7.48 (4 H, m), 7.42 (2 H, dd, *J* 7.9, 7.0 Hz), 7.36 (2 H, dd, *J* 7.0, 1.2 Hz), 3.53 (4 H, s, Ha).
^{13}C-NMR:	δ_C ppm (101 MHz, $CDCl_3$) 138.21 (2 C), 134.08 (2 C), 132.00 (2 C), 129.02 (2 CH), 126.97 (2 CH), 126.08 (4 CH), 125.75 (2 CH), 125.67 (2 CH), 123.81 (2 CH), 34.24 (2 CH_2, Ca).
LRMS (EI):	*m/z*: 282 ($[M]^{+\bullet}$, 75%), 265 (16%), 152 (27%), 141 ($[CH_2Np]$, 100%), 128 (10%), 115 (71%), 89 (10%), 75 (4%).

Characterisation data was consistent with that reported in the literature.[247]

5.4.2.10 - 1,2-Di-o-tolylethane (333)



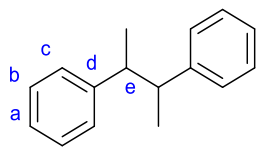
$C_{16}H_{18}$ (210.32)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. 2-Methylbenzyl chloride (142 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C, the reaction was then allowed to warm to RT and subsequently stirred for 2 hours at RT. The reaction was quenched with 2 M $HCl_{(aq)}$ (4 mL) and stirred for an hour at RT. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined, washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 100% hexane over silica to afford the title compound as a white solid (19 mg, 0.09 mmol, 9%).

GC (AP40):	Rt 7.20 mins.
^{1}H-NMR:	δ_H ppm (400 MHz, $CDCl_3$) 7.22 – 7.12 (8 H, m, ArH), 2.89 (4 H, s, Hg), 2.35 (6 H, s, Me).
^{13}C-NMR:	δ_C ppm (101 MHz, $CDCl_3$) 140.31 (2 C, Ca/f), 136.05 (2 C, Ca/f), 130.34 (2 CH), 129.00 (2 CH), 126.25 (2 CH), 126.19 (2 CH), 34.28 (2 CH_2, Cg), 19.41 (2 CH_3, Me).
LRMS (EI):	*m/z*: 210 ($[M]^{+\bullet}$, 55%), 178 (13%), 115 (8%), 105 ($[C_8H_9]^{+\bullet}$, 100%), 91 (18%), 77 (35%).

Characterisation data was consistent with that reported in the literature.[246, 247]

5.4.2.11 - Butane-2,3-diyldibenzene (334)



$C_{16}H_{18}$ (210.32)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. (1-Chloroethyl)benzene (141 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C, the reaction was then allowed to warm

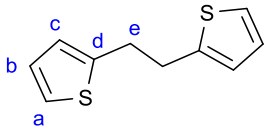
to RT and subsequently stirred for 2 hours at RT. The reaction was quenched with 2 M $HCl_{(aq)}$ (4 mL) and stirred for an hour at RT. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined, washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* and purified by column chromatography using 100% hexane over silica to afford the title compound as a white solid (37 mg, 0.18 mmol, 18%, 1:1.3 *dl*:*meso* ratio by ^{1}H-NMR).

(^{1}H-NMR and GC of the crude mixture showed a 1:1 mixture of *dl* and *meso* diastereomers).

GC (AP40):	Rt 6.58, 6.69 mins (1:1.3 ratio)
(BP140):	Rt 9.03, 9.34, 11.07 mins (1:1:2.7 ratio).
^{1}H-NMR:	*dl:* δ_H ppm (400 MHz, $CDCl_3$) 7.16 (4 H, m, ArH), 7.09 (2 H, m, ArH), 7.01 (4 H, m, ArH), 2.99 – 2.90 (2 H, m, He), 1.32 – 1.25 (6 H, m, Me). *meso*: δ_H ppm (400 MHz, $CDCl_3$) 7.35 – 7.27 (4 H, m, ArH), 7.25 – 7.20 (6 H, m, ArH), 2.83 – 2.76 (2 H, m, He), 1.07 – 0.98 (6 H, m, Me).
^{13}C-NMR:	*dl*: δ_C ppm (101 MHz, $CDCl_3$) 145.98 (2 C, Cd), 127.97 (4 CH, Cb/c), 127.92 (4 CH, Cb/c), 125.83 (2 CH, Ca), 46.62 (2 CH, Ce), 18.09 (2 CH_3, Me). *meso*: δ_C ppm (101 MHz, $CDCl_3$) 146.63 (2 C, Cd), 128.42 (4 CH, Cb/c), 127.76 (4 CH, Cb/c), 126.19 (2 CH, Ca), 47.40 (2 CH, Ce), 21.18 (2 CH_3, Me).
LRMS (EI):	7.34 mins (*dl*): *m/z*: 210 ($[M]^{+\bullet}$, 2%), 178 (6%), 115 (9%), 105 ($[CH(Me)Ph]^{+\bullet}$, 100%), 91 (19%), 77 (51%). 7.41 mins (*meso*): *m/z*: 210 ($[M]^{+\bullet}$, 2%), 178 (6%), 115 (9%), 105 ($[CH(Me)Ph]^{+\bullet}$, 100%), 91 (19%), 77 (51%).

Characterisation data was consistent with that reported in the literature.[246, 254]

5.4.2.12 - 1,2-Di(thiophen-2-yl)ethane (335)



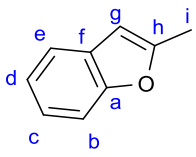
$C_{10}H_{10}S_2$ (194.31) Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. Thiophene methyl chloride (133

mg, 1.0 mmol) in THF (2 mL) was added at -78 °C and then allowed to warm to RT, stirring for 2 hours at RT. The reaction mixture was poured into water (50 mL) and extracted with EtOAc (4× 50 mL). The organic phases were combined, washed with brine (3× 50 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 10% CH_2Cl_2 in hexane over silica to afford the title compound as an off-white crystalline solid (15 mg, 0.08 mmol, 8%).

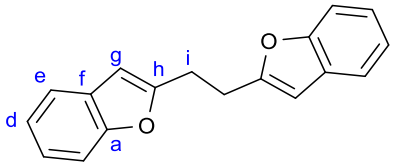
GC (AP40):	Rt 6.35 mins.
^{1}H-NMR:	δ_H ppm (400 MHz, $CDCl_3$) 7.14 (2 H, dd, *J* 5.1, 1.2 Hz, Ha), 6.93 (2 H, dd, *J* 5.1, 3.4 Hz, Hb), 6.82 (2 H, dd, *J* 3.4, 0.4 Hz, Hc), 3.21 (4 H, s, He).
^{13}C-NMR:	δ_C ppm (101 MHz, $CDCl_3$) 143.82 (2 C, Cd), 126.87 (2 CH), 124.77 (2 CH), 123.46 (2 CH), 32.29 (2 CH_2, Ce).
LRMS (EI):	*m/z*: 194 ($[M]^{+\bullet}$, 50%), 160 (2%), 134 (2%), 115 (3%), 97 ($[C_5H_5S]^{+\bullet}$, 100%), 84 (2%), 77 (2%), 69 (7%).

Characterisation data was consistent with that reported in the literature.[255]

5.4.2.13 - 2-Methylbenzofuran (331) and 1,2-Di(benzofuran-2-yl)ethane (336)



C_9H_8O (132.16)



$C_{18}H_{14}O_2$ (262.31)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL) was added *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. 2-(Chloromethyl)benzofuran **230** (167 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C and then allowed to warm to RT, stirring for 2 hours at RT. The reaction mixture was poured into water (50 mL) and extracted with EtOAc (4× 50 mL). The organic phases were combined, washed with brine (3 50 mL), dried over MgSO4, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 10% CH_2Cl_2 in hexane over silica to afford a colourless oil (methylbenzofuran **331**, 14 mg, 0.11 mmol, 11%) and a white solid (benzofuran dimer **336**, 26 mg, 0.10 mmol, 10%).

2-Methylbenzofuran **331**

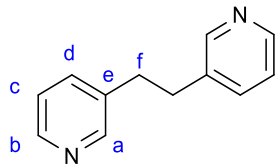
GC (AP40):	Rt 3.99 mins.
^{1}H-NMR:	δ_H ppm (400 MHz, $CDCl_3$) 7.48 (1 H, m, ArH), 7.42 (1 H, m, ArH), 7.24 – 7.15 (2 H, m, ArH), 6.38 (1 H, quin, *J* 1.0 Hz, Hg), 2.47 (3 H, d, *J* 1.1 Hz, Hi).
^{13}C-NMR:	δ_C ppm (101 MHz, $CDCl_3$) 155.42 (C, Ca/h), 154.76 (C, Ch/a), 129.21 (C), 123.05 (CH), 122.42 (CH), 120.07 (CH), 110.63 (CH, Cb), 102.58 (CH, Cg), 14.07 (CH_3, Ci).
LRMS (EI):	*m/z*: 132 ($[M]^{+\bullet}$, 75%), 131 ($[M-H]^{+\bullet}$, 100%), 103 (14%), 84 (20%), 77 (23%), 63 (17%).

Characterisation data was consistent with that reported in the literature.[256]

1,2-Di(benzofuran-2-yl)ethane **336**

GC (AP40):	Rt 9.28 mins
^{1}H-NMR:	δ_H ppm (400 MHz, $CDCl_3$) 7.48 (2 H, m, ArH) 7.43 (2 H, d*, *J* 8.2 Hz, ArH), 7.23 (2 H, td, *J* 7.7, 1.6 Hz, ArH), 7.19 (2 H, td, *J* 7.4, 1.3 Hz, ArH), 6.44 (2 H, s, Hg), 3.25 (4 H, s, Hi). *Doublet with second order effects.
^{13}C-NMR:	δ_C ppm (101 MHz, $CDCl_3$) 157.65 (2 C, Ca/h), 154.86 (2 C, Ch/a), 128.92 (2 C), 123.56 (2 CH), 122.68 (2 CH), 120.56 (2 CH), 110.95 (2 CH, Cb), 102.75 (2 CH, Cg), 27.01 (2 CH_2, Ci).
LRMS (EI):	*m/z*: 262 ($[M]^{+\bullet}$, 19%), 207 (1%), 131 ($[C_9H_7O]^{+\bullet}$, 100%), 115 (2%), 103 (5%), 77 (14%).
HRMS (APPI):	Found *m/z*: 262.0990 $[M]^+$. Calculated 262.0988 Da.
IR (ATR):	ν_{max}/ cm^{-1} 3109w (=C-H), 3085w (=C-H), 3068w (=C-H), 3053w (=C-H), 2965w (C-H), 2952w (C-H), 2922w (C-H), 2921w (C-H), 2850w (C-H), 1600m (Ar), 1587m (Ar), 1453m (Ar), 1145m (C-O), 942m, 806s, 737s.
Mp:	117.6 °C.

5.4.2.14 - 1,2-Di(pyridin-3-yl)ethane (337)



$C_{12}H_{12}N_2$ (184.24)

Procedure: [3-(Chloromethyl)pyridine hydrochloride (246 mg, 1.5 mmol) was washed with sat. $NaHCO_{3\,(aq)}$ (10 mL) and extracted with Et_2O (2× 10 mL). The organic phases were combined, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford 3(chloromethyl)pyridine as a pale yellow oil (141 mg, 1.1 mmol).] To a stirring solution of Cp_2ZrCl_2 (324 mg, 1.1 mmol) in THF (5.6 mL), *n*-BuLi (2.5 M in hexanes, 0.89 mL, 2.2 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. 3-(Chloromethyl)pyridine (141 mg, 1.1 mmol) in THF (2.2 mL) was added at -78 °C and then allowed to warm to RT, stirring for 2 hours at RT. The reaction mixture was poured into water (50 mL) and extracted with EtOAc (4× 50 mL). The organic phases were combined, washed with brine (3× 50 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 5% MeOH in CH_2Cl_2 over silica to afford the title compound as a white solid (12 mg, 0.07 mmol, 7%).

^{1}H-NMR:	δ_H ppm (400 MHz, $CDCl_3$) 8.44 (4 H, d, *J* 14.1 Hz, Ha & Hb), 7.42 (2 H, dt, *J* 7.8, 1.7 Hz, Hd), 7.19 (2 H, dd, *J* 7.6, 4.8 Hz, Hc), 2.93 (4 H, s, Hf).
^{13}C-NMR:	δ_C ppm (101 MHz, $CDCl_3$) 150.07 (2 CH, Ca/b), 147.91 (2 CH, Cb/a), 136.13 (2 C, Ce), 136.04 (2 CH, Cd), 123.47 (2 CH, Cc), 34.63 (2 CH_2, Cf).
LRMS (ESI$^+$):	*m/z*: 185 ($[M+H]^+$, 100%).
HRMS (ESI$^+$):	Found *m/z*: 185.1075 $[M+H]^+$. Calculated 185.1073 Da.
IR (ATR):	ν_{max}/ cm^{-1} 3087 (=C-H), 3055 (=C-H), 3034 (=C-H), 2999 (=C-H), 2952 (C-H), 2917 (C-H), 2850 (C-H), 1591w (Ar), 1574s (Ar), 1477s (Ar), 1454w (Ar), 1425s (Ar), 1025s, 809s, 712s, 629s.
Mp:	55.6 °C.

5.4.2 – ^{1}H-NMR Ratio between Diarylethanes and Methylaryls

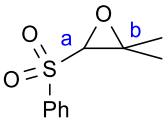
To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. Benzyl chloride (1.0 mmol) in THF (2 mL) was added at -78 °C, the reaction was then allowed to warm to RT and subsequently stirred for 2 hours.

Reaction mixture (0.5 mL) was withdrawn and dispensed into a vial containing 2 M $HCl_{(aq)}$ (0.5 mL) and $CDCl_3$ (0.5 mL). The vial was shook, left standing for 1 hour at room temperature to allow for layer separation. The aqueous layer was removed by pipette and the organic phase was filtered over a plug of cotton wool and anhydrous $MgSO_4$ (1 inch high) in a pipette directly into an NMR tube. The spectrum obtained was referenced to THF (1.85 ppm) with the diarylethanes and methylaryls peaks observed in between both THF peaks (1.85 ppm and 3.85 ppm).

The reaction for each benzyl chloride was conducted twice and the ratios reported are an average of both reactions, unless stated otherwise.

5.4.3 – Carbenoid Precursors

5.4.3.1 - 2,2-Dimethyl-3-(phenylsulfonyl)oxirane (358)



$C_{10}H_{12}O_3S$ (212.26) Procedure:[188, 189] To a stirring solution of chloromethyl phenyl sulfone (953 mg, 5.0 mmol) and benzyltriethylammonium chloride (18 mg, 0.08 mmol) in MeCN (0.65 mL), acetone (0.44 mL) and NaOH (50% wt in H_2O, 3.35 mL, 0.13 mmol) was added at RT and stirred overnight (15 hours). The reaction mixture was dissolved in EtOAc (100 mL) and washed with water (50 mL). The aqueous was subsequently extracted with EtOAc (2× 100 mL) and all organic phases were combined. The organic phase was washed with water (2× 50 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 20% EtOAc in hexane over silica to afford the title compound as a white solid (1.05 g, 4.95 mmol, 99%).

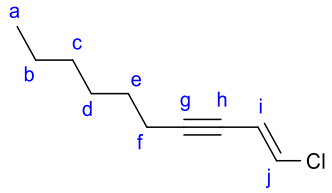
GC (AP40):	Rt 6.67 mins.
^{1}H-NMR:	δ_H ppm (400 MHz, $CDCl_3$) 8.04 – 7.87 (2 H, m, ArH), 7.70 (1 H, m, ArH), 7.60 (2 H, m, ArH), 3.80 (1 H, s), 1.82 (3 H, s, Me), 1.41 (3 H, s, Me).
^{13}C-NMR:	δ_C ppm (101 MHz, $CDCl_3$) 139.08 (C, *i*-Ph), 134.37 (CH, *p*-Ph), 129.59 (2 CH, *o*-/*m*-Ph), 128.41 (2 CH, *o*-/*m*-Ph), 74.52 (CH, Ca), 64.57 (C, Cb), 25.21 (CH_3, Me), 18.51 (CH_3, Me).
LRMS (ESI$^+$):	*m/z*: 213 $[M+H]^+$, 100%.

HRMS (ESI$^+$): Found *m/z*: 235.0399 $[M+Na]^+$. Calculated 235.0399 Da.

IR (ATR): ν_{max}/ cm^{-1} 2983m (=C-H), 2936w (C-H), 1320s (S=O), 1291m (C-O), 1152s (S=O), 1583w (Ar), 1478w (Ar), 1447m (Ar), 1152s (C-O), 681s, 590s, 556s.

Mp: 79.4 °C (Lit. 94 °C).[257]

5.4.3.2 - (*E*)-1-Chlorodec-1-en-3-yne (393)



$C_{10}H_{15}Cl$ (170.68)

Procedure:[207] To a stirring solution of $Pd(PPh_3)_4$ (231 mg, 0.02 mmol) and CuI (38 mg, 0.02 mmol) in degassed Et_2O (40 mL), degassed piperidine (4.01 mL, 40.6 mmol), octyne (3.00 mL, 20.3 mmol) and *trans*-1,2-dichloroethene (2.35 mL, 30.5 mmol) were added at RT and under nitrogen and stirred for 16 hours. The reaction mixture was poured into sat. $NH_4Cl_{(aq)}$ (50 mL) and extracted with Et_2O (3× 100 mL). The organic phases were combined, washed with 2 M $HCl_{(aq)}$ (50 mL), brine (50 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 100% hexane over silica to afford the title compound as a colourless oil (3.07 g, 17.87 mmol, 90%).

GC (AP40): Rt 4.84 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 6.42 (1 H, dt, *J* 13.6, 0.4 Hz, Hj), 5.91 (1 H, dt, *J* 13.6, 2.3 Hz, Hi), 2.29 (2 H, tdd, *J* 7.1, 2.1, 0.6 Hz, Hf), 1.52 (2 H, quin, *J* 7.3 Hz, He), 1.44 – 1.13 (6 H, m, Hb-d), 0.89 (3 H, t, *J* 6.9 Hz, Ha).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 128.82 (CH, Cj), 114.47 (CH, Ci), 93.64 (C, Cg), 75.79 (C, Ch), 31.46 (CH_2), 28.69 (CH_2), 28.60 (CH_2), 22.68 (CH_2), 19.55 (CH_2), 14.18 (CH_3, Ca).

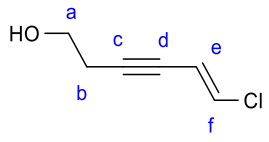
LRMS (EI): *m/z*: 170 ($[M]^{+\bullet}$, 9%), 141 ($[M-Et]^{+\bullet}$, 24%), 135 ($[M-Cl]^{+\bullet}$, 27%), 127 ($[M-Pr]^{+\bullet}$, 18%), 105 (38%), 99 ($[M-Pe]^{+\bullet}$, 26%), 91 (73%), 79 (100%).

HRMS (EI): Found *m/z*: 170.0864 $[M]^{+\bullet}$. Calculated 170.0857 Da.

IR (ATR): ν_{max}/ cm^{-1} 3074w (=C-H), 3023w (=C-H), 2956s (C-H), 2929s (C-H), 2858s (C-H), 2219 (C≡C), 1586m (C=C), 1466m (C-H),1228m, 915s, 847s.

^{1}H- & ^{13}C-NMR were consistent with that reported in the literature.[258]

5.4.3.3 - (*E*)-6-Chlorohex-5-en-3-yn-1-ol (396)



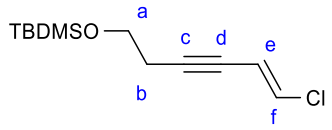
C_6H_7ClO (130.57)

Procedure:[208] To a stirring solution of $PdCl_2(PPh_3)_2$ (246 mg, 0.35 mmol) and CuI (667 mg, 3.5 mmol) in degassed Et_2O (52 mL), degassed piperidine (10.4 mL, 105 mmol), *trans*-1,2-dichloroethylene (5.40 mL, 70.0 mmol) and 3-butyn-1-ol (2.65 mL, 35.0 mmol) were added at RT and under nitrogen. The reaction was stirred at Rt for 16 hours. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ (10 mL), poured into water (100 mL) and extracted with Et_2O (3× 100 mL). The organic phases were combined and washed with 2 M $HCl_{(aq)}$ (50 mL), sat. $NaHCO_{3\,(aq)}$ (50 mL), water (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 15% EtOAc in hexane over silica and subsequently by Kugelrohr distillation at 72 °C and 0.1 mbar to afford the title compound as a colourless oil (2.70 g, 20.7 mmol, 59%).

GC (AP40):	Rt 4.01 mins.
^{1}H-NMR:	δ_H ppm (400 MHz, $CDCl_3$) 6.48 (1 H, dt, *J* 13.6, 0.6 Hz, Hf), 5.90 (1 H, dt, *J* 13.6, 2.3 Hz, He), 3.73 (2 H, t, *J* 6.3 Hz, Ha), 2.56 (2 H, tdd, *J* 6.3, 2.3, 0.6 Hz, Hb), 2.00 (1 H, s, OH).
^{13}C-NMR:	δ_C ppm (101 MHz, $CDCl_3$) 129.96 (CH, Cf), 113.88 (CH, Ce), 89.61 (C, Cc), 77.50 (C, Cd), 60.99 (CH_2, Ca), 23.84 (CH_2, Cb).
LRMS (EI):	*m/z:* 130 ($[M]^{+\bullet}$, 57%), 112 ($[M\text{-}H_2O]^{+\bullet}$, 7%), 100 (45%), 95 (8%), 89 (6%), 73 (37%), 65 (100%), 51 (20%).
HRMS (EI):	Found *m/z*: 130.0173 $[M]^{+\bullet}$. Calculated 130.0180 Da.
IR (ATR):	ν_{max}/ cm^{-1} 3331brm (OH), 3073m (=C-C-H), 3024w(=C-H), 2944m (C-H), 2887m (C-H), 2221m (C≡C), 1585m (C=C), 1470m (C-H), 1420m (C-H), 1038s (C-O), 916s, 846s.

^{1}H- and ^{13}C-NMR were consistent with that reported in the literature.[208]

5.4.3.4 - (*E*)-*tert*-Butyl((6-chlorohex-5-en-3-yn-1-yl)oxy)dimethylsilane (397)



$C_{12}H_{21}ClOSi$ (244.83)

Procedure:[209] To a stirring solution of (*E*)-6-chlorohex-5-en-3-yn-1-ol **396** (1.0 g, 7.66 mmol) in DMF (8 mL), 1H-imidazole (782 mg, 11.49 mmol) and TBDMSCl (1.27 g, 8.43 mmol) was added at RT and under nitrogen. The reaction was stirred at RT for 66 hours. The reaction mixture was poured into sat. $NaHCO_{3\,(aq)}$ (120 mL) and extracted with Et_2O (3× 100 mL). The organic phases were combined and washed with sat. $NaHCO_{3\,(aq)}$ (120 mL), brine (120 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 1% Et_2O in hexane over silica to afford the title compound as a colourless oil (1.82 g, 7.43 mmol, 97%).

GC (AP40): Rt 5.90 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 6.44 (1 H, dt, *J* 13.6, 0.6 Hz, Hf), 5.90 (1 H, dt, *J* 13.6, 2.3 Hz, He), 3.73 (2 H, t, *J* 7.0 Hz, Ha), 2.51 (2 H, tdd, *J* 7.0, 2.3, 0.5 Hz, Hb), 0.90 (9 H, s, *t*Bu), 0.07 (6 H, s, $SiMe_2$).

^{13}C-NMR: δ_C ppm (101 MHz, CDCl3) 129.35 (CH, Cf), 114.24 (CH, Ce), 90.45 (C, Cc),* 61.77 (CH_2, Ca), 26.01 (3 CH_3, *t*Bu), 23.96 (CH_2, Cb), 18.49 (C, *t*Bu), -5.13 (2 CH_3, $SiMe_2$).

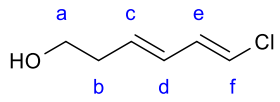
*Cd quaternary carbon missing, likely under $CDCl_3$.

LRMS (CI): *m/z:* 245 ($[M+H]^+$, 100%), 204 (11%), 187 ($[M-tBu]^+$, 63%), 151 (8%), 132 (27%), 115 ($[TBDMS]^{+\bullet}$, 10%), 93 (24%), 74 (21%).

HRMS (EI): Found *m/z*: 245.1116 $[M]^{+\bullet}$. Calculated 245.1123 Da.

IR (ATR): ν_{max}/ cm^{-1} 3075w (=C-H), 3024w (=C-H), 2954m (C-H), 2929m (C-H), 2857m (C-H), 2222m (C≡C), 1585m (C=C), 1471m (C-H), 1254s, 1101s (C-O), 834s, 805S, 774s.

5.4.3.5 - (3*E*,5*E*)-6-Chlorohexa-3,5-dien-1-ol (398)



C_6H_9ClO (132.59)

Procedure:[208] To a stirring solution of Red-Al (≥60% wt in toluene, 3.23 mL, 9.96 mmol) in anhydrous Et_2O (5 mL), (*E*)-6-chlorohex-5-en-3-yn-1-ol **396** (1.0 g, 7.66 mmol) in Et_2O (5 mL) was added at -15 °C over 5 minutes. The reaction was subsequently refluxed for 5 hours at 50 °C. The reaction was allowed to cool to RT and

quenched with the dropwise addition of 2 M $HCl_{(aq)}$ (5 mL) at -70 °C. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined, washed with water (50 mL), brine (50 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 30% EtOAc in hexane over silica to afford the title compound as a colourless oil (864 mg, 6.52 mmol, 85%).

GC (AP40): Rt 4.07 mins.

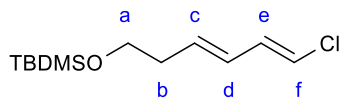
^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 6.43 (1 H, dd, *J* 13.2, 10.8 Hz, He), 6.13 (1 H, d, *J* 13.2 Hz, Hf), 6.08 (1 H, ddtd, *J* 15.4, 10.8, 1.4, 0.5 Hz, Hd), 5.69 (1 H, dtt, *J* 15.1, 7.2, 0.6 Hz, Hc), 3.68 (2 H, t, *J* 6.3 Hz, Ha), 2.34 (2 H, qd, *J* 6.6, 1.3 Hz Hb), 1.65 (1 H, s, OH).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 133.48 (CH), 131.52 (CH), 128.88 (CH), 119.88 (CH), 61.83 (CH_2), 36.02 (CH_2).

LRMS (EI): *m/z:* 132 ($[M]^{+\bullet}$, 83%), 114 ($[M\text{-}H_2O]^{+\bullet}$, 3%), 101 ($[M\text{-}CH_2OH]^{+\bullet}$, 85%), 88 (35%), 79 (24%), 67 (70%), 65 (100%), 51 (23%).

Characterisation data was consistent with that reported in the literature.[208, 259]

5.4.3.6 - *tert*-Butyl(((3*E*,5*E*)-6-chlorohexa-3,5-dien-1-yl)oxy)dimethylsilane (399)



$C_{12}H_{23}ClOSi$ (246.85)

Procedure:[209] To a stirring solution of (3*E*,5*E*)-6-chlorohexa-3,5-dien-1-ol **398** (814 mg, 6.13 mmol) in DMF (6 mL), 1H-imidazole (626 mg, 9.20 mmol) and TBDMSCl (1.02 g, 6.74 mmol) was added at RT. The reaction was stirred at RT for 44 hours. The reaction mixture was subsequently poured into sat. $NaHCO_{3\,(aq)}$ (120 mL) and extracted with Et_2O (3× 100 mL). The organic phases were combined and washed with sat. $NaHCO_{3\,(aq)}$ (120 mL) and brine (120 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 0.5% EtOAc in hexane over silica to afford the title compound as a colourless oil (1.36 g, 5.51 mmol, 90%).

GC (AP40): Rt: 5.86 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 6.42 (1 H, ddd, *J* 13.0, 10.9, 0.6 Hz, He), 6.10 (1 H, dt, *J* 13.2, 0.4 Hz, Hf), 6.02 (1 H, ddtd, *J* 15.4, 10.8, 1.4, 0.5 Hz, Hd), 5.71 (1 H, dtt, *J* 15.1, 7.1, 0.6 Hz, Hc), 3.65 (2 H, t, *J* 6.6 Hz,

Ha), 2.29 (2 H, qd, *J* 6.9, 1.2 Hz, Hb), 0.89 (9 H, s, *t*Bu), 0.04 (6 H, s, $SiMe_2$).

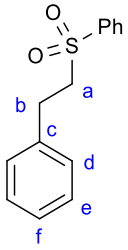
^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 133.86 (CH), 132.46 (CH), 128.02 (CH), 119.04 (CH), 62.69 (CH_2), 36.38 (CH_2), 26.06 (3 CH_3), 18.48 (C), -5.13 (2 CH_3).

LRMS (CI): *m/z*: 247 ($[M+H]^+$, 66%), 231 ($[M\text{-}Me]^{+\bullet}$, 9%), 206 (71%), 189 ($[M\text{-}t\text{Bu}]^{+\bullet}$, 84%), 132 (43%), 123 (21%), 115 ($[M\text{-}OTBDMS]^{+\bullet}$, 100%), 106 (38%).

Characterisation data was consistent with that reported in the literature.[259]

5.4.4 – Two-Component Couplings

5.4.4.1 - (Phenethylsulfonyl)benzene (348)



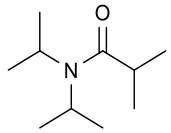
$C_{14}H_{14}O_2S$ (246.32) Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. Benzyl chloride (127 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C and then allowed to warm to RT, stirring for 2 hours at RT. The reaction was cooled to -90 °C and chloromethyl phenyl sulfone (191 mg, 1.0 mmol) in THF (1 mL) was added followed by LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) added dropwise over 1 minute to a stirring solution of *i*-Pr_2NH (0.28 mL, 2.0 mmol) in THF (1 mL) at 0 °C and stirred for 15 minutes] dropwise over 1 minutes and stirred for 30 minutes. The reaction was allowed to warm to RT and was stirred for 15 hours before being quenched with 2 M $HCl_{(aq)}$ (4 mL) and stirred for a further hour at RT. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined, washed with water (50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 40% Et_2O in hexane over silica to afford the title compound as a yellow oil (65 mg, 2.3:1

chloromethyl phenyl sulfone to product by ^{1}H-NMR). Estimated yield of 19.7 mg, 0.08 mmol, 8%.

GC (AP40):	Rt 8.92 mins.
^{1}H-NMR:	δ_H ppm (400 MHz, $CDCl_3$) 7.95 – 7.86 (2 H, m, ArH), 7.65 (1 H, m, ArH), 7.57 – 7.51 (2 H, m, ArH), 7.29 – 7.15 (3 H, m, ArH), 7.13 – 7.06 (2 H, m, ArH), 3.39 – 3.32 (2 H, m, Ha), 3.07 – 3.00 (2 H, m, Hb).
^{13}C-NMR:	δ_C ppm (101 MHz, $CDCl_3$) 139.08 (C), 137.52 (C), 133.90 (CH, *p*-Ph/ Cf), 129.45 (2 CH), 128.89 (2 CH), 128.36 (2 CH), 128.15 (2 CH), 127.00 (CH, *p*-Ph/ Cf), 57.58 (CH_2, Ca), 28.80 (CH_2, Cb).
LRMS (CI):	*m/z*: 264 ($[M+NH_4]^+$, 100%), 247 ($[M+H]^+$, 19%), 122 (3%), 104 (96%), 94 (5%), 91 (5%), 78 (9%), 77 (10%).

Characterisation data was consistent with that reported in the literature.[187]

5.4.4.2 - *N,N*-Diisopropylisobutyramide (361)

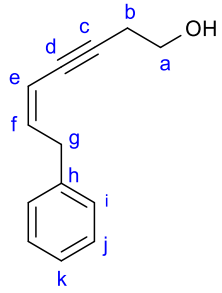


$C_{10}H_{21}NO$ (171.28) Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL) was added *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. Benzyl chloride (127 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C and then allowed to warm to RT, stirring for 2 hours at RT. The reaction was cooled to -90 °C and sulfonyl oxirane **358** (212 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) added dropwise over 1 minute to a stirring solution of *i*-Pr_2NH (0.21 mL, 1.5 mmol) in THF (1 mL) at 0 °C and stirred for 15 minutes] was added dropwise over 1 minute and stirred for 1 hour at low temperature. The reaction was then allowed to warm to RT and stirred overnight (16 hours). The reaction was quenched with degassed sat. $NaHCO_{3\,(aq)}$ (6 mL) at RT and stirred for 16 hours. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined, washed with 2 M $HCl_{(aq)}$ (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 0-20% EtOAc in hexane to afford the title compound as an orange oil (38 mg, 0.22 mmol, 22%).

GC (AP40):	Rt 4.20 mins.
^{1}H-NMR:	δ_H (400 MHz, $CDCl_3$) 3.99 (1 H, spt, *J* 6.3 Hz), 3.55 (1 H, br s), 2.69 (1 H, spt, *J* 6.7 Hz), 1.33 (6 H, d, *J* 6.7 Hz, *i*Pr), 1.20 (6 H, d, *J* 6.7 Hz, *i*Pr), 1.08 (6 H, d, *J* 6.7 Hz, *i*Pr).
^{13}C-NMR:	δ_C ppm (101 MHz, $CDCl_3$) 176.26 (C, C=O), 47.59 (CH), 45.59 (CH), 31.84 (CH), 21.48 (2 CH_3, *i*Pr), 20.83 (2 CH_3, *i*Pr), 19.82 (2 CH_3, *i*Pr).
LRMS (ESI$^+$):	*m/z*: 172 ($[M+H]^+$, 100%).

Characterisation data was consistent with that reported in the literature.[260]

5.4.4.3 - (*Z*)-7-Phenylhept-5-en-3-yn-1-ol (400)



$C_{13}H_{14}O$ (186.25)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL) was added *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. Benzyl chloride (127 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C and then allowed to warm to RT, stirring for 2 hours at RT. The reaction was cooled to -90 °C and enyne **397** (245 mg, 1.0 mmol) in THF (1 mL) was added followed by LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) added dropwise over 1 minute to a stirring solution of *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C and stirred for 15 minutes] was added dropwise over 1.5 minutes and stirred for 30 minutes at low temperature. The reaction was subsequently stirred at RT for 17 hours. The reaction was quenched with 2 M $HCl_{(aq)}$ (4 mL) and stirred for 1 hour at RT. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined, washed with 2 M $HCl_{(aq)}$ (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was re-dissolved in THF (2 mL) and 2 M $HCl_{(aq)}$ (0.5 mL) was added and solution stirred for 1 hour at RT. The solution was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined, washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 20% EtOAc in hexane over silica

and subsequently heated at 80 °C at 0.2 mbar Kugelrohr distillation equipment (for excess **396** removal). The compound was then Kugelrohr distilled at 170 °C at 0.2 mbar to afford the title compound as a colourless oil (68 mg, 0.37 mmol, 37%).

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.34 – 7.27 (2 H, m, Hj), 7.25 – 7.15 (3 H, m, Hi & Hk), 6.04 (1 H, dtt, *J* 10.6, 7.5, 0.5 Hz, Hf), 5.58 (1 H, dtt, *J* 10.6, 2.1, 1.4 Hz, He), 3.77 (2 H, q, *J* 5.8 Hz, Ha), 3.65 (2 H, brd, *J* 7.5 Hz, Hg), 2.65 (2 H, td, *J* 6.2, 2.0 Hz, Hb), 1.70 (1 H, s, OH).

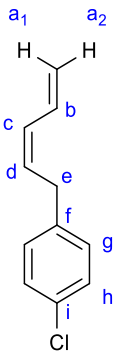
^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 141.32 (CH, Cf), 139.86 (C, Ch), 128.66 (2 CH, Ci/j), 128.57 (2 CH, Ci/j), 126.34 (CH, Ck), 110.06 (CH, Ce), 90.94 (C, Cc/d), 79.22 (C, Cd/c), 61.36 (CH_2, Ca), 36.51 (CH_2, Cg), 24.10 (CH_2, Cb).

LRMS (CI): *m/z*: 204 ($[M+NH_4]^+$, 19%), 187 ($[M+H]^+$, 49%), 171 (37%), 141 ($[M-(CH_2)_2OH]^{+\bullet}$, 30%), 128 (30%), 115 (32%), 104 (44%), 91 ($[C_7H_7]^{+\bullet}$, 100%).

HRMS (EI): Found m/z: 186.1031 $[M]^{+\bullet}$. Calculated 186.1039 Da

IR (ATR): ν_{max}/ cm^{-1} 3338mbr (OH), 3084w (=C-H), 3061w (=C-H), 3026m (=C-H), 2938m (=C-H), 2938m (=C-H), 2886m (=C-H), 2215w (C≡C), 1601m (Ar), 1495m (Ar), 1453m (Ar), 1429m (Ar), 1041s (C-O), 905m, 733s, 696s.

5.4.4.4 - (*Z*)-1-Chloro-4-(penta-2,4-dien-1-yl)benzene (355)

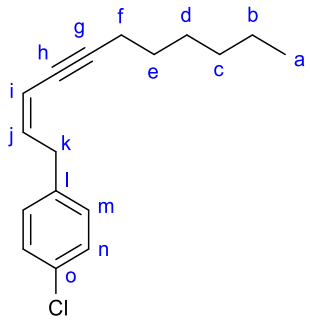


$C_{11}H_{11}Cl$ (178.66) Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. 4-Chlorobenzyl chloride (161 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C and then allowed to warm to RT, stirring for 2 hours at RT. The reaction was cooled to -90 °C and *cis*-1,4-dichloro-2-butene (0.11 mL, 1.0 mmol) was added dropwise followed by LDA [*n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0

mmol) added dropwise over 2 minutes to a stirring solution of *i*-Pr_2NH (0.34 mL, 2.4 mmol) in THF (2 mL) at 0 °C and stirred for 15 minutes] dropwise over 1 minute and stirred for 30 minutes at low temperature (-90 to -70 °C). The reaction was quenched with 2 M $HCl_{(aq)}$ (4 mL) and stirred at RT overnight (16 hours). The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined and washed with water (50 mL), brine (50 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified twice by column chromatography using 100% hexane over silica to afford the title compound as a colourless oil (67 mg, 0.38 mmol, 38%).

GC (AP40):	Rt 5.57 mins.
^{1}H-NMR:	δ_H (400 MHz, $CDCl_3$) 7.27 – 7.23 (2 H, m, Hh), 7.15 – 7.09 (2 H, m, Hg), 6.73 (1 H, dddd, *J* 16.8, 11.2, 10.2, 1.1 Hz, Hb), 6.15 (1 H, ttt, *J* 10.8, 1.6, 0.8 Hz, Hc), 5.57 (1 H, m, Hd), 5.29 (1 H, d+fs, *J* 16.8Hz, Ha_1), 5.19 (1 H, d+fs, *J* 10.2 Hz, Ha_2), 3.51 (2 H, dd, *J* 7.8, 0.7 Hz, He).
^{13}C-NMR:	δ_C ppm (101 MHz, $CDCl_3$) 139.00 (C, Cf/i), 131.98 (C, Ci/f), 131.83 (CH, Cb), 130.54 (CH, Cc/d), 129.97 (CH, Cc/d), 129.87 (2 CH, Cg/h), 128.71 (2 CH, Ch/g), 118.57 (CH_2, Ca), 33.36 (CH_2, Ce).
LRMS (EI):	*m/z*: 178 ($[M]^{+\bullet}$, 25%), 163 ($[M\text{-}Me]^{+\bullet}$, 12%), 149 (5%), 143 ($[M\text{-}Cl]^{+\bullet}$, 83%), 128 ($[M\text{-}Cl\&Me]^{+\bullet}$, 100%), 115 (38%), 89 (17%), 75 (15%).
HRMS (CI):	Found *m/z*: 179.0659 $[M+H]^{+\bullet}$. Calculated 179.0622 Da.
IR (ATR):	ν_{max}/ cm^{-1} 3085w (=C-H), 3026w (=C-H), 2965w (C-H), 2988w (C-H), 2918w (C-H), 2854w (C-H), 1643w (C=C), 1592w (Ar), 1489s (Ar), 1432m (Ar), 1405m (Ar), 1089s, 906s, 804s, 614s.

5.4.4.5 - (*Z*)-1-Chloro-4-(undec-2-en-4-yn-1-yl)benzene (405)



$C_{17}H_{21}Cl$ (260.81)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. 4-Chlorobenzyl chloride (161 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C and then allowed to warm to RT, stirring for 2

hours at RT. The reaction was cooled to -90 °C and enyne **393** (171 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) added dropwise over 2 minutes to a stirring solution of *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C and stirred for 15 minutes] dropwise over 1 minute and stirred for 30 minutes at low temperature. The reaction was quenched with 2 M $HCl_{(aq)}$ (4 mL) and stirred at RT overnight. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined and washed with water (50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 100% hexane over silica and subsequently by HPLC using 100% hexane on a LiChrospher® Si60 column (10 µm, 25 cm x 10 mm at 5 mL min^{-1}) to afford the title compound as a colourless oil (114 mg, 0.44 mmol, 0.44%).

GC (AP40): Rt 8.24 mins.

^{1}H-NMR: δ_H (400 MHz, $CDCl_3$) 7.25 (2 H, d*, *J* 8.3 Hz, Hn), 7.15 (2 H, d*, *J* 8.6 Hz, Hm), 5.91 (1 H, dtt, *J* 10.5, 7.5, 0.5 Hz, Hj), 5.58 (1 H, dtt, *J* 10.5, 2.2, 1.4 Hz, Hi), 3.60 (2 H, brd, *J* 7.5 Hz, Hk), 2.36 (2 H, td, *J* 7.0, 2.1 Hz, Hf), 1.61 – 1.50 (2 H, m, He), 1.47 – 1.36 (2 H, m, Hd), 1.36 – 1.22 (4 H, m, Hc & Hb), 0.88 (3 H, t, *J* 7.0 Hz, Ha).
*Doublets with second order effects.

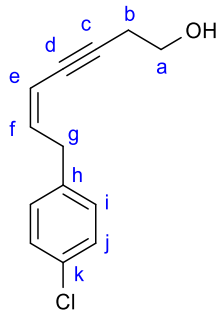
^{13}C-NMR: δ_C (101 MHz, $CDCl_3$) 139.58 (CH, Cj), 138.67 (C, Cl/o), 132.00 (C, Co/l), 129.96 (2 CH, Cm/n), 128.68 (2 CH, Cn/m), 111.05 (CH, Ci), 95.43 (C, Cg),* 35.75 (CH_2), 31.49 (CH_2), 28.93 (CH_2), 28.74 (CH_2), 22.71 (CH_2), 19.70 (CH_2), 14.19 (CH_3, Ca).
*Ch quaternary carbon not visible, likely hidden under $CDCl_3$ peak.

LRMS (EI): *m/z*: 260 ($[M]^{+\bullet}$, 26%), 231 ($[M\text{-}Et]^{+\bullet}$, 7%), 217 ($[M\text{-}Pr]^{+\bullet}$, 6%), 203 ($[M\text{-}Bu]^{+\bullet}$, 8%), 189 ($[M\text{-}Pe]^{+\bullet}$, 36%), 175 ($[M\text{-}Hx]^{+\bullet}$, 47%), 165 (34%), 153 (76%), 141 (63%), 125 ($M\text{-}C_7H_6Cl]^{+\bullet}$, 100%).

HRMS (APPI): Found *m/z*: 260.1322 $[M]^+$. Calculated 260.1326 Da

IR (ATR): ν_{max}/ cm^{-1} 3025w (=C-H), 2955m (C-H), 2929s (C-H), 2870m (C-H), 2857m (C-H), 2212w (C≡C), 1616w (Ar), 1596w (Ar), 1576w (Ar), 1490s (Ar), 1466m (Ar), 1457m (Ar), 1430m (Ar), 1407m (Ar), 1092s, 1015s, 807s, 733s

5.4.4.6 - (*Z*)-7-(4-Chlorophenyl)hept-5-en-3-yn-1-ol (406)



$C_{13}H_{13}ClO$ (220.70)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. 4-Chlorobenzyl chloride (161 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C and then allowed to warm to RT, stirring for 2 hours at RT. The reaction was cooled to -90 °C and enyne **397** (245 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) added dropwise over 1 minute to a stirring solution of *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C and stirred for 15 minutes] dropwise over 1 minute and stirred for 30 minutes at low temperature. The reaction was quenched with 2 M $HCl_{(aq)}$ (4 mL) and stirred at RT overnight (16 hours). The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined and washed with water (50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was re-dissolved in THF (1 mL) and 2 M $HCl_{(aq)}$ (0.25 mL) was added and stirred for 1 hour at RT. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined and washed with water (50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 20% EtOAc in hexane over silica and subsequently heated to 80 °C at 0.5 mbar in Kugelrohr distillation equipment (for removal of unreacted **396**) to afford the title compound as a yellow oil (99 mg, 0.45 mmol, 45%).

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.33 – 7.21 (2 H, m, Hj), 7.14 (2 H, d*, *J* 8.3 Hz, Hi), 5.99 (1 H, dtt, *J* 10.6, 7.5, 0.5 Hz, Hf), 5.60 (1 H, dtt, *J* 10.6, 2.3, 1.2 Hz, He), 3.78 (2 H, t, *J* 6.2 Hz, Ha), 3.61 (2 H, br d, *J* 7.5 Hz, Hg), 2.66 (2 H, td, *J* 6.3, 2.1 Hz, Hb), 1.80 (1 H, brs, OH).
*Doublet with second order effects.

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 140.59 (CH, Cf), 138.31 (C, Ch/k), 132.12 (C, Ck/h), 129.92 (2 CH, Ci/j), 128.74 (2 CH, Cj/i), 110.55 (CH, Ce),

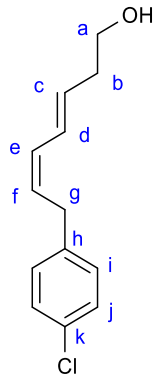
91.29 (C, Cc), 79.02 (C, Cd), 61.34 (CH_2, Ca), 35.81 (CH_2, Cg), 24.09 (CH_2, Cb).

LRMS (CI): *m/z*: 238 ($[M+NH_4]^{+\bullet}$, 4%), 221 ($[M+H]^{+\bullet}$, 16%), 205 (10%), 189 ($[M-CH_2OH]^{+\bullet}$, 12%), 171 (23%), 154 ($[M-CH_2OH-Cl]^{+\bullet}$, 16%), 128 (28%), 108 (35%), 91 ($[M-C_6H^7O-Cl]^{+\bullet}$, 100%).

HRMS (EI): Found *m/z*: 220.0649 $[M]^{+\bullet}$. Calculated 220.0649 Da.

IR (ATR): ν_{max}/ cm^{-1} 3348mbr (OH), 3098w (=C-H), 3084w (=C-H), 3061w (=C-H), 3026m (=C-H), 2916m (C-H), 2887m (C-H), 2854m (C-H), 2213w (C≡C), 1616w (Ar), 1596w (Ar), 1576w (Ar), 1490m (Ar), 1422m (Ar), 1407m (Ar), 1091s, 1041s (C-O), 1014s, 806s.

5.4.4.7 - (3*E*,5*Z*)-7-(4-Chlorophenyl)hepta-3,5-dien-1-ol (407)



$C_{13}H_{15}ClO$ (222.71) Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. 4-Chlorobenzyl chloride (161 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C and then allowed to warm to RT, stirring for 2 hours at RT. The reaction was cooled to -90 °C and diene **399** (247 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) added dropwise over 1 minutes to a stirring solution of *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C and stirred for 15 minutes] dropwise over 1 minute and stirred for 30 minutes at low temperature. The reaction was quenched with 2 M $HCl_{(aq)}$ (2 mL) and stirred at RT overnight. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined and washed with water (50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was re-dissolved in THF (1 mL) and $HCl_{(aq)}$ (0.25 mL) and stirred at RT for 1 hour. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined and washed with water (50 mL) and brine (50 mL), dried over

$MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 25% EtOAc in hexane over silica followed by HPLC using 4% IPA in hexane on a LiChrospher® Si60 column (10 µm, 25 cm x 10 mm at 5 mL min^{-1}) to afford the title compound as a colourless oil (73 mg, 0.33 mmol, 33%).

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.25 (2 H, d*, *J* 8.5 Hz, Hj), 7.12 (2 H, d*, *J* 8.6 Hz, Hi), 6.51 (1 H, ddq, *J* 15.0, 11.0, 1.3 Hz, Hd), 6.12 (1 H, tt, *J* 11.1, 1.6 Hz, He), 5.75 (1 H, dt, *J* 14.9, 7.3 Hz, Hc), 5.48 (1 H, dt, *J* 10.7, 7.8 Hz, Hf), 3.71 (2 H, t, *J* 6.4 Hz, Ha), 3.50 (2 H, brd, *J* 7.7 Hz, Hg), 2.42 (2 H, dtd, *J* 7.2, 6.3, 1.3 Hz, Hb), 1.54 (1 H, brs, OH).
*Doublets with second order effects.

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 139.15 (C, Ch/k), 131.91 (C, Ck/h), 131.56 (CH, Cc), 129.83 (2 CH, Ci/j), 129.61 (CH, Ce), 128.67 (2 CH, Cj/i), 128.28 (CH, Cf), 128.08 (CH, Cd), 62.09 (CH_2, Ca), 36.42 (CH_2, Cb), 33.34 (CH_2, Cg).

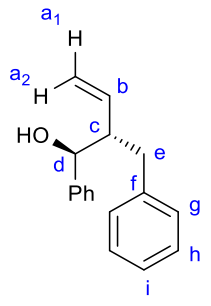
LRMS (EI): *m/z:* 222 ($[M]^{+\bullet}$, 27%), 204 ($[M\text{-}H_2O]^{+\bullet}$, 42%), 189 (21%), 177 ($[M\text{-}(CH_2)_2OH]^{+\bullet}$, 30%), 169 (54%), 153 (49%), 141 (74%), 125 ($[C_7H_6Cl]^{+\bullet}$, 100%).

HRMS (EI): Found m/z: 222.08059 $[M]^{+\bullet}$. Calculated 222.08059 Da.

IR (ATR): ν_{max}/ cm^{-1} 3344brm (OH), 3022m (=C-H), 2925m (C-H), 2881m (C-H), 1685 (C=C), 1651 (C=C), 1595 (Ar), 1575 (Ar), 1490s (Ar), 1426 (Ar), 1405 (Ar), 1089s (C-O), 1042s, 1014s, 802s.

5.4.5 – Three-Component Couplings

5.4.5.1 - *Rac*-(1*R*,2*S*)-2-benzyl-1-phenylbut-3-en-1-ol (346)



$C_{17}H_{18}O$ (238.33)
Anti

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes

at -78 °C under nitrogen and stirred for 30 minutes. Benzyl chloride (127 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C and then allowed to warm to RT, stirring for 2.5 hours at RT. The reaction was cooled to -90 °C and allyl chloride (0.08 mL, 1.0 mmol) was added followed by LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise over 1 minute to a stirring solution of *i*-Pr_2NH (0.21 mL, 1.5 mmol) in THF (1 mL) at 0 °C and stirred for 10 minutes] dropwise over 1.5 minutes and stirred for 30 minutes at low temperature (-90 to -70 °C). Benzaldehyde (0.11 mL, 1.1 mmol) followed by $BF_3.OEt_2$ (0.14 mL, 1.1 mmol) were added and the reaction was allowed to warm to -50 °C over 45 mins. The reaction was quenched with 2 M $HCl_{(aq)}$ (4 mL) and stirred at RT for 1 hour. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined, washed with water (50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 10% Et_2O in hexane over silica followed by HPLC using 1% IPA in hexane on a LiChrospher® Si60 column (10 µm, 25 cm x 10 mm at 5 mL min^{-1}) to afford the title compound as a colourless oil (18 mg, 0.08 mmol, 8%, 92:8 *anti*:*syn* by ^{1}H-NMR).

(^{1}H-NMR of the crude compound showed d.r. of 88:12 *anti*:*syn* respectively).

(Estimated total yield is 17% due to mixed samples with other impurities).

GC (AP40): Rt 8.01

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.40 – 7.26 (5 H, m, ArH), 7.24 (2 H, d*, *J* 7.7 Hz, ArH), 7.17 (1 H, t*, *J* 7.3 Hz, ArH), 7.08(2 H, m, Hg), 5.73 (1 H, ddd, *J* 17.3, 10.3, 8.4 Hz, Hb), 5.14 (1 H, dd, *J* 10.4, 1.7 Hz, Ha_1), 4.98 (1 H, d+fs, *J* 17.3 Hz, Ha_2), 4.55 (1 H, d, *J* 6.2 Hz, Hd), 2.73 (1 H, dd, *J* 12.6, 5.2 Hz, He), 2.66 (1 H, m, Hc), 2.54 (1 H, dd, *J* 12.7, 8.5 Hz, He), 2.09 (1 H, s, OH).

[Characteristic signals for *syn* isomer: 5.58 (1 H, ddd, *J* 17.2, 10.3, 8.8 Hz, Hb'), 4.84 (1 H, ddd *J* 17.2, 1.7, 0.9 Hz, Ha') and 2.95 (dd, *J* 13.7, 7.4 Hz, He')].

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 142.67 (C), 140.10 (C), 137.89 (CH, Cb), 129.28 (2 CH, Cg), 128.46 (2 CH), 128.32 (2 CH), 127.80 (CH *p*-Ph/Ci), 126.86 (2 CH), 126.08, (CH, *p*-Ph/Ci) 119.14 (CH_2, Ca), 75.69 (CH, Cd), 53.98 (CH, Cc), 37.38 (CH_2, Ce).

[Visible peaks for the *syn* isomer: 142.48 (C), 137.76 (CH, Cb'), 129.44 (2 CH), 128.24 (2 CH), 127.72 (CH, *p*-Ph'/Ci'), 126.90 (2 CH), 125.98

(CH *p*-Ph'/Ci'), 117.89 (CH_2, Ca'), 76.58 (CH, Cd'), 52.86 (CH, Cc'), 36.34 (CH_2, Ce')].

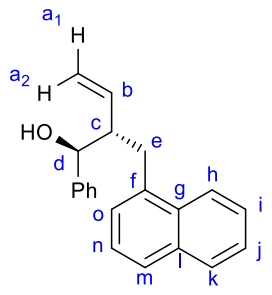
LRMS (ESI$^+$): *m/z*: 256 ($[M+NH_4]^+$, 10%), 221 ($[M\text{-}OH]^{+\bullet}$, 100%).

HRMS (ESI$^+$): Found *m/z*: 261.1253 $[M+Na]^+$. Calculated 261.1253 Da.

IR (ATR): ν_{max}/ cm^{-1} 3429 brm (OH), 3101w (=C-H), 3083m (=C-H), 3062m (=C-H), 3027m (=C-H), 3003w (=C-H), 2978w (C-H), 2917m (C-H), 2871m (C-H), 2858m (C-H), 1639w (C=C), 1603w (C=C), 1494m (Ar), 1453m (Ar), 1420m (Ar), 1054m (C-O), 914m, 763m, 742m, 697s.

Characterisation data was consistent with that reported in the literature for the *anti* isomer.[213, 214]

5.4.5.2 – *Rac*-(1*R*,2*S*)-2-(naphthalen-1-ylmethyl)-1-phenylbut-3-en-1-ol (439)



$C_{21}H_{20}O$ (288.39)

Anti

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 15 minutes. 1-(Chloromethyl)naphthalene (177 mg, 1.0 mmol) in THF (2 mL) was added and the reaction was allowed to warm to RT and stirred for 2 hours. The reaction was re-cooled to -90 °C and allyl chloride (0.08 mL, 1.0 mmol) followed by LDA (1 M in THF/ Hexanes, 1.0 mL, 1.0 mmol) was added dropwise over 3 minutes and the reaction was stirred for 15 minutes. Benzaldehyde (0.15 mL, 1.5 mmol) was added followed by $BF_3.OEt_2$ (0.19 mL, 1.5 mmol) and the reaction was stirred at RT for 30 minutes. The reaction mixture was quenched with 2 M $HCl_{(aq)}$ (4 mL), stirred at RT overnight. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined, washed with water (50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 15% Et_2O in hexane over silica three times, 75% CH_2Cl_2 in hexane over silica twice and finally by HPLC using 1% IPA in hexane on a LiChrospher®

Si60 column (10 µm, 25 cm x 10 mm at 5 mL min^{-1}) to afford the title compound as a colourless oil (75 mg, 0.26 mmol, 26%, *anti* isomer only by ^{1}H-NMR).

(^{1}H-NMR of the crude compound showed d.r. of 89:11 *anti*:*syn* respectively).

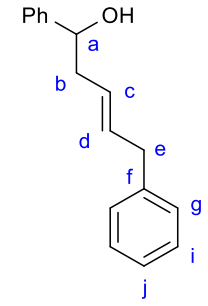
(Estimated total yield is 29% due to mixed samples with other impurities).

GC (AP40):	Rt 10.03 mins.
^{1}H-NMR:	δ_H (400 MHz, $CDCl_3$) 7.83 (1 H, d+fs, *J* 8.1 Hz ArH), 7.69 (1 H, d, *J* 8.2 Hz, ArH), 7.61 (1 H, d, *J* 8.3 Hz, ArH), 7.47 – 7.36 (6 H, m, ArH), 7.33 (2 H, m, ArH), 7.23 (1 H, dd, *J* 6.9, 0.7 Hz, ArH), 5.80 (1 H, ddd, *J* 17.2, 10.3, 8.6 Hz, Hb), 5.11 (1 H, dd, *J* 10.3, 1.6 Hz, Ha_2), 4.88 (1 H, ddd, *J* 17.2, 1.6, 0.8 Hz, Ha_1), 4.62 (1 H, dd, *J* 6.6, 3.1 Hz, Hd), 3.25 (1 H, dd, *J* 13.5, 4.7 Hz, He), 2.89 (1 H, dd, *J* 13.5, 9.2 Hz, He), 2.80 (1 H, tdd, *J* 9.0, 6.6, 4.9 Hz, Hc), 2.22 (1 H, d, *J* 3.1 Hz, OH).
^{13}C-NMR:	δ_C ppm (101 MHz, $CDCl_3$) 142.67 (C), 138.05 (CH, Cb), 136.11 (C), 134.04 (C), 132.09 (C), 128.90 (CH), 128.49 (2 CH, *o*-/*m*-Ph), 127.95 (CH), 127.57 (CH), 127.03 (2 CH, *o*-/*m*-Ph), 126.98 (CH), 125.83 (CH), 125.47 (CH), 125.33 (CH), 123.92 (CH), 119.30 (CH_2, Ca), 75.93 (CH, Cd), 53.36 (CH, Cc), 34.51 (CH_2, Ce).
LRMS (ESI$^+$):	*m/z*: 306 ($[M+NH_4]^+$, 16%), 271 ($[M\text{-}OH]^{+\bullet}$, 100%).
HRMS (APPI)	Found *m/z*: 288.1514 $[M]^+$. Calculated 288.1509 Da.
IR (ATR):	ν_{max}/ cm^{-1} 3438brm (OH), 3063m (=C-H), 3033m (=C-H), 3007w (=C-H), 297w7 (C-H), 2900w (C-H), 2872w (C-H), 1638w (C=C), 1597m (Ar), 1510m (Ar), 1453m (Ar), 1028m (C-O), 790s, 777s, 701s.

^{1}H-NMR of a mixed sample showed the following peaks for **439-*syn***.

^{1}H-NMR:	δ_H ppm (400 MHz, $CDCl_3$) 5.68 (1 H, m, Hb'), 5.21 (1 H, dd, *J* 10.4, 1.8 Hz, Ha_2').

5.4.5.3 - (*E*)-1,5-Diphenylpent-3-en-1-ol (448)



$C_{17}H_{18}O$ (238.33)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. Benzyl chloride (127 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C and then allowed to warm to RT, stirring for 2 hours at RT. The reaction was cooled to -90 °C and allyl chloride (0.08 mL, 1.0 mmol) was added followed by LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise over 1 minute to a stirring solution of *i*-Pr_2NH (0.21 mL, 1.5 mmol) in THF (1 mL) at 0 °C and stirred for 10 minutes] dropwise over 2 minutes and stirred for 30 minutes at low temperature (-90 to -70 °C). Benzaldehyde (0.11 mL, 1.1 mmol) followed by $BF_3.OEt_2$ (0.14 mL, 1.1 mmol) were added and the reaction was allowed to warm to -30 °C over 1.5 hours. The reaction was quenched with 2 M $HCl_{(aq)}$ (2 mL) and stirred at RT for 16 hour. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined, washed with water (50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 10-20% Et_2O in hexane over silica followed by HPLC using 1% IPA in hexane on a LiChrospher® Si60 column (10 µm, 25 cm x 10 mm at 5 mL min^{-1}) to afford the title compound as a colourless oil (36 mg, 0.15 mmol, 15%).

(Estimated total yield of 19% due to mixed samples with other impurities).

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.39 – 7.32 (4 H, m, ArH), 7.32 – 7.26 (3 H, m, ArH), 7.19 (1 H, t*, *J* 7.3 Hz, ArH), 7.14 (2 H, d+fs, *J* 7.8 Hz, Hf), 5.72 (1 H, dtt, *J* 14.8, 6.7, 1.2 Hz, Hd), 5.51 (1 H, dtt, *J* 15.2, 7.3, 1.3 Hz, Hc), 4.73 (1 H, ddd, *J* 7.5, 5.5, 3.3 Hz, Ha), 3.36 (2 H, d, *J* 6.8, He), 2.57 – 2.43 (2 H, m, Hb), 2.03 – 2.00 (1 H, m, OH).

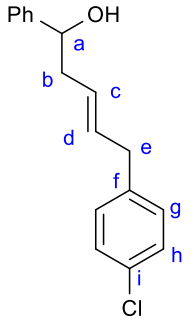
^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 144.08 (C), 140.55 (C), 133.38 (CH, Cd), 128.61 (2 CH), 128.56 (2 CH), 128.55 (2 CH), 127.63 (CH), 127.28 (CH), 126.17 (CH), 126.00 (2 CH), 73.76 (CH, Ca), 42.75 (CH_2, Cb), 39.20 (CH_2, Ce).

LRMS (ESI$^+$) *m/z*: 256 ([M+NH_4]$^+$, 82%), 221 ([M-OH]$^{+\bullet}$, 100%).

HRMS (ESI$^+$): Found *m/z*: 261.1248 [M+Na]$^+$. Calculated 261.1250 Da.

IR (ATR): ν_{max}/ cm^{-1} 3371brm (OH), 3104w (=C-H), 3083w (=C-H), 3061w (=C-H), 3027m (=C-H), 3003w (=C-H), 2964w (C-H), 2899m (C-H), 2838w (C-H), 1603m (C=C), 1494m (Ar), 1452m (Ar), 1428m (Ar), 1027m (C-O), 969m, 746m, 696s.

5.4.5.4 - (*E*)-5-(4-Chlorophenyl)-1-phenylpent-3-en-1-ol (449)



$C_{17}H_{17}ClO$ (272.77) Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. 4-Chlorobenzyl chloride (161 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C and then allowed to warm to RT, stirring for 2 hours at RT. The reaction was cooled to -90 °C and allyl chloride (0.08 mL, 1.0 mmol) was added followed by LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise over 1 minute to a stirring solution of *i*-Pr_2NH (0.21 mL, 1.5 mmol) in THF (1 mL) at 0 °C and stirred for 15 minutes] dropwise over 2 minutes and stirred for 30 minutes at low temperature (-90 to -70 °C). Benzaldehyde (0.11 mL, 1.1 mmol) followed by $BF_3.OEt_2$ (0.14 mL, 1.1 mmol) were added at -70 °C and the reaction was allowed to warm to -30 °C 1.5 hours. The reaction was quenched with 2 M $HCl_{(aq)}$ (2 mL), stirred at RT for 16 hour. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined, washed with water (50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 10-20% Et_2O in hexane over silica followed by HPLC using 1% IPA in hexane on a LiChrospher® Si60 column (10 µm, 25 cm x 10 mm at 5 mL min^{-1}) to afford the title compound as a colourless oil (33 mg, 0.12 mmol, 12%).

(Estimated total yield of 17% due to mixed samples with other impurities).

GC (AP40): Rt 9.22 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.37 – 7.31 (4 H, m, ArH), 7.28 (1 H, m, ArH), 7.23 (2 H, d*, *J* 8.4 Hz Hh), 7.07 – 6.98 (2 H, d*, *J* 8.6 Hz, Hg), 5.64 (1 H, dtt, *J* 15.8, 6.6, 1.1 Hz, Hd), 5.49 (1 H, dtt, *J* 15.3, 7.0, 1.3 Hz, Hc), 4.72 (1 H, t, *J* 6.5 Hz, Ha), 3.30 (2 H, d, *J* 6.6 Hz, He), 2.55 – 2.43 (2 H, m, Hb), 1.98 (1 H, s, OH).

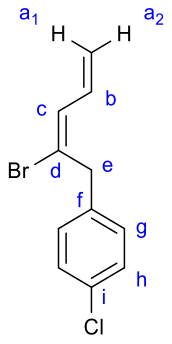
^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 144.03 (C), 138.99 (C), 132.60 (CH, Cd), 131.91 (C), 129.95 (2 CH, Hg), 128.61 (2 CH, Ch/ *o*-/*m*-Ph), 128.57 (2 CH, Ch/ *o*-/*m*-Ph), 127.81 (CH, Cc/ *p*-Ph), 127.70 (CH, Cc/ *p*-Ph), 126.01 (2 CH, *o*/*m*-Ph), 73.83 (CH, Ca), 42.62 (CH_2, Cb), 38.45 (CH_2, Ce).

LRMS (ESI$^+$): *m/z*: 290 ($[M+NH_4]^+$, 100%), 255 ($[M-OH]^{+\bullet}$, 70%).

HRMS (ESI$^+$): Found *m/z*: 295.0858 $[M+Na]^+$. Calculated 295.0860 Da.

IR (ATR): ν_{max}/ cm^{-1} 3363brm (OH), 3085w (=C-H), 3062w (=C-H), 3028m (=C-H), 3009w (=C-H), 2965w (C-H), 2900m (C-H), 2842w (C-H), 1602w (C=C), 1453s (Ar), 1428m (Ar), 1406m (Ar), 1090m (C-O), 1015s, 970s, 699s.

5.4.5.5 - (*E*)-1-(2-bromopenta-2,4-dien-1-yl)-4-chlorobenzene (411)



$C_{11}H_{10}BrCl$ (257.55) Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. 4-Chlorobenzyl chloride (161 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C and then allowed to warm to RT, stirring for 2 hours at RT. The reaction was cooled to -90 °C and *cis*-1,4-dichloro-2-butene (0.11 mL, 1.0 mmol) was added dropwise followed by LDA [*n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes to a stirring solution of *i*-Pr_2NH (0.34 mL, 2.4 mmol) in THF (2 mL) at 0 °C and stirred for 15 minutes] dropwise over 2 minutes and stirred for 30 minutes at low temperature (-90 to -70 °C). NBS (428 mg, 2.4 mmol) in THF (5 mL) was added at -70 °C and the reaction was stirred for 1 hour allowing to warm to -50 °C. The

reaction was quenched with 2 M $HCl_{(aq)}$ (2 mL) at -50 °C and stirred for 1 hour at 0 °C. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined, washed with 2 M $HCl_{(aq)}$ (50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* at 0 °C. The compound was purified by column chromatography using 100% hexane over silica followed by HPLC using 100% hexane on a LiChrospher® Si60 column (10 µm, 25 cm x 10 mm at 5 mL min^{-1}) to afford the title compound as a colourless oil (31 mg, 0.12 mmol, 12%).

GC (AP40): Rt 6.77 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.29 (2 H, d*, *J* 8.4 Hz, H, Hh), 7.15 (2 H, d*, *J* 8.3 Hz, Hg), 6.66 (1 H, dt, *J* 11.0, 0.6 Hz, Hc), 6.55 (1 H, ddd, *J* 16.5, 11.0, 10.0 Hz, Hb), 5.34 (1 H, dd, *J* 16.4, 1.4 Hz, Ha_1), 5.24 (1 H, dd, *J* 10.0, 1.5 Hz, Ha_2), 3.89 (2 H, s, He).

*Doublet with second order effects.

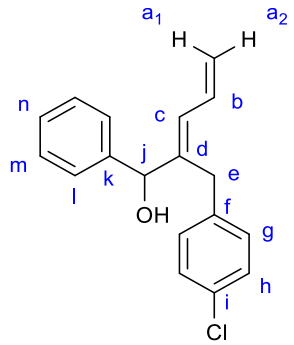
^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 135.99 (C, Cf/i), 134.36 (CH, Cc), 132.90 (C, Ci/f), 131.17 (CH, Cb), 130.07 (2 CH, Cg), 128.88 (2 CH, Ch), 126.60 (C, Cd), 119.79 (CH_2, Ca), 41.52 (CH_2, Ce).

LRMS (EI): *m/z*: 256 ($[M]^{+\bullet}$, 12%), 177 ($[M\text{-}Br]^{+\bullet}$, 36%), 162 (18%), 142 ([M-Br&Cl]$^{+\bullet}$, 100%), 125 ($[C_7H_6Cl]^{+\bullet}$, 16%), 115 (43%), 101 (8%), 89 (23%).

HRMS (APPI): Found *m/z*: 255.9648 $[M]^+$. Calculated 255.9649 Da.

IR (ATR): ν_{max}/ cm^{-1} 3088w (=C-H), 3061w (=C-H), 3029w (=C-H), 3012w (=C-H), 2972w (C-H), 2921w (C-H), 1630m (C=C), 1595w (C=C), 1489s (Ar), 1427m (Ar), 1415m (C-H), 1089s, 1015s, 981s, 911s, 639s, 550s.

5.4.5.6 - (*E*)-2-(4-Chlorobenzyl)-1-phenylpenta-2,4-dien-1-ol (412)



$C_{18}H_{17}ClO$ (284.78)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2

minutes at -78 °C under nitrogen and stirred for 30 minutes. 4-Chlorobenzyl chloride (161 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C and then allowed to warm to RT, stirring for 2 hours at RT. The reaction was cooled to -90 °C and *cis*-1,4-dichloro-2-butene (0.11 mL, 1.0 mmol) in THF (1 mL) was added dropwise followed by LDA [*n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes to a stirring solution of *i*-Pr_2NH (0.34 mL, 2.4 mmol) in THF (2 mL) at 0 °C and stirred for 15 minutes] dropwise over 2 minutes, stirred for 30 minutes at low temperature and then at 10 °C overnight (16 hours). The reaction was subsequently placed under vacuum for solvent removal, re-dissolved in CH_2Cl_2 (6 mL) and cooled to -65 °C. Diethyl zinc (1 M in hexanes, 1.5 mL, 1.5 mmol) was added dropwise over 5 minutes. The reaction was cooled to 0 °C and benzaldehyde (0.15 mL, 1.5 mmol) in CH_2Cl_2 (2 mL) was added dropwise over 10 minutes. The reaction was stirred at RT for 17 hours. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ (4 mL) and stirred for 1 hour at RT. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined, washed with 2 M HCl $_{(aq)}$ (50 mL), brine (50 mL), dried over $MgSO_4$, filtered through florisil® and concentrated *in vacuo*. The compound was purified by column chromatography using 10% EtOAc in hexane over silica followed by 25% hexane in CH_2Cl_2 over silica to afford the title compound as a yellow oil (89 mg, 0.31 mmol, 31%).

GC (AP40): Rt 9.26 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.37 – 7.26 (5 H, m, ArH), 7.20 (2 H, d*, *J* 8.4 Hz, Hh), 7.03 (2 H, d*, *J* 8.5 Hz, Hg), 6.65 (1 H, ddd, *J* 16.5, 11.0, 10.1 Hz, Hb), 6.53 (1 H, d, *J* 11.0 Hz, Hc), 5.39 (1 H, dd, *J* 16.5, 2.0 Hz, Ha_1), 5.24 (1 H, dd, *J* 10.0, 2.0 Hz, Ha_2), 5.10 (1 H, d, *J* 3.2 Hz, Hj), 3.61 (1 H, d, *J* 15.4 Hz, He), 3.19 (1 H, d, *J* 15.4 Hz, He), 1.83 (1 H, d, *J* 3.5 Hz, OH).

*Doublets with second order effects.

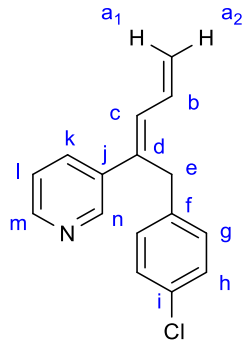
^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 141.99 (C, Ck/d), 141.67 (C, Cd/k), 138.20 (C, Cf/i), 132.43 (CH, Cb), 132.02 (C, Ci/f), 129.93 (2 CH), 128.67 (2 CH), 128.66 (2 CH), 128.08 (CH, Cc/Cn), 127.63 (CH, Cc/Cn), 127.02 (2 CH), 119.54 (CH_2, Ca), 76.96 (CH, Cj), 33.34 (CH_2, Ce).

LRMS (CI): *m/z:* 285 ($[M+H]^{+\bullet}$, 8%), 267 ($[M-OH]^{+\bullet}$, 100%), 231 (5%), 159 (62%), 141 (14%), 125 ($[C_7H_6Cl]^{+\bullet}$, 22%), 115 (13%), 105 (37%).

HRMS (EI): Found *m/z*: 284.0960 $[M]^{+\bullet}$. Calculated 284.0962 Da.

IR (ATR): ν_{max}/ cm^{-1} 3351brm (OH), 3084w (=C-H), 3062w (=C-H), 3028w (=C-H), 2972w (C-H), 2922w (C-H), 2861w (C-H), 1647w (C=C), 1599w (C=C), 1574w (C=C), 1489s (Ar), 1452m (Ar), 1418m (C-H), 1090s (C-O), 1014s, 988s, 911s, 699s.

5.4.5.7 - (*E*)-3-(1-(4-Chlorophenyl)penta-2,4-dien-2-yl)pyridine (413)



$C_{16}H_{14}ClN$ (255.74)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. Benzyl chloride (127 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C and then allowed to warm to RT, stirring for 2 hours at RT. The reaction was cooled to -90 °C and *cis*-1,4-dichloro-2-butene (0.12 mL, 1.1 mmol) was added dropwise followed by LDA [*n*-BuLi (2.5 M in hexanes, 0.84 mL, 2.2 mmol) was added dropwise over 2 minutes to a stirring solution of *i*-Pr_2NH (0.34 mL, 2.4 mmol) in THF (2 mL) at 0 °C and stirred for 15 minutes] dropwise over 2.5 minutes and stirred for 30 minutes at low temperature (-90 to -70 °C). The reaction was warmed to RT and zinc chloride (1.5 M in THF, 1.0 mL, 1.5 mmol) was added dropwise over 1 minute and stirred at RT for 1 hour. The reaction mixture was transferred to a stirring solution of $Pd(PPh_3)_4$ (69 mg, 0.06 mmol) and degassed 3-bromopyridine (0.12 mL, 1.2 mmol) in THF (5 mL). The reaction was refluxed at 75 °C for 16 hours, allowed to cool to RT, quenched with sat. $NaHCO_{3\,(aq)}$ (4 mL) and stirred for 1 hour at RT. The reaction mixture was poured into water (50 mL) and extracted with EtOAc (4× 50 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 1% Et_3N with 29% EtOAc in hexane over silica followed by 5% EtOAc in CH_2Cl_2 over silica to afford the title compound as a pale pink oil (84 mg, 0.33 mmol, 33%).

GC (AP40): Rt 8.79 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 8.64 (1 H, dd, *J* 2.4, 0.7 Hz, Hn), 8.44 (1 H, dd, *J* 4.8, 1.6 Hz, Hm), 7.61 (1 H, ddd, *J* 8.0, 2.4, 1.6 Hz, Hk), 7.21 (2 H, d*, *J* 8.5 Hz, Hh), 7.18 (1 H, ddd, *J* 8.0, 4.8, 0.8 Hz, Hl), 7.09 (2 H, d*, *J* 8.6 Hz, Hg), 6.77 (1 H, ddd, *J* 16.4, 10.9, 10.0 Hz, Hb), 6.66 (1 H, d, *J* 11.0 Hz, Hc), 5.50 (1 H, dd, *J* 16.4, 1.6 Hz, Ha_1), 5.34 (1 H, dd, *J* 9.9, 1.6 Hz, Ha_2), 3.96 (2 H, s, He).

*Doublets with second order effects.

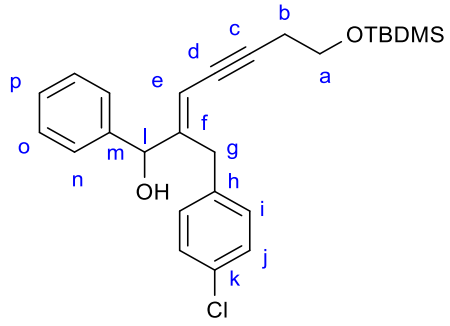
^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 148.53 (CH, Cm), 147.82 (CH, Cn), 137.32 (C, Cj/Cd), 137.26 (C, Cj/Cd), 135.72 (C, Cf/i), 133.50 (CH, Ck), 132.71 (CH, Cb), 132.29 (C, Ci/f), 131.42 (CH, Cc), 129.63 (2 CH, Cg/h), 128.90 (2 CH, Ch/g), 123.29 (CH, Cl), 120.96 (CH_2, Ca), 35.05 (CH_2, Ce).

LRMS (ESI$^+$): *m/z*: 256 ($[M+H]^+$, 100%).

HRMS (ESI$^+$): Found *m/z*: 256.0888 $[M+H]^+$. Calculated 256.0888 Da.

IR (ATR): ν_{max}/ cm^{-1} 3083w (=C-H), 3028m (=C-H), 2926w (C-H), 2868w (C-H), 1672w (C=C), 1626w (C=C), 1582w (C=C), 1563m (C=C), 1489s (Ar), 144m5 (Ar), 1424m (C-H), 1090s, 1014s, 911s, 810s, 707s.

5.4.5.8 - (*E*)-7-((*tert*-Butyldimethylsilyl)oxy)-2-(4-chlorobenzyl)-1-phenylhept-2-en-4-yn-1-ol (415)



$C_{26}H_{33}ClO_2Si$ (441.08)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. 4-Chlorobenzyl chloride (161 mg, 1.0 mmol) in THF (2 mL) was added dropwise over 10 minutes at -78 °C and then allowed to warm to RT, stirring for 2 hours at RT. The reaction was cooled to -90 °C and enyne **397** (245 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise over 1 minute to a stirring solution of *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C and stirred for 15

minutes] dropwise over 1 minute, stirred for 30 minutes at low temperature (-90 to -70 °C). The reaction was subsequently placed under vacuum for solvent removal, re-dissolved in CH_2Cl_2 (6 mL) and cooled to -65 °C. Diethyl zinc (1 M in hexanes, 1.5 mL, 1.5 mmol) was added dropwise over 5 minutes followed by benzaldehyde (0.15 mL, 1.5 mmol) in CH_2Cl_2 (2 mL) dropwise over 10 minutes at 0 °C and stirred at RT for 15 hours. The reaction was re-treated with $ZnEt_2$ (1 M in Hexanes, 0.75 mL, 0.75 mmol) and benzaldehyde (0.08 mL, 0.75 mmol) at RT and under nitrogen, stirred at RT for 72 hours. The reaction was quenched with 2 M $HCl_{(aq)}$ (4 mL), stirred for 1 hour at RT. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3× 50 mL). The organic phases were combined, washed with 2 M $HCl_{(aq)}$ (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 15% EtOAc in hexane over silica, followed by 10-20% Et_2O in hexane over silica, 70-90% CH_2Cl_2 in hexane over silica and finally by HPLC using 1% IPA in hexane on a LiChrospher® Si60 column (10 µm, 25 cm x 10 mm at 5 mL min^{-1}) to afford the title compound as a colourless oil (155 mg, 0.35 mmol, 35%).

GC (AP40L): Rt 13.53 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 7.32 (3 H, m, ArH), 7.25 (2 H, m, ArH), 7.21(2 H, d*, *J* 8.5 Hz, Hj), 7.15 – 7.08 (2 H, d*, *J* 8.5 Hz, Hi), 5.94 (1 H, q, *J* 2.0 Hz, He), 5.04 (1 H, br d, *J* 3.7 Hz, Hl), 3.82 (1 H, d, *J* 14.4 Hz, Hg), 3.73 (2 H, t, *J* 7.1 Hz, Ha), 3.15 (1 H, d, *J* 14.5 Hz, Hg), 2.56 (2 H, td, *J* 7.1, 2.2 Hz, Hb), 1.78 (1 H, d, *J* 3.7 Hz, OH), 0.88 (9 H, s, *t*Bu), 0.05 (6 H, s, $SiMe_2$).

*Doublets with second order effects.

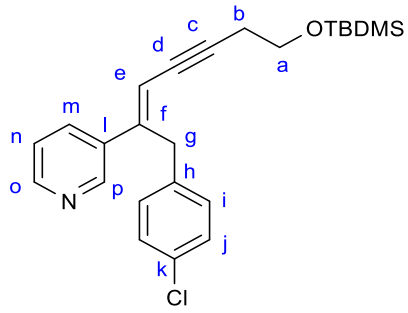
^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 152.60 (C, Cf), 141.45 (C, Cm), 137.93 (C, Ch/k), 132.10 (C, Ck/h), 130.28 (2 CH, Ci), 128.78 (2 CH, Ar), 128.60 (2 CH, Ar), 128.33 (CH, Cp), 127.18 (2 CH, Ar), 107.67 (CH, Ce), 92.08 (C, Cc/d), 78.91 (C, Cc/d), 75.75 (CH, Cl), 62.09 (CH_2, Ca), 35.99 (CH_2, Cg), 26.01 (3 CH_3, *t*Bu), 24.20 (CH_2, Cb), 18.45 (C, *t*Bu), -5.15 (2 CH_3, $SiMe_2$).

LRMS (CI): *m/z*: 441 ($[M+H]^{+\bullet}$, 1%), 425 (5%), 391 (6%), 367 (5%), 309 (6%), 295 ($M-CH_2OTBDMS]^{+\bullet}$, 23%), 261 (17%), 167 (23%), 125 ($[C_7H_6Cl]^{+\bullet}$, 36%), 91 ($[C_7H_7]$, 100%).

HRMS (APPI) Found *m/z*: 440.1929 $[M]^+$. Calculated 440.1933 Da.

IR (ATR): ν_{max}/ cm^{-1} 3421brw (OH), 3063w (=C-H), 3029w (=C-H), 2954m (C-H), 2929m (C-H), 2883m (C-H), 2856m (C-H), 1601vw (C=C), 1490m (Ar), 1471w (Ar), 1463w (Ar), 1455w (Ar), 1432w (C-H), 1255m, 1092s (C-O), 906s, 835s, 729s, 700s.

5.4.5.9 - (*E*)-3-(7-((*tert*-Butyldimethylsilyl)oxy)-1-(4-chlorophenyl)hept-2-en-4-yn-2-yl)pyridine (416)



$C_{24}H_{30}ClNOSi$ (412.05)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. 4-Chlorobenzyl chloride (161 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C and then allowed to warm to RT, stirring for 2 hours at RT. The reaction was cooled to -90 °C and enyne **397** (245 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise over 1 minute to a stirring solution of *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C and stirred for 15 minutes] dropwise over 1 minute and stirred for 30 minutes at low temperature (-90 to -70 °C). The reaction was warmed to RT, zinc chloride (1.4 M in THF, 1.1 mL, 1.5 mmol) was added and the reaction was stirred at RT for 1 hour. The reaction mixture was transferred to a stirring solution of $Pd(PPh_3)_4$ (69 mg, 0.06 mmol) and degassed 3-bromopyridine (0.15 mL, 1.5 mmol) in THF (5 mL) and refluxed at 85 °C for 22 hours. The reaction mixture was allowed to cool to RT, poured into water (50 mL) and extracted with EtOAc (4× 50 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified twice by column chromatography using 1% Et_3N, 20% EtOAc in hexane over silica followed by 5% EtOAc in CH_2Cl_2 over silica to afford the title compound as a pale yellow oil (183 mg, 0.44 mmol, 44%).

GC (AP40L): Rt 12.50 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 8.59 (1 H, dd, *J* 2.4, 0.8 Hz, Hp), 8.44 (1 H, dd, *J* 4.8, 1.6 Hz, Ho), 7.56 (1 H, ddd, *J* 8.0, 2.4, 1.6 Hz, Hm), 7.21

– 7.15 (3 H, m, Hj & Hn), 7.13 (2 H, d*, *J* 8.7 Hz, Hi), 6.03 (1 H, t, *J* 2.2 Hz, He), 4.08 (2 H, s, Hg), 3.76 (2 H, t, *J* 7.0 Hz, Ha), 2.62 (2 H, td, *J* 7.0, 2.2 Hz, Hb), 0.89 (9 H, s, *t*Bu), 0.06 (6 H, s, $SiMe_2$).
*Doublet with second order effects.

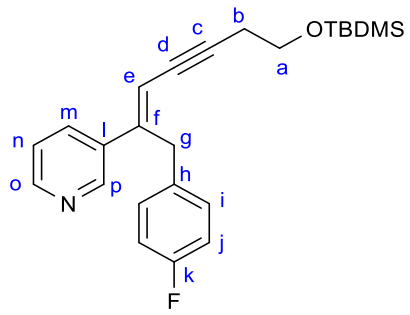
^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 149.12 (CH, Co), 147.52 (CH, Cp), 146.38 (C, Cf), 137.09 (C, Cl), 135.32 (C, Ch/k), 133.32 (CH, Cm), 132.19 (C, Ck/h), 129.87 (2 CH, Ci), 128.78 (2 CH, Cj), 123.31 (CH, Cn), 111.01 (CH, Ce), 94.39 (C, Cc/d), 79.36 (C, Cc/d), 61.94 (CH_2, Ca), 37.37 (CH_2, Cg), 25.99 (3 CH_3, *t*Bu), 24.31 (CH_2, Cb), 18.44 (C, *t*Bu), -5.16 (2 CH_3, $SiMe_2$).

LRMS (ESI$^+$): *m/z*: 412 ($[M+H]^+$, 100%).

HRMS (ESI$^+$): Found *m/z*: 412.1866 $[M+H]^+$. Calculated 412.1858 Da.

IR (ATR): ν_{max}/ cm^{-1} 3031w (=C-H), 2953m (C-H), 2928m (C-H), 2883m (C-H), 2855m (C-H), 2212w (C≡C), 1597w (Ar), 1583w (Ar), 1564w (Ar), 1490m (Ar), 1471m (Ar), 1463m (Ar), 1436m (Ar), 1413m (Ar), 1407m (Ar), 1254m, 1092s (C-O), 833s, 774s, 706s.

5.4.5.10 - (*E*)-3-(7-((*tert*-Butyldimethylsilyl)oxy)-1-(4-fluorophenyl)hept-2-en-4-yn-2-yl)pyridine (418)



$C_{24}H_{30}FNOSi$ (395.59)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. 4-Fluorobenzyl chloride (145 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C and then allowed to warm to RT, stirring for 2 hours at RT. The reaction was cooled to -90 °C and enyne **397** (245 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise over 1 minute to a stirring solution of *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C and stirred for 15 minutes] dropwise over 1 minute and stirred for 30 minutes at low temperature (-90 to -70 °C). The reaction was warmed to RT, zinc chloride (1.4 M in THF, 1.1 mL, 1.5 mmol) was added and the reaction

was stirred at RT for 1 hour. The reaction mixture was transferred to a stirring solution of $Pd(PPh_3)_4$ (69 mg, 0.06 mmol) and degassed 3-bromopyridine (0.15 mL, 1.5 mmol) in THF (5 mL) and refluxed at 85 °C for 23 hours. The reaction mixture was allowed to cool to RT, poured into water (50 mL) and extracted with EtOAc (4× 50 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified twice by column chromatography using 1% Et_3N, 20% EtOAc in hexane over silica followed by 5% EtOAc in CH_2Cl_2 over silica to afford the title compound as a pale yellow oil (169 mg, 0.43 mmol, 43%).

GC (AP40L): Rt 11.07 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 8.59 (1 H, d, *J* 2.0 Hz, Hp), 8.44 (1 H, dd, *J* 4.7, 1.4 Hz, Ho), 7.57 (1 H, ddd, *J* 8.0, 2.3, 1.7 Hz, Hm), 7.20 – 7.09 (3 H, m, Hi & Hn), 6.90 (2 H, t*, *J* 8.7 Hz, Hj), 6.01 (1 H, t, *J* 2.2 Hz, He), 4.09 (2 H, s, Hg), 3.77 (2 H, t, *J* 7.0 Hz, Ha), 2.62 (2 H, td, *J* 7.0, 2.2 Hz, Hb), 0.89 (9 H, s, *t*Bu), 0.06 (6 H, s, $SiMe_2$).
*Triplet with second order effects.

^{13}C-NMR: δ_C (101 MHz, $CDCl_3$) 161.63 (d, *J* 244.3 Hz, C, Ck), 149.08 (CH, Co), 147.59 (CH, Cp), 146.81 (C, Cf), 135.48 (C, Cl), 134.25 (d, *J* 3.2 Hz, C, Ch), 133.37 (CH, Cm), 129.95 (d, *J* 7.8 Hz, 2 CH, Ci), 123.30 (CH, Cn), 115.46 (d, *J* 21.3 Hz, 2 CH, Cj), 110.81 (CH, Ce), 94.22 (C, Cc/d), 79.43 (C, Cc/d), 61.98 (CH_2, Ca), 37.25 (CH_2, Cg), 26.00 (3 CH_3, *t*Bu), 24.33 (CH_2, Cb), 18.45 (C, *t*Bu), -5.16 (2 CH_3, $SiMe_2$).

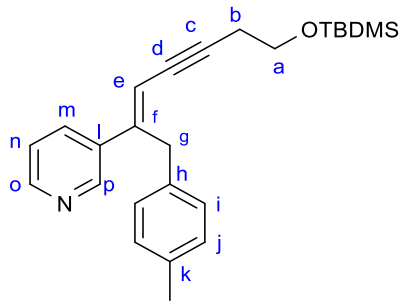
^{19}F-NMR: δ_F ppm (376 MHz, $CDCl_3$) -117.10.

LRMS (ESI$^+$): *m/z*: 396 ($[M+H]^+$, 100%).

HRMS (ESI$^+$): Found *m/z*: 396.162$[M+H]^+$. Calculated 396.2153 Da.

IR (ATR): ν_{max}/ cm^{-1} 3036w (=C-H), 2953m (C-H), 2928m (C-H), 2883m (C-H), 2956m (C-H), 2214w (C≡C), 1604m (C=C), 1564w (Ar), 1507s (Ar), 1471m (Ar), 1463m (Ar), 1439m (C-H), 1254s, 1221s (C-F), 1095s (C-O), 833s, 775s.

5.4.5.11 - (*E*)-3-(7-((*tert*-Butyldimethylsilyl)oxy)-1-(p-tolyl)hept-2-en-4-yn-2-yl)pyridine (419)



$C_{25}H_{33}NOSi$ (391.63)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. 4-Methylbenzyl chloride (141 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C and then allowed to warm to RT, stirring for 2 hours at RT. The reaction was cooled to -90 °C and enyne **397** (245 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise over 1 minute to a stirring solution of *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C and stirred for 15 minutes] dropwise over 1 minute and stirred for 30 minutes at low temperature (-90 to -70 °C). The reaction was warmed to RT, zinc chloride (1.4 M in THF, 1.1 mL, 1.5 mmol) was added and the reaction was stirred at RT for 1 hour. The reaction mixture was transferred to a stirring solution of $Pd(PPh_3)_4$ (69 mg, 0.06 mmol) and degassed 3-bromopyridine (0.15 mL, 1.5 mmol) in THF (5 mL) and refluxed at 85 °C for 16 hours. The reaction mixture was allowed to cool to RT, poured into water (50 mL) and extracted with EtOAc (4× 50 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified twice by column chromatography using 1% Et_3N, 20% EtOAc in hexane over silica followed by 5% EtOAc in CH_2Cl_2 over silica to afford the title compound as a pale yellow oil (116 mg, 0.30 mmol, 30%).

GC (AP40L): Rt 11.67 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 8.61 (1 H, d, *J* 1.8, Hp), 8.43 (1 H, dd, *J* 4.8, 1.5, Ho), 7.59 (1 H, ddd, *J* 8.0, 2.4, 1.6, Hm), 7.15 (1 H, ddd, *J* 8.0, 4.8, 0.8, Hn), 7.09 (2 H, d, *J* 8.1, ArH), 7.03 (2 H, d, *J* 7.9, ArH), 6.01 (1 H, t, *J* 2.2, He), 4.08 (2 H, s, Hg), 3.77 (2 H, t, *J* 7.1, Ha), 2.62 (2 H, td, *J* 7.1, 2.2, Hb), 2.27 (3 H, s, Me), 0.90 (9 H, s, *t*Bu), 0.07 (6 H, s, $SiMe_2$).

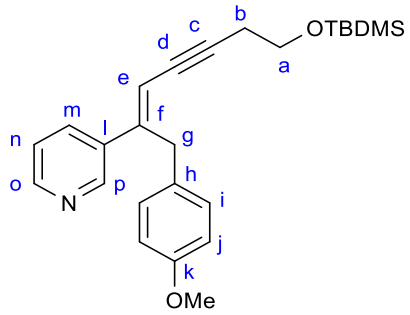
^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 148.91 (CH, Co), 147.62 (CH, Cp), 147.13 (C, Cf), 135.89 (C, Ch/k/l), 135.69 (C, Ch/k/l), 135.49 (C, Ch/k/l), 133.41 (CH, Cm), 129.34 (2 CH, Ci/j), 128.42 (2 CH, Ci/j), 123.23 (CH, Cn), 110.47 (CH, Ce), 93.79 (C, Cc/d), 79.61 (C, Cc/d), 62.03 (CH_2, Ca), 37.61 (CH_2, Cg), 26.01 (C, *t*Bu), 24.32 (CH_2, Cb), 21.12 (CH_3, Me), 18.46 (3 CH_3, *t*Bu), -5.15 (2 CH_3, $SiMe_2$).

LRMS (ESI$^+$): *m/z*: 392 ($[M+H]^+$, 100%).

HRMS (ESI$^+$): Found *m/z*: 392.2408 $[M+H]^+$. Calculated 392.2404 Da.

IR (ATR): ν_{max}/ cm^{-1} 3023w (=C-H), 2953m (C-H), 2927m (C-H), 2883m (C-H), 2886m (C-H), 2214w (C≡C), 1601w (C=C), 1583w (C=C), 1564w (Ar), 1513m (Ar), 1471m (Ar), 1463m (Ar), 1440m (Ar), 1253m (Ar), 1098s (C-O), 832s, 771s.

5.4.5.12 - (*E*)-3-(7-((*tert*-Butyldimethylsilyl)oxy)-1-(4-methoxyphenyl)hept-2-en-4-yn-2-yl)pyridine (420)



$C_{25}H_{33}NO_2Si$ (407.63)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. 4-Methoxybenzyl chloride (157 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C and then allowed to warm to RT, stirring for 2 hours at RT. The reaction was cooled to -90 °C and enyne **397** (245 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise over 1 minute to a stirring solution of *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C and stirred for 15 minutes] dropwise over 1 minute and stirred for 30 minutes at low temperature (-90 to -70 °C). The reaction was warmed to RT, zinc chloride (1.4 M in THF, 1.1 mL, 1.5 mmol) was added and the reaction was stirred at RT for 1 hour. The reaction mixture was transferred to a stirring solution of $Pd(PPh_3)_4$ (69 mg, 0.06 mmol) and degassed 3-bromopyridine (0.15 mL, 1.5 mmol) in THF (5 mL) and refluxed at 85 °C for 22 hours. The reaction mixture was allowed to cool to RT,

poured into water (50 mL) and extracted with EtOAc (4× 50 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified twice by column chromatography using 1% Et_3N, 20% EtOAc in hexane over silica followed by 8% EtOAc in CH_2Cl_2 over silica to afford the title compound as a pale yellow oil (133 mg, 0.33 mmol, 33%).

GC (AP40L): Rt 12.89 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 8.61 (1 H, d, *J* 1.9 Hz, Hp), 8.43 (1 H, dd, *J* 4.8, 1.5 Hz, Ho), 7.58 (1 H, ddd, *J* 8.0, 2.4, 1.6 Hz, Hm), 7.15 (1 H, ddd, *J* 8.1, 4.8, 0.7 Hz, Hn), 7.12 (2 H, d*, *J* 8.8 Hz, ArH), 6.76 (2 H, d*, *J* 8.7 Hz, ArH), 5.99 (1 H, t, *J* 2.2 Hz, He), 4.06 (2 H, s, Hg), 3.77 (2 H, t, *J* 7.1 Hz, Ha), 3.74 (3 H, s, Me), 2.62 (2 H, td, *J* 7.1, 2.2 Hz, Hb), 0.89 (9 H, s, *t*Bu), 0.07 (6 H, s, $SiMe_2$).

*Doublets with second order effects.

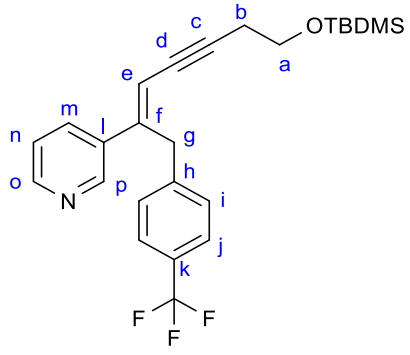
^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 158.19 (C, Ck), 148.91 (CH, Co), 147.63 (CH, Cp), 147.33 (C, Cf), 135.70 (C, Ch/l), 133.43 (CH, Cm), 130.61 (C, Ch/l), 129.51 (2 CH, Ci/j), 123.24 (CH, Cn), 114.06 (2 CH, Ci/j), 110.32 (CH, Ce), 93.75 (C, Cc/d), 79.59 (C, Cc/d), 62.03 (CH_2, Ca), 55.31 (CH_3, OMe), 37.17 (CH_2, Cg), 26.01 (3 CH_3, *t*Bu), 24.32 (CH_2, Cb), 18.46 (C, *t*Bu), -5.15 (2 CH_3, $SiMe_2$).

LRMS (ESI$^+$): *m/z*: 408 ($[M+H]^+$, 100%).

HRMS (ESI$^+$): Found *m/z*: 408.2362$[M+H]^+$. Calculated 408.2353 Da.

IR (ATR): ν_{max}/ cm^{-1} 3031w (=C-H), 3003w (=C-H), 2952m (C-H), 2928m (C-H), 2855m (C-H), 2213w (C≡C), 1601m (C=), 1583w (C=C), 1564w (Ar), 1510s (Ar), 1471m (Ar), 1463m (Ar), 1441m (Ar), 1245s, 1176m, 1098s (C-O), 832s, 775s.

5.4.5.13 - (*E*)-3-(7-((*tert*-Butyldimethylsilyl)oxy)-1-(4-(trifluoromethyl)phenyl)hept-2-en-4-yn-2-yl)pyridine (421)



$C_{25}H_{30}F_3NOSi$ (445.60)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. 4-(Trifluoromethyl)benzyl chloride (195 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C and then allowed to warm to RT, stirring for 70 minutes at RT. The reaction was cooled to -90 °C and enyne **397** (245 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) added dropwise over 1 minute to a stirring solution of *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C and stirred for 15 minutes] dropwise over 1 minute, stirred for 30 minutes at low temperature (-90 to -70 °C) and then at RT for 16 hours. Zinc chloride (1.4 M in THF, 1.1 mL, 1.5 mmol) was added and stirred at RT for 1 hour. The reaction mixture was transferred to a stirring solution of $Pd(PPh_3)_4$ (69 mg, 0.06 mmol) and degassed 3-bromopyridine (0.15 mL, 1.5 mmol) in THF (5 mL) and refluxed at 85 °C for 28 hours. The reaction mixture was allowed to cool to RT, poured into water (50 mL) and extracted with EtOAc (4× 50 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 1% Et_3N, 20% EtOAc in hexane over silica to afford the title compound as a pale yellow oil (162 mg, 0.36 mmol, 36%).

GC (AP40L): Rt 10.73 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 8.60 (1 H, d, *J* 2.0 Hz, Hp), 8.46 (1 H, dd, *J* 4.7, 1.3 Hz, Ho), 7.58 (1 H, ddd, *J* 8.0, 2.4, 1.6 Hz, Hm), 7.48 (2 H, d, *J* 8.1 Hz, ArH), 7.32 (2 H, d, *J* 8.0 Hz, ArH), 7.18 (1 H, ddd, *J* 8.0, 4.8, 0.6 Hz, Hn), 6.08 (1 H, t, *J* 2.2 Hz, He), 4.18 (2 H, s, Hg), 3.76 (2 H, t, *J* 6.9 Hz, Ha), 2.62 (2 H, td, *J* 6.9, 2.2 Hz, Hb), 0.88 (9 H, s, *t*Bu), 0.05 (6 H, s, $SiMe_2$).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 149.22 (CH, Co), 147.45 (CH, Cp), 145.78 (C), 142.79 (q, *J* 1.2 Hz, C, Ch), 135.17 (C), 133.26 (CH, Cm), 128.81 (q, *J* 32.4 Hz, C, Ck), 128.80 (2 CH, Ci), 125.61 (q, *J* 3.8 Hz, 2 CH, Cj), 123.41 (CH, Cn), 111.46 (CH, Ce), 94.76 (C, Cc/d), 79.29 (C, Cc/d), 61.91 (CH_2, Ca), 37.80 (CH_2, Cg), 25.97 (3 CH_3, *t*Bu), 24.31 (CH_2, Cb), 18.43 (C, *t*Bu), -5.19 (2 CH_3, $SiMe_2$).

*Peak corresponding to one of the CF_3 quartet signal observed at 122.96 ppm but other remaining peaks of the quartet were not visible.

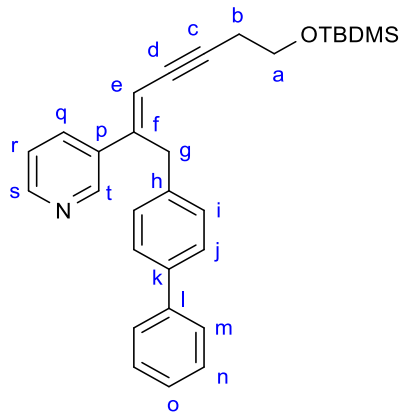
^{19}F-NMR: δ_F ppm (376 MHz, $CDCl_3$) -62.68.

LRMS (ESI$^+$): *m/z*: 446 ($[M+H]^+$, 100%).

HRMS (ESI$^+$): Found *m/z*: 446.2131 $[M+H]^+$. Calculated 446.2122 Da.

IR (ATR): ν_{max}/ cm^{-1} 3032w (=C-H), 2954m (C-H), 2929m (C-H), 2884m (C-H), 2857m (C-H), 2213w (C≡C), 1617m (C=C), 1584w (C=C), 1565w (Ar), 1472w (Ar), 1464w (Ar), 1414w (C-H), 1322s (C-F), 1106s (C-O), 1066s, 833s, 776s.

5.4.5.14 - (*E*)-3-(1-([1,1'-Biphenyl]-4-yl)-7-((*tert*-butyldimethylsilyl)oxy)hept-2-en-4-yn-2-yl)pyridine (422)



$C_{30}H_{35}NOSi$ (453.70)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. 4-Phenylbenzyl chloride (203 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C and then allowed to warm to RT, stirring for 2 hours at RT. The reaction was cooled to -90 °C and enyne **397** (245 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise over 1 minute to a stirring solution of *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C and stirred for 15 minutes] dropwise over 1 minute and stirred for 30 minutes at low temperature (-90 to -70 °C). The reaction was

warmed to RT, zinc chloride (1.5 M in THF, 1.0 mL, 1.5 mmol) was added and the reaction was stirred at RT for 1 hour. The reaction mixture was transferred to a stirring solution of $Pd(PPh_3)_4$ (69 mg, 0.06 mmol) and degassed 3-bromopyridine (0.10 mL, 1.0 mmol) in THF (5 mL) and refluxed at 85 °C for 24 hours. The reaction mixture was allowed to cool to RT, poured into water (50 mL) and extracted with EtOAc (4× 50 mL). The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The compound was purified by column chromatography using 1% Et_3N, 20% EtOAc in hexane over silica followed by 5% EtOAc in CH_2Cl_2 over silica to afford the title compound as a yellow solid (209 mg, 0.46 mmol, 46%).

^{1}H-NMR: δ_H (400 MHz, $CDCl_3$) 8.66 (1 H, d, *J* 1.9 Hz, Ht), 8.45 (1 H, dd, *J* 4.8, 1.5 Hz, Hs), 7.63 (1 H, ddd, *J* 8.0, 2.4, 1.6 Hz, Hq), 7.56 – 7.51 (2 H, m, ArH), 7.49 – 7.43 (2 H, m, ArH), 7.43 – 7.37 (2 H, m, ArH), 7.32 (1 H, m, ArH), 7.28 (2 H, d, *J* 8.4 Hz, ArH), 7.18 (1 H, ddd, *J* 8.0, 4.8, 0.8 Hz, Hr), 6.07 (1 H, t, *J* 2.2 Hz, He), 4.17 (2 H, s, Hg), 3.79 (2 H, t, *J* 7.0 Hz, Ha), 2.64 (2 H, td, *J* 7.0, 2.2 Hz, Hb), 0.90 (9 H, s, *t*Bu), 0.07 (6 H, s, $SiMe_2$).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 149.03 (CH, Cs), 147.64 (CH, Ct) , 146.78 (C, Cf), 141.03 (C), 139.38 (C), 137.74 (C), 135.64 (C), 133.43 (CH, Cr), 128.97 (2 CH), 128.84 (2 CH), 127.42 (2 CH), 127.23 (CH), 127.10 (2 CH), 123.31 (CH, Cq), 110.81 (CH, Ce), 94.14 (C, Cc/d), 79.59 (C, Cc/d), 62.03 (CH_2, Ca), 37.71 (CH_2, Cg), 26.03 (3 CH_3, *t*Bu), 24.37 (CH_2, Cb), 18.47 (C, *t*Bu), -5.13 (2 CH_3, $SiMe_2$).

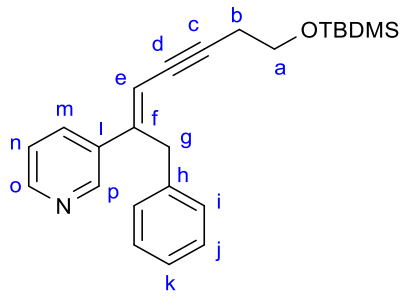
LRMS (ESI$^+$): *m/z*: 454 ($[M+H]^+$, 100%).

HRMS (ESI$^+$): Found *m/z*: 454.2571 $[M+H]^+$. Calculated 454.2561 Da

IR (ATR): ν_{max}/ cm^{-1} 3072w (=C-H), 3043e (=C-H), 3024w (=C-H), 2948 m(C-H), 2929m (C-H), 2897m (C-H), 2855m (C-H), 2210vw (C≡C), 1601w (C=C), 1580w (C=C), 1567w (Ar), 1516w (Ar), 1485m (Ar), 1470m (Ar), 1449m (Ar), 1412m (C-H), 1092s (C-O), 833s, 756s, 697s.

Mp: 102.8 °C.

5.4.5.15 - (*E*)-3-(7-((*tert*-Butyldimethylsilyl)oxy)-1-phenylhept-2-en-4-yn-2-yl)pyridine (423)



$C_{24}H_{31}NOSi$ (377.60)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. Benzyl chloride (127 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C and then allowed to warm to RT, stirring for 2 hours at RT. The reaction was cooled to -90 °C and enyne **397** (245 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise over 1 minute to a stirring solution of *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C and stirred for 15 minutes] dropwise over 1 minute and stirred for 30 minutes at low temperature (-90 to -70 °C). The reaction was warmed to RT, zinc chloride (1.4 M in THF, 1.1 mL, 1.5 mmol) was added and the reaction was stirred at RT for 1 hour. The reaction mixture was transferred to a stirring solution of $Pd(PPh_3)_4$ (69 mg, 0.06 mmol) and degassed 3-bromopyridine (0.15 mL, 1.5 mmol) in THF (5 mL) and refluxed at 85 °C for 19.5 hours. The reaction mixture was allowed to cool to RT, poured into water (50 mL) and extracted with EtOAc (4× 50 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified twice by column chromatography using 1% Et_3N, 20% EtOAc in hexane over silica followed by 5% EtOAc in CH_2Cl_2 over silica to afford the title compound as a pale yellow oil (130 mg, 0.34 mmol, 34%).

GC (AP40L): Rt 11.17 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 8.67 (1 H, dd, *J* 2.4, 0.7 Hz, Hp), 8.48 (1 H, dd, *J* 4.8, 1.6 Hz, Ho), 7.64 (1 H, ddd, *J* 8.0, 2.4, 1.7 Hz, Hm), 7.32 – 7.23 (4 H, m, ArH & Hn), 7.23 – 7.16 (2 H, m, ArH), 6.08 (1 H, t, *J* 2.2 Hz, He), 4.18 (2 H, s, Hg), 3.82 (2 H, t, *J* 7.1 Hz, Ha), 2.67 (2 H, td, *J* 7.1, 2.2 Hz, Hb), 0.94 (9 H, s, *t*Bu), 0.12 (6 H, s, $SiMe_2$).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 148.96 (CH, Co), 147.61 (CH, Cp), 146.88 (C, Cf), 138.61 (C, Ch/l), 135.62 (C, Ch/l), 133.39 (CH, Cm), 128.65

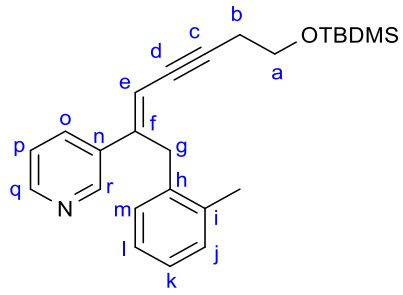
(2 CH, Ci/j), 128.56 (2 CH, Ci/j), 126.41 (CH, Ck), 123.24 (CH, Cn), 110.69 (CH, Ce), 93.96 (C, Cc/d), 79.56 (C, Cc/d), 62.00 (CH_2, Ca), 38.04 (CH_2, Cg), 26.01 (3 CH_3, *t*Bu), 24.32 (CH_2, Cb), 18.45 (C, *t*Bu), -5.16 (2 CH_3, $SiMe_2$).

LRMS (ESI$^+$): *m/z*: 378 ($[M+H]^+$, 100%).

HRMS (ESI$^+$): Found *m/z*: 378.2255 $[M+H]^+$. Calculated 378.2248 Da.

IR (ATR): ν_{max}/ cm^{-1} 3084w (=C-H), 3061w (=C-H), 3028w (=C-H), 2953m (C-H), 2974m (C-H), 2883m (C-H), 2855m (C-H), 2214w (C≡C), 1601w (C=C), 1583w (C=C), 1564w (Ar), 1495m (Ar), 1471m (Ar), 1463m (Ar), 1453m (Ar), 1413m (C-H), 1253m, 1099s (C-O), 833s, 775s, 697s.

5.4.5.16 - (*E*)-3-(7-((*tert*-Butyldimethylsilyl)oxy)-1-(o-tolyl)hept-2-en-4-yn-2-yl)pyridine (424)



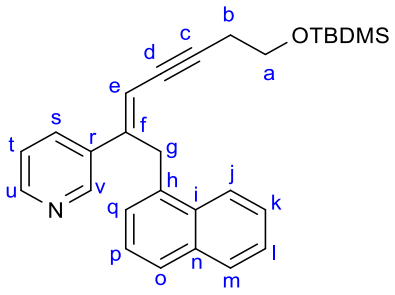
$C_{25}H_{33}NOSi$ (391.63)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. 2-Methylbenzyl chloride (141 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C and then allowed to warm to RT, stirring for 2 hours at RT. The reaction was cooled to -90 °C and enyne **397** (245 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise over 1 minute to a stirring solution of *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C and stirred for 15 minutes] dropwise over 1 minute and stirred for 30 minutes at low temperature (-90 to -70 °C). The reaction was warmed to RT, zinc chloride (1.5 M in THF, 1.0 mL, 1.5 mmol) was added and the reaction was stirred at RT for 1 hour. The reaction mixture was transferred to a stirring solution of $Pd(PPh_3)_4$ (69 mg, 0.06 mmol) and degassed 3-bromopyridine (0.15 mL, 1.5 mmol) in THF (5 mL) and refluxed at 85 °C for 18 hours. The reaction mixture was allowed to cool to RT, poured into water (50 mL) and extracted with EtOAc (4× 50 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was

purified by column chromatography using 5-40% Et_2O in hexane over silica followed by 1% Et_3N, 15% EtOAc in hexane over silica to afford the title compound as a yellow oil (123 mg, 0.33 mmol, 33%).

GC (AP40L):	Rt 11.64 mins.
^{1}H-NMR:	δ_H (400 MHz, $CDCl_3$) 8.57 (1 H, d, *J* 2.0, Hr), 8.42 (1 H, dd, *J* 4.8, 1.4, Hq), 7.52 (1 H, ddd, *J* 8.0, 2.4, 1.7, Ho), 7.14 (1 H, ddd, *J* 7.9, 4.8, 0.6, Hp), 7.12 – 7.02 (4 H, m, ArH), 6.07 (1 H, t, *J* 2.2, He), 4.08 (2 H, s, Hg), 3.73 (2 H, t, *J* 7.1 Ha), 2.59 (2 H, td, *J* 7.1, 2.2, Hb), 2.35 (3 H, s, Me), 0.89 (9 H, s, *t*Bu), 0.06 (6 H, s, $SiMe_2$).
^{13}C-NMR:	δ_C ppm (101 MHz, $CDCl_3$) 148.89 (CH, Cq), 147.50 (CH, Cr), 146.49 (C), 136.48 (C), 136.33 (C), 135.90 (C), 133.39 (CH, Co), 130.28 (CH), 128.46 (CH), 126.40 (CH), 126.20 (CH), 123.21 (CH, Cp), 111.34 (CH, Ce), 94.40 (C, Cc/d), 79.38 (C, Cc/d), 61.98 (CH_2, Ca), 35.47 (CH_2, Cg), 26.00 (3 CH_3, *t*Bu), 24.30 (CH_2, Cb), 20.01 (CH_3, Me), 18.44 (C, *t*Bu), -5.18 (2 CH_3, *t*Bu).
LRMS (ESI$^+$):	*m/z*: 392 ($[M+H]^+$, 100%).
HRMS (ESI$^+$):	Found m/z: 392.2409 $[M+H]^+$. Calculated 392.2404 Da
IR (ATR):	ν_{max}/ cm^{-1} 3026w (=C-H), 3018w (=C-H), 2953m (C-H), 2928m (C-H), 2901m (C-H), 2896m (C-H), 2883m (C-H), 2855m (C-H), 2213w (C≡C), 1604w (C=C), 1583w (C=C), 1490w (Ar), 1471m (Ar), 1462m (Ar), 1413m (C-H), 1098s (C-O), 833s, 775s, 739s.

5.4.5.17 - (*E*)-3-(7-((*tert*-Butyldimethylsilyl)oxy)-1-(naphthalen-1-yl)hept-2-en-4-yn-2-yl)pyridine (425)



$C_{28}H_{33}NOSi$ (427.66)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. 1-Naphthylmethyl chloride (177 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C and then allowed to warm

to RT, stirring for 2 hours at RT. The reaction was cooled to -90 °C and enyne **397** (245 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise over 1 minute to a stirring solution of *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C and stirred for 15 minutes] dropwise over 1 minute, stirred for 30 minutes at low temperature (-90 °C to -70 °C) and then at RT for 16 hours. Zinc chloride (1.4 M in THF, 1.1 mL, 1.5 mmol) was added and stirred at RT for 1 hour. The reaction mixture was transferred to a stirring solution of $Pd(PPh_3)_4$ (69 mg, 0.06 mmol) and degassed 3-bromopyridine (0.15 mL, 1.5 mmol) in THF (5 mL) and refluxed at 85 °C for 28 hours. The reaction mixture was allowed to cool to RT, poured into water (50 mL) and extracted with EtOAc (4× 50 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified twice by column chromatography using 1% Et_3N, 20% EtOAc in hexane over silica followed by 5% EtOAc in CH_2Cl_2 over silica to afford the title compound as a pale yellow oil (163 mg, 0.38 mmol, 38%).

^{1}H-NMR: δ_H (400 MHz, $CDCl_3$) 8.60 (1 H, d, *J* 2.0 Hz, Hv), 8.39 (1 H, dd, *J* 4.8, 1.4 Hz, Hu), 8.20 (1 H, dd, *J* 8.6, 0.8 Hz, Hs), 7.84 (1 H, dd, *J* 8.0, 1.4 Hz, Np), 7.68 (1 H, d, *J* 8.1 Hz, Np), 7.52 (3 H, m, Np), 7.30 (1 H, dd, *J* 8.1, 7.1 Hz, Np), 7.22 (1 H, dd, *J* 7.1, 1.0 Hz, Np), 7.08 (1 H, ddd, *J* 8.0, 4.8, 0.7 Hz, Ht), 6.16 (1 H, t, *J* 2.2 Hz, He), 4.56 (2 H, s, Hg), 3.69 (2 H, t, *J* 7.1 Hz, Ha), 2.57 (2 H, td, *J* 7.1, 2.2 Hz, Hb), 0.85 (9 H, s, *t*Bu), 0.01 (6 H, s, $SiMe_2$).

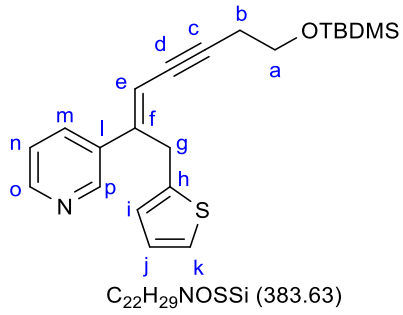
^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 148.90 (CH, Cu), 147.51 (CH, Cv), 146.59 (C, Cf), 135.79 (C), 134.08 (C), 133.94 (C), 133.43 (CH), 132.25 (C), 128.93 (CH, Cm), 127.18 (CH), 126.19 (CH), 126.15 (CH), 125.74 (CH), 125.66 (CH), 123.65 (CH, Cs), 123.17 (CH, Ct), 111.52 (CH, Ce), 94.94 (C, Cc/d), 79.36 (C, Cc/d), 61.96 (CH_2, Ca), 35.17 (CH_2, Cg), 25.99 (3 CH_3, *t*Bu), 24.32 (CH_2, Cb), 18.41 (C, *t*Bu), -5.20 (2 CH_3, $SiMe_2$).

LRMS (ESI$^+$): *m/z*: 428 ($[M+H]^+$, 100%).

HRMS (ESI$^+$): Found *m/z*: 428.2410$[M+H]^+$. Calculated 428.2404 Da.

IR (ATR): ν_{max}/ cm^{-1} 3045w (=C-H), 2953m (C-H), 2927m (C-H), 2897m (C-H), 2882m (C-H), 2855m (C-H), 2213w (C≡C), 1597w (C=C), 1582w (C=C), 1564w (Ar), 1510w (Ar), 1471m (Ar), 1463m (Ar), 1434w (Ar), 1413m (C-H), 1099s (C-O), 834s, 778s, 706m.

5.4.5.18 - (*E*)-3-(7-((*tert*-Butyldimethylsilyl)oxy)-1-(thiophen-2-yl)hept-2-en-4-yn-2-yl)pyridine (426)



$C_{22}H_{29}NOSSi$ (383.63)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. 2-(Chloromethyl)thiophene (133 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C and then allowed to warm to RT, stirring for 2 hours at RT. The reaction was cooled to -90 °C and enyne **397** (245 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise over 1 minute to a stirring solution of *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C and stirred for 15 minutes] dropwise over 1 minute and stirred for 30 minutes at low temperature (-90 to -70 °C). The reaction was warmed to RT, zinc chloride (1.4 M in THF, 1.1 mL, 1.5 mmol) was added and the reaction was stirred at RT for 1 hour. The reaction mixture was transferred to a stirring solution of $Pd(PPh_3)_4$ (69 mg, 0.06 mmol) and degassed 3-bromopyridine (0.15 mL, 1.5 mmol) in THF (5 mL) and refluxed at 85 °C for 18 hours. The reaction mixture was allowed to cool to RT, poured into water (50 mL) and extracted with EtOAc (4× 50 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified twice by column chromatography using 1% Et_3N, 20% EtOAc in hexane over silica followed by 3% EtOAc in CH_2Cl_2 over silica to afford the title compound as a pale yellow oil (156 mg, 0.41 mmol, 41%).

GC (AP40L): Rt 11.31 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 8.66 (1 H, dd, *J* 2.3, 0.6, Hp), 8.47 (1 H, dd, *J* 4.8, 1.6, Ho), 7.65 (1 H, ddd, *J* 8.0, 2.4, 1.6, Hm), 7.20 (1 H, ddd, *J* 8.0, 4.8, 0.8, Hn), 7.07 (1 H, dd, *J* 5.1, 1.2, Hk), 6.85 (1 H, dd, *J* 5.1, 3.5, Hj), 6.80 (1 H, dq, Hi), 5.99 (1 H, t, *J* 2.2, He), 4.28 (2 H, brs, Hg), 3.79 (2 H, t, *J* 7.1, Ha), 2.64 (2 H, td, *J* 7.1, 2.3, Hb), 0.90 (9 H, s, *t*Bu), 0.07 (6 H, s, $SiMe_2$).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 149.13 (CH, Co), 147.53 (CH, Cp), 146.29 (C, Cf), 141.33 (C), 135.26 (C), 133.33 (CH, Cm), 126.91 (CH), 125.38

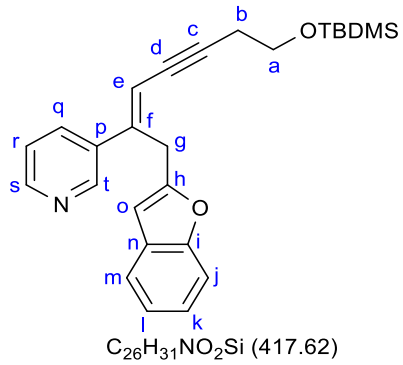
(CH), 123.97 (CH), 123.31 (CH), 110.62 (CH, Ce), 94.83 (C, Cc/d), 79.15 (C, Cc/d), 61.98 (CH_2, Ca), 32.52 (CH_2, Cg), 26.02 (3 CH_3, *t*Bu), 24.35 (CH_2, Cb), 18.46 (C, *t*Bu), -5.15 (2 CH_3, $SiMe_2$).

LRMS (ESI$^+$): *m/z*: 384 ($[M+H]^+$, 100%).

HRMS (ESI$^+$): Found *m/z*: 384.1815$[M+H]^+$. Calculated 384.1812 Da.

IR (ATR): ν_{max}/ cm^{-1} 3032w (=C-H), 2952m (C-H), 2927m (C-H), 2882m (C-H), 2855m (C-H), 2215w (C≡C), 1602vw (C=C), 1583vw (C=C), 1564w (Ar), 1474m (Ar), 1463M (Ar), 1436M (Ar), 1099s (C-O), 832s, 775s, 692s.

5.4.5.19 - (*E*)-3-(1-(Benzofuran-2-yl)-7-((*tert*-butyldimethylsilyl)oxy)hept-2-en-4-yn-2-yl)pyridine (427)



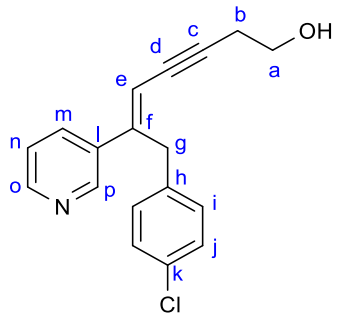
$C_{26}H_{31}NO_2Si$ (417.62)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. 2-(Chloromethyl)benzofuran (167 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C and then allowed to warm to RT, stirring for 2 hours at RT. The reaction was cooled to -90 °C and enyne **397** (245 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise over 1 minute to a stirring solution of *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C and stirred for 15 minutes] dropwise over 1 minute, stirred for 30 minutes at low temperature (-90 to -70 °C) and then at RT for 21 hours. Zinc chloride (1.4 M in THF, 1.1 mL, 1.5 mmol) was added and stirred at RT for 1 hour. The reaction mixture was transferred to a stirring solution of $Pd(PPh_3)_4$ (69 mg, 0.06 mmol) and degassed 3-bromopyridine (0.15 mL, 1.5 mmol) in THF (5 mL) and refluxed at 85 °C for 22 hours. The reaction mixture was allowed to cool to RT, poured into water (50 mL) and extracted with EtOAc (4× 50 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was by column chromatography using 1% Et_3N, 20% EtOAc in hexane over silica followed by 5% EtOAc

in CH_2Cl_2 over silica to afford the title compound as a pale yellow oil (136 mg, 0.33 mmol, 33%).

GC (AP40L):	Rt 13.84 mins.
^{1}H-NMR:	δ_H ppm (400 MHz, $CDCl_3$) 8.73 (1 H, d, *J* 2.0, Ht), 8.48 (1 H, dd, *J* 4.8, 1.4, Hs), 7.70 (1 H, ddd, *J* 8.0, 2.4, 1.6, Hq), 7.42 (1 H, m, ArH), 7.39 (1 H, m, ArH), 7.21 (1 H, m, ArH), 7.18 (1 H, m, ArH), 7.15 (1 H, td, *J* 7.4, 1.3, ArH), 6.35 (1 H, d, *J* 0.9, Ho), 6.11 (1 H, t, *J* 2.2, He), 4.26 (2 H, brs, Hg), 3.77 (2 H, t, *J* 7.0, Ha), 2.63 (2 H, td, *J* 7.0, 2.2, Hb), 0.89 (9 H, s, *t*Bu), 0.06 (6 H, s, $SiMe_2$).
^{13}C-NMR:	δ_C ppm (101 MHz, $CDCl_3$) 155.50 (C), 154.83 (C), 149.23 (CH, Cs), 147.33 (CH, Ct), 143.11 (C), 135.16 (C), 133.17 (CH), 128.88 (C), 123.57 (CH), 123.37 (CH), 122.68 (CH), 120.52 (CH), 111.87 (CH), 111.00 (CH), 103.77 (CH), 95.58 (C, Cc/d), 78.95 (C, Cc/d), 61.94 (CH_2, Ca), 31.49 (CH_2, Cg), 26.00 (3 CH_3, *t*Bu), 24.37 (CH_2, Cb), 18.44 (C, *t*Bu), -5.17 (2 CH_3, $SiMe_2$).
LRMS (ESI$^+$):	*m/z*: 418 ($[M+H]^+$, 100%).
HRMS (ESI$^+$):	Found *m/z*: 418.2206 $[M+H]^+$. Calculated 418.2197 Da.
IR (ATR):	ν_{max}/ cm^{-1} 3034w (=C-H), 2953m (C-H), 2928m (C-H), 2855m (C-H), 2214w (C≡C), 1599w (C=C), 1585w (C=C), 1564w (Ar), 1471w (Ar), 1454m (Ar), 1414w (C-H), 1253m (C-O), 1100m (C-O), 833s, 776s, 750s.

5.4.5.20 - (*E*)-7-(4-Chlorophenyl)-6-(pyridin-3-yl)hept-5-en-3-yn-1-ol (429)



$C_{18}H_{16}ClNO$ (297.78)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. 4-Chlorobenzyl chloride (161 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C and then allowed to warm to RT, stirring for 2 hours at RT. The reaction was cooled to -90 °C and enyne **397** (245 mg, 1.0 mmol) in

THF (1 mL) was added dropwise followed by LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise over 1 minute to a stirring solution of *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C and stirred for 15 minutes] dropwise over 1 minute and stirred for 30 minutes at low temperature (-90 to -70 °C). The reaction was warmed to RT and zinc chloride (1.5 M in THF, 1.0 mL, 1.5 mmol) was added and stirred at RT for 1 hour. The reaction mixture was transferred to a stirring solution of $Pd(PPh_3)_4$ (69 mg, 0.06 mmol) and degassed 3-bromopyridine (0.10 mL, 1.0 mmol) in THF (5 mL) and refluxed at 85 °C for 24 hours. The reaction mixture was allowed to cool to RT, poured into water (50 mL) and extracted with EtOAc (4× 50 mL). The organic phases were combined, dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 1% Et_3N, 20% EtOAc in hexane over silica. The isolated oil was dissolved in THF (1 mL) and TBAF (1 M in THF, 1.0 mL, 1.0 mmol) was added dropwise at RT and stirred for 1 hour. The reaction mixture was poured into water (50 mL) and extracted with EtOAc (4× 50 mL). The organic phases were combined, washed with brine (3× 50 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 1% MeOH in CH_2Cl_2 over silica to afford the title compound as a pale yellow solid (103 mg, 0.35 mmol, 35%).

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 8.60 (1 H, d, *J* 1.8 Hz, Hp), 8.45 (1 H, dd, *J* 4.6, 1.0 Hz, Ho), 7.57 (1 H, ddd, *J* 8.0, 2.3, 1.7 Hz, Hm), 7.23 – 7.16 (3 H, m, Hj & Hn), 7.13 (2 H, d*, *J* 8.6 Hz, Hi), 6.04 (1 H, t, *J* 2.2 Hz, He), 4.08 (2 H, s, Hg), 3.80 (2 H, t, *J* 6.3 Hz, Ha), 2.68 (2 H, td, *J* 6.3, 2.2 Hz, Hb), 1.97 (1 H, s, OH).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 149.20 (CH, Co), 147.46 (CH, Cp), 146.87 (C, Cf), 136.93 (C), 135.34 (C), 133.40 (CH, Cm), 132.34 (C), 129.80 (2 CH, Ci/j), 128.88 (2 CH, Ci/j), 123.40 (CH, Cn), 110.80 (CH, Ce), 93.71 (C, Cc/d), 80.09 (C, Cc/d), 61.26 (CH_2, Ca), 37.48 (CH_2, Cg), 24.28 (CH_2, Cb).

*Doublet with second order effects.

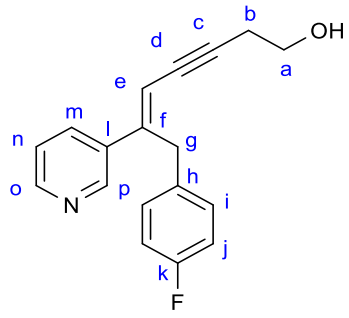
LRMS (ESI$^+$): *m/z*: 298 ($[M+H]^+$, 100%.

HRMS (ESI$^+$): Found *m/z*: 298.0995 $[M+H]^+$. Calculated 298.0993 Da.

IR (ATR): ν_{max}/ cm^{-1} 3236brw (OH), 3089w (=C-H), 3043w (=C-H), 2933w (C-H), 2916w (C-H), 2882w (C-H), 2245w (C≡C), 2215w (C≡C), 1587w (C=C), 1568w (Ar), 1490m (Ar), 1436m (Ar), 1416m (C-H), 1407m (Ar), 1049m (C-O), 1015m, 904s, 724s.

Mp: 86.6 °C.

5.4.5.21 - (*E*)-7-(4-Fluorophenyl)-6-(pyridin-3-yl)hept-5-en-3-yn-1-ol (430)



$C_{18}H_{16}FNO$ (281.33)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. 4-Fluorobenzyl chloride (145 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C and then allowed to warm to RT, stirring for 2 hours at RT. The reaction was cooled to -90 °C and enyne **397** (245 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise over 1 minute to a stirring solution of *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C and stirred for 15 minutes] dropwise over 1 minute and stirred for 30 minutes at low temperature (-90 to -70 °C). The reaction was warmed to RT and zinc chloride (1.5 M in THF, 1.0 mL, 1.5 mmol) was added and stirred at RT for 1 hour. The reaction mixture was transferred to a stirring solution of $Pd(PPh_3)_4$ (69 mg, 0.06 mmol) and degassed 3-bromopyridine (0.15 mL, 1.5 mmol) in THF (5 mL) and refluxed at 85 °C for 16 hours. The reaction mixture was allowed to cool to RT, poured into water (50 mL) and extracted with EtOAc (4× 50 mL). The organic phases were combined, dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 1% Et_3N, 20% EtOAc in hexane over silica. The isolated oil was dissolved in THF (1 mL) and TBAF (1 M in THF) was added dropwise at RT and stirred for 1 hour. The reaction mixture was poured into water (50 mL) and extracted with EtOAc (4× 50 mL). The organic phases were combined, washed with brine (3× 50 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 1% MeOH in CH_2Cl_2 over silica to afford the title compound as a yellow oil (108 mg, 0.38 mmol, 38%).

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 8.59 (1 H, d, *J* 1.9 Hz, Hp), 8.44 (1 H, brd, *J* 4.1 Hz, Ho), 7.57 (1 H, ddd, *J* 8.0, 2.3, 1.7 Hz, Hm), 7.22 – 7.09 (3 H, m, Hn & Hi), 6.90 (2 H, t*, *J* 8.7 Hz, Hj), 6.02 (1 H, t, *J* 2.2 Hz, He), 4.08 (2 H, s, Hg), 3.77 (2 H, t, *J* 6.3 Hz, Ha), 2.68 (2 H, td, *J* 6.3, 2.2 Hz, Hb), 2.35 (1 H, br s, OH).

*Triplet with second order effects.

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 161.64 (d, *J* 244.6 Hz, C, Ck), 149.05 (CH, Co), 147.43 (CH, Cp), 147.16 (C, Cf), 135.46 (C, Cl), 134.04 (d, *J* 3.3 Hz, C, Ch), 133.47 (CH, Cm), 129.85 (d, *J* 7.8 Hz, 2 CH, Ci), 123.38 (CH, Cn), 115.53 (d, *J* 21.3 Hz, 2 CH, Cj), 110.62 (CH, Ce), 93.67 (C, Cc/d), 80.05 (C, Cc/d), 61.20 (CH_2, Ca), 37.29 (CH_2, Cg), 24.28 (CH_2, Cb).

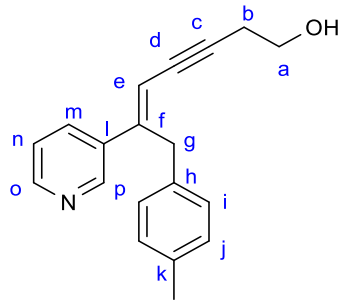
^{19}F-NMR: δ_F ppm (376 MHz, $CDCl_3$) -116.85.

LRMS (ESI$^+$): *m/z*: 282 ($[M+H]^+$, 100%.

HRMS (ESI$^+$): Found *m/z*: 282.1293 $[M+H]^+$. Calculated 282.1289 Da

IR (ATR): ν_{max}/ cm^{-1} 3248brw (OH), 3040w (=C-H), 2918w (C-H), 2880w (C-H), 2245w (C≡C), 2215w (C≡C), 1603m (C=C), 1588w (C=C), 1568w (Ar), 1507s (Ar), 1478m (Ar), 1438m (Ar), 1414m (C-H), 1221s (C-F), 1049s (C-O), 833s, 775s, 739s.

5.4.5.22 - (*E*)-6-(Pyridin-3-yl)-7-(p-tolyl)hept-5-en-3-yn-1-ol (431)



$C_{19}H_{19}NO$ (277.37)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. 4-Methylbenzyl chloride (141 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C and then allowed to warm to RT, stirring for 2 hours at RT. The reaction was cooled to -90 °C and enyne **397** (245 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise over 1 minute to a stirring solution of *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C and stirred for 15 minutes] dropwise over 1 minute and stirred for 30 minutes at low temperature (-90 to -70 °C). The reaction was warmed to RT, zinc chloride (1.5 M in THF, 1.0 mL, 1.5 mmol) was added and the reaction was stirred at RT for 1 hour. The reaction mixture was transferred to a stirring solution of $Pd(PPh_3)_4$ (69 mg, 0.06 mmol) and degassed 3-bromopyridine (0.10 mL, 1.0 mmol) in THF (5 mL) and refluxed at 85 °C for 18 hours. The reaction mixture was allowed to cool to RT, poured into water (50

mL) and extracted with EtOAc (4× 50 mL). The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The compound was purified by column chromatography using 1% Et_3N, 20% EtOAc in hexane over silica. The isolated oil was dissolved in THF (1 mL) and TBAF (1 M in THF) was added dropwise at RT and stirred for 1 hour. The reaction mixture was poured into water (50 mL) and extracted with EtOAc (4× 50 mL). The organic phases were combined, washed with brine (3× 50 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified twice by column chromatography using 1% MeOH in CH_2Cl_2 over silica to afford the title compound as a colourless oil (84 mg, 0.30 mmol, 30%).

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 8.62 (1 H, d, *J* 2.1, Hp), 8.43 (1 H, dd, *J* 4.7, 1.3, Ho), 7.59 (1 H, ddd, *J* 8.0, 2.3, 1.7, Hm), 7.16 (1 H, ddd, *J* 8.0, 4.8, 0.6, Hn), 7.09 (2 H, d, *J* 8.1, Hi), 7.04 (2 H, d, *J* 8.0, Hj), 6.03 (1 H, t, *J* 2.2, He), 4.08 (2 H, s, Hg), 3.76 (2 H, t, *J* 6.0, Ha), 2.67 (2 H, td, *J* 6.3, 2.2, Hb), 2.27 (3 H, s, Me), 2.19 (1H, brs, OH)

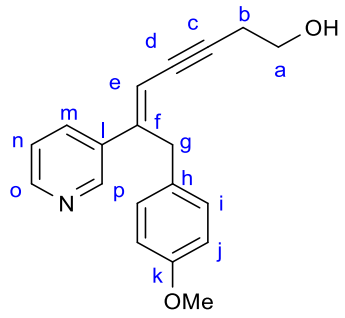
^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 148.92 (CH, Co), 147.51 (C, Cf), 47.48 (CH, Cp), 136.04 (C, Ci/k/h), 135.72 (C, Ci/k/h), 135.30 (C, Ch), 133.47 (CH, Cm), 129.43 (2 CH, Cj), 128.30 (2 CH, Ci), 123.30 (CH, Cn), 110.31 (CH, Ce), 93.36 (C, Cc/d), 80.29 (C, Cc/d), 61.24 (CH_2, Ca), 37.69 (CH_2, Cg), 24.32 (CH_2, Cb), 21.10 (CH_3, Me).

LRMS (ESI$^+$): *m/z*: 278 ($[M+H]^+$, 100%).

HRMS (ESI$^+$): Found *m/z*: 278.1542 $[M+H]^+$. Calculated 278.1539 Da.

IR (ATR): ν_{max}/ cm^{-1} 3238brm (OH), 3090w (=C-H), 3046w (=C-H), 3021w (=C-H), 2921w (C-H), 2875w (C-H), 2242w (C≡C), 2215w (C≡C), 1601w (C=C), 1586w (C=C), 1568w (Ar), 1512m (Ar), 1478w (Ar), 1438w (Ar), 1414m (C-H), 1048m (C-O), 833s, 756s, 697s.

5.4.5.23 - (*E*)-7-(4-Methoxyphenyl)-6-(pyridin-3-yl)hept-5-en-3-yn-1-ol (432)



$C_{19}H_{19}NO_2$ (293.37)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. 4-Methoxybenzyl chloride (157 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C and then allowed to warm to RT, stirring for 2 hours at RT. The reaction was cooled to -90 °C and enyne **397** (245 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise over 1 minute to a stirring solution of *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C and stirred for 15 minutes] dropwise over 1 minute and stirred for 30 minutes at low temperature (-90 to -70 °C). The reaction was allowed to warm to RT, zinc chloride (1.4 M in THF, 1.1 mL, 1.5 mmol) was added and the reaction was stirred at RT for 1 hour. The reaction mixture was transferred to a stirring solution of $Pd(PPh_3)_4$ (69 mg, 0.06 mmol) and degassed 3-bromopyridine (0.15 mL, 1.5 mmol) in THF (5 mL) and refluxed at 85 °C for 24 hours. The reaction mixture was allowed to cool to RT, poured into water (50 mL) and extracted with EtOAc (4× 50 mL). The organic phases were combined, dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 1% Et_3N, 20% EtOAc in hexane over silica. The isolated oil was dissolved in THF (1 mL) and treated with TBAF (1 M in THF, 1.0 mL, 1.0 mmol) at RT and stirred for 16 hours. The reaction mixture was poured into water (50 mL) and extracted with EtOAc (4× 50 mL). The organic phases were combined, washed with brine (3× 50 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 0.5-2% MeOH in CH_2Cl_2 over silica. The compound was treated with 2 M $HCl_{(aq)}$ (50 mL) and extracted with EtOAc (3× 50 mL). The aqueous phase was neutralised to pH 7 and extracted with EtOAc (3× 50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the title compound as a pale yellow oil (108 mg, 0.37 mmol, 37%).

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 8.61 (1 H, brs, Hp), 8.44 (1 H, brd, *J* 4.0 Hz, Ho), 7.59 (1 H, ddd, *J* 8.0, 2.3, 1.7 Hz, Hm), 7.17 (1 H, dd, *J* 8.0, 4.8 Hz, Hn), 7.12 (2 H, d*, *J* 8.7 Hz, Hi), 6.77 (2 H, d*, *J* 8.7 Hz, Hj),

6.01 (1 H, t, *J* 2.2 Hz, He), 4.06 (2 H, s, Hg), 3.77 (2 H, t, *J* 6.2 Hz, Ha), 3.74 (3 H, s, Me), 2.68 (2 H, td, *J* 6.2, 2.2 Hz, Hb), 2.01 (1 H, brs, OH).

*Doublets with second order effects.

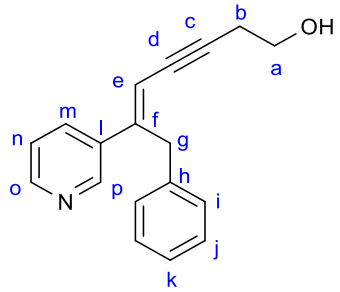
^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 158.29 (C, Ck), 149.00 (CH, Cp), 147.80 (C, Cf), 147.55 (CH, Co), 135.71 (C, Cl/h), 133.48 (CH, Cm), 130.40 (C, Ch/l), 129.41 (2 CH, Ci), 123.31 (CH, Cn), 114.17 (2 CH, Cj), 110.13 (CH, Ce), 93.16 (C, Cc/d), 80.36 (C, Cc/d), 61.29 (CH_2, Ca), 55.35 (CH_3, Me), 37.28 (CH_2, Cg), 24.32 (CH_2, Cb).

LRMS (ESI$^+$): *m/z*: 294 ($[M+H]^+$, 100%).

HRMS (ESI$^+$): Found *m/z*: 294.1491 $[M+H]^+$. Calculated 294.1489 Da

IR (ATR): ν_{max}/ cm^{-1} 3243brm (OH), 3032w (=C-H), 3006w (=C-H), 2932w (C-H), 2909w (C-H), 2835w (C-H), 2244w (C≡C), 2211w (C≡C), 1609m (C=C), 1583m (C=C), 1567m (Ar), 1509s (Ar), 1477m (Ar), 1463m (Ar), 1440m (Ar), 1414m (C-H), 1034brs (C-O), 728s, 706s.

5.4.5.24 - (*E*)-7-Phenyl-6-(pyridin-3-yl)hept-5-en-3-yn-1-ol (433)



$C_{18}H_{17}NO$ (263.34)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. Benzyl chloride (127 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C and then allowed to warm to RT, stirring for 2 hours at RT. The reaction was cooled to -90 °C and enyne **397** (245 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise over 1 minute to a stirring solution of *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C and stirred for 15 minutes] dropwise over 1 minute and stirred for 30 minutes at low temperature (-90 to -70 °C). The reaction was warmed to RT, zinc chloride (1.5 M in THF, 1.0 mL, 1.5 mmol) was added and the reaction was stirred at RT for 1 hour. The reaction mixture was transferred to a stirring solution of $Pd(PPh_3)_4$ (69 mg, 0.06

mmol) and degassed 3-bromopyridine (0.15 mL, 1.5 mmol) in THF (5 mL) and refluxed at 85 °C for 24 hours. The reaction mixture was allowed to cool to RT, poured into water (50 mL) and extracted with EtOAc (4× 50 mL). The organic phases were combined, dried over MgSO4, filtered, concentrated *in vacuo* and purified by column chromatography using 1% Et_3N, 10% EtOAc in hexane over silica. The isolated oil was dissolved in THF (1 mL) and TBAF (1 M in THF) was added dropwise at RT and stirred for 1 hour. The reaction mixture was poured into water (50 mL) and extracted with EtOAc (4× 50 mL). The organic phases were combined, washed with brine (3× 50 mL), dried over MgSO4, filtered, concentrated *in vacuo* and purified by column chromatography using 1% MeOH in CH_2Cl_2 over silica to afford the title compound as a yellow oil (105 mg, 0.40 mmol, 40%).

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 8.63 (1 H, d, *J* 2.0 Hz, Hp), 8.44 (1 H, dd, *J* 4.8, 1.4 Hz, Ho), 7.60 (1 H, ddd, *J* 8.0, 2.4, 1.6 Hz, Hm), 7.26 – 7.19 (4 H, m, Hi & Hj), 7.17 (2 H, m, Hk & Hn), 6.05 (1 H, t, *J* 2.2 Hz, He), 4.13 (2 H, s, Hg), 3.76 (2 H, t, *J* 6.2 Hz, Ha), 2.67 (2 H, td, *J* 6.2, 2.2 Hz, Hb), 1.92 (1 H, s, OH).

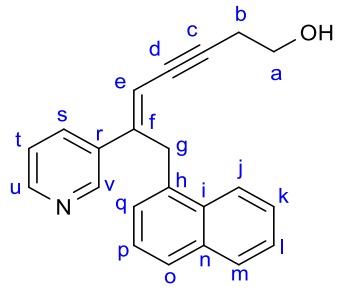
^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 149.04 (CH, Co), 147.52 (CH, Cp), 147.35 (C, Cf), 138.44 (C), 135.67 (C), 133.45 (CH, Cm), 128.76 (2 CH, Ci/j), 128.45 (2 CH, Ci/j), 126.55 (CH, Ck), 123.32 (CH, Cn), 110.52 (CH, Ce), 93.41 (C, Cc/d), 80.33 (C, Cc/d), 61.28 (CH_2, Ca), 38.15 (CH_2, Cg), 24.32 (CH_2, Cb).

LRMS (ESI$^+$): *m/z*: 264 ($[M+H]^+$, 100%).

HRMS (ESI$^+$): Found *m/z*: 264.1388 $[M+H]^+$. Calculated 264.1383 Da

IR (ATR): ν_{max}/ cm^{-1} 3246brm (OH), 3083w (=C-H), 3060w (=C-H), 3026w (=C-H), 2916m (C-H), 2873m (C-H), 2244w (C≡C), 2212w (C≡C), 1600w (C=C), 1584w (C=C), 1567w (Ar), 1494w (Ar), 1478w (Ar), 1453w (Ar), 1415w (C-H), 1045m (C-O), 908m, 727s, 697s.

5.4.5.25 - (*E*)-7-(Naphthalen-1-yl)-6-(pyridin-3-yl)hept-5-en-3-yn-1-ol (434)



$C_{22}H_{19}NO$ (313.40)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. 1-(Chloromethyl)naphthalene (177 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C and then allowed to warm to RT, stirring for 2 hours at RT. The reaction was cooled to -90 °C and enyne **397** (245 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise over 1 minute to a stirring solution of *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C and stirred for 15 minutes] dropwise over 1 minute and stirred for 30 minutes at low temperature (-90 to -70 °C) and then at RT for 21 hours. Zinc chloride (1.5 M in THF, 1.0 mL, 1.5 mmol) was added and stirred at RT for 1 hour. The reaction mixture was transferred to a stirring solution of $Pd(PPh_3)_4$ (69 mg, 0.06 mmol) and degassed 3-bromopyridine (0.15 mL, 1.5 mmol) in THF (5 mL) and refluxed at 85 °C for 24 hours. The reaction mixture was allowed to cool to RT, poured into water (50 mL) and extracted with EtOAc (4× 50 mL). The organic phases were combined, filtered, concentrated *in vacuo* and purified by column chromatography using 1% Et_3N, 15% EtOAc in hexane over silica to afford an orange oil.The compound was dissolved in THF (1 mL) and TBAF (1 M in THF, 1.0 mL, 1.0 mmol) was added dropwise at RT and stirred for 1 hour. The reaction mixture was poured into water (50 mL) and extracted with EtOAc (4× 50 mL). The organic phases were combined, washed with brine (3× 50 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 3% MeOH in CH_2Cl_2 over silica to afford the title compound as a white solid (81 mg, 0.26 mmol, 26%).

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 8.62 (1 H, d, *J* 1.8 Hz, Hv), 8.41 (1 H, dd, *J* 4.8, 1.6 Hz, Hu), 8.19 (1 H, d, *J* 8.6 Hz, Hs), 7.86 (1 H, m, Hm), 7.70 (1 H, d, *J* 8.2 Hz, Hq), 7.59 – 7.47 (3 H, m, Hj, Hk, Hl), 7.31 (1 H, dd, *J* 8.2, 7.2 Hz, Hp), 7.23 (1 H, dd, *J* 7.1, 1.0 Hz, Ho), 7.10 (1 H, ddd, *J* 8.0, 4.8, 0.8 Hz, Ht), 6.18 (1 H, t, *J* 2.2 Hz, He), 4.56 (2 H, s, Hg), 3.65

(2 H, q, *J* 6.1 Hz, Ha), 2.61 (2 H, td, *J* 6.2, 2.2 Hz, Hb), 1.70 (1 H, t, *J* 6.2, OH).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 149.05 (CH, Cu), 147.47 (CH, Cv), 147.10 (C), 135.77 (C), 133.96 (C), 133.92 (C), 133.43 (CH, Cj/k/l/o/q), 132.19 (C), 129.02 (CH, Cm), 127.32 (CH), 126.31 (CH, Cj/k/l/o/q), 125.93 (CH, Cj/k/l/o/q), 125.85 (CH, Cj/k/l/o/q), 125.68 (CH, Cj/k/l/o/q), 123.51 (CH, Cs), 123.24 (CH, Ct), 111.29 (CH, Ce), 94.37 (C, Cc/d), 80.11 (C, Cc/d), 61.23 (CH_2, Ca), 35.29 (CH_2, Cg), 24.29 (CH_2, Cb).

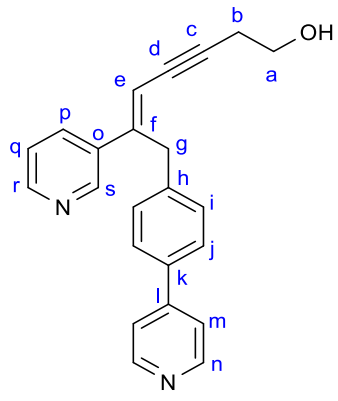
LRMS (ESI$^+$): *m/z*: 314 ($[M+H]^+$, 100%).

HRMS (ESI$^+$): Found *m/z*: 314.1545 $[M+H]^+$. Calculated 314.1539 Da

IR (ATR): ν_{max}/ cm^{-1} 3230brm (OH), 3092w (=C-H), 3044w (=C-H), 3012w (=C-H), 2930w (=C-H), 2906w (C-H), 2876w (C-H), 2241w (C≡C), 2211w (C≡C), 1596w (C=C), 1585w (C=C), 1567w (Ar), 1475w (Ar), 1415m (C-H), 1047s (C-O), 782s, 728s, 706s.

Mp: 146 °C

5.4.5.26 - (*E*)-6-(Pyridin-3-yl)-7-(4-(pyridin-4-yl)phenyl)hept-5-en-3-yn-1-ol (435)



$C_{23}H_{20}N_2O$ (340.43)

Procedure: 4-(4-(chloromethyl)phenyl)pyridine hydrochloride **321** (343 mg, 1.4 mmol) was washed with sat. $NaHCO_{3\,(aq)}$ (10 mL) and extracted with Et_2O (2× 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* at 0 °C to afford 4-(4-(chloromethyl)phenyl)pyridine as a yellow oil (223 mg, 1.09 mmol). To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. 4-Pyridinebenzyl chloride (204 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C and then allowed to warm to RT, stirring for 2 hours at RT. The reaction was cooled to -90 °C and enyne **397** (245 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by LDA

[*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise over 1 minute to a stirring solution of *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C and stirred for 15 minutes] dropwise over 1.5 minute and stirred for 30 minutes at low temperature (-90 to -70 °C). The reaction was warmed to RT, zinc chloride (1.4 M in THF, 1.1 mL, 1.5 mmol) was added and the reaction was stirred at RT for 1 hour. The reaction mixture was transferred to a stirring solution of $Pd(PPh_3)_4$ (69 mg, 0.06 mmol) and degassed 3-bromopyridine (0.15 mL, 1.5 mmol) in THF (5 mL) and refluxed at 85 °C for 64 hours. The reaction mixture was allowed to cool to RT, poured into water (50 mL) and extracted with EtOAc (4× 50 mL). The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The compound was purified by column chromatography using 1% Et_3N, 70% EtOAc in hexane over silica followed by 2% MeOH in CH_2Cl_2 over silica. The isolated oil was dissolved in THF (1 mL) and TBAF (1 M in THF, 1.0 mL, 1.0 mmol) was added dropwise at RT and stirred for 1 hour. The reaction mixture was poured into water (50 mL) and extracted with EtOAc (4× 50 mL). The organic phases were combined, washed with brine (3× 50 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography using 1-5% MeOH in CH_2Cl_2 over silica to afford the title compound as a pale yellow oil (42 mg, 0.12 mmol, 12%).

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 8.63 (1 H, s, Hs), 8.60 (2 H, d, *J* 3.3 Hz, Hn), 8.45 (1 H, d, *J* 4.0 Hz, Hr), 7.62 (1 H, ddd, *J* 8.0, 2.3, 1.7 Hz, Hp), 7.50 (2 H, d, *J* 8.3 Hz, Hj), 7.43 (2 H, d, *J* 6.0 Hz, Hm), 7.32 (2 H, d, *J* 8.4 Hz, Hi), 7.19 (1 H, dd, *J* 7.9, 4.8 Hz, Hq), 6.08 (1 H, t, *J* 2.2 Hz, He), 4.18 (2 H, s, Hg), 3.78 (2 H, t, *J* 6.3 Hz, Ha), 2.69 (2 H, td, *J* 6.3, 2.2 Hz, Hb), 2.51 (1 H, brs, OH).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 150.27 (2 CH, Cn), 149.16 (CH, Cr), 148.09 (C, Cf), 147.49 (CH, Cs), 146.72 (C), 139.76 (C), 136.28 (C), 135.42 (C), 133.39 (CH, Cp), 129.23 (2 CH), 127.34 (2 CH), 123.41 (CH, Cq), 121.56 (2 CH), 110.91 (CH, Ce), 93.96 (C, Cc/d), 80.07 (C, Cc/d), 61.18 (CH_2, Ca), 37.79 (CH_2, Cg), 24.32 (CH_2, Cb).

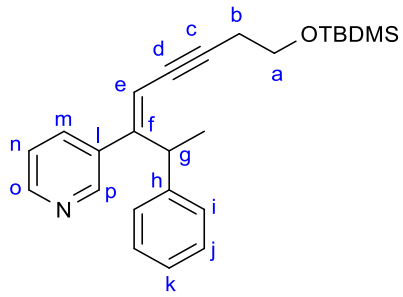
LRMS (ESI$^+$): *m/z*: 341 ($[M+H]^+$, 100%).

HRMS (ESI$^+$): Found *m/z*: 341.1649 $[M+H]^+$. Calculated 341.1648 Da.

IR (ATR): ν_{max}/ cm^{-1} 3221brm (OH), 3029m (=C-H), 2926m (C-H), 2912m (C-H), 2873m (C-H), 2211w (C≡C), 1597m (C=C), 1566w (Ar), 1542w (Ar), 1517w (Ar), 1488m (Ar), 1053m (C-O), 727s, 706s.

Mp: 129.8 °C.

5.4.5.27 - (*E*)-3-(8-((*tert*-Butyldimethylsilyl)oxy)-2-phenyloct-3-en-5-yn-3-yl)pyridine (436)



$C_{25}H_{33}NOSi$ (391.63)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. (1-Chloroethyl)benzene (141 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C and then allowed to warm to RT, stirring for 2 hours at RT. The reaction was cooled to -90 °C and enyne **397** (245 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise over 1 minute to a stirring solution of *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C and stirred for 15 minutes] dropwise over 1 minute, stirred for 30 minutes at low temperature (-90 to -70 °C) and then at RT for 24 hours. Zinc chloride (1.4 M in THF, 1.1 mL, 1.5 mmol) was added and stirred at RT for 16 hours. The reaction mixture was transferred to a stirring solution of $Pd(PPh_3)_4$ (69 mg, 0.06 mmol) and degassed 3-bromopyridine (0.15 mL, 1.5 mmol) in THF (5 mL) and refluxed at 85 °C for 24 hours. The reaction mixture was allowed to cool to RT, poured into water (50 mL) and extracted with EtOAc (4× 50 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was by column chromatography using 1% Et_3N, 20% EtOAc in hexane over silica followed by 5% EtOAc in CH_2Cl_2 over silica to afford the title compound as a pale yellow oil (102 mg, 0.26 mmol, 26%).

GC (AP40L): Rt 11.19 mins.

^{1}H-NMR: δ_H ppm (400 MHz, $CDCl_3$) 8.42 (1 H, dd, *J* 4.6, 1.7 Hz, Ho), 8.24 (1 H, brd, *J* 1.4 Hz, Hp), 7.35 – 7.27 (4 H, m, ArH), 7.23 (1 H, m, ArH), 7.09 (1 H, dt, *J* 7.9, 2.0 Hz, Hm), 7.05 (1 H, ddd, *J* 7.9, 4.6, 0.8 Hz, Hn), 5.68 (1 H, t, *J* 2.3 Hz, He), 4.80 (1 H, q, *J* 7.2 Hz, Hg), 3.79 (2 H, t, *J* 7.0 Hz, Ha), 2.63 (2 H, td, *J* 7.0, 2.3 Hz, Hb), 1.41 (3 H, d, *J* 7.2 Hz, Me), 0.90 (9 H, s, *t*Bu), 0.08 (6 H, s, $SiMe_2$).

^{13}C-NMR: δ_C ppm (101 MHz, $CDCl_3$) 153.28 (C, Cf), 148.70 (CH, Co), 148.62 (CH, Cp), 142.73 (C, Cl/h), 135.97 (C, Cl/h), 135.10 (CH, Cm), 128.56

(2 CH, Ci/j), 127.49 (2 CH, Ci/j), 126.56 (CH, Ck), 122.67 (CH, Cn), 110.74 (CH, Ce), 93.37 (C, Cc/d), 79.03 (C, Cc/d), 62.02 (CH_2, Ca), 41.19 (CH, Cg), 26.02 (3 CH_3, *t*Bu), 24.33 (CH_2, Cb), 18.47 (C, *t*Bu), 17.14 (CH_3, Me), -5.13 (2 CH_3, $SiMe_2$).

LRMS (ESI$^+$): *m/z*: 392 ($[M+H]^+$, 100%).

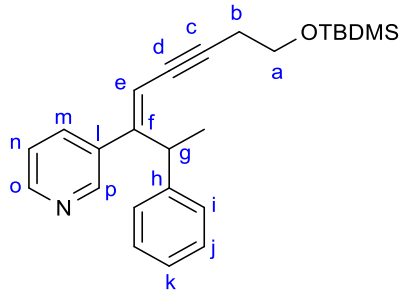
HRMS (ESI$^+$): Found *m/z*: 392.2412 $[M+H]^+$. Calculated 392.2404 Da.

IR (ATR): ν_{max}/ cm^{-1} 3085w (=C-H), 3026w (=C-H), 2954m (C-H), 2928m (C-H), 2829m (C-H), 2881m (C-H), 2856m (C-H), 2215w (C≡C), 1600w (C=C), 1582w (C=C), 1562w (Ar), 1495w (Ar), 1471m (Ar), 1462m (Ar), 1448w (Ar), 1100s (C-O), 834s, 774s, 698s.

Enantiopurity using NMR chiral solvating agent:

^{1}H-NMR (400 MHz, $CDCl_3$, 298K) of **436** (0.03 M) showed enantiodifferentiation of 5.67 ppm (1 H, t, *J* 2.3 Hz, He) signal to 5.65 ppm (t, *J* 2.2 Hz) and 5.63 ppm (t, *J* 2.2 Hz) in 1:1 ratio using (*R*)-(+)-1,1'-bi(2-naphthol) (0.21 M).

5.4.5.28 - (*E*)-3-(8-((*tert*-Butyldimethylsilyl)oxy)-2-phenyloct-3-en-5-yn-3-yl)pyridine (436b)



$C_{25}H_{33}NOSi$ (391.63)

Procedure: To a stirring solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL), *n*-BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise over 2 minutes at -78 °C under nitrogen and stirred for 30 minutes. (*R*)-(1-Chloroethyl)benzene **344-*R*** (141 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C and then allowed to warm to RT, stirring for 2 hours at RT. The reaction was cooled to -90 °C and enyne **397** (245 mg, 1.0 mmol) in THF (1 mL) was added dropwise followed by LDA [*n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise over 1 minute to a stirring solution of *i*-Pr_2NH (0.17 mL, 1.2 mmol) in THF (1 mL) at 0 °C and stirred for 15 minutes] dropwise over 1 minute, stirred for 30 minutes at low temperature (-90 to -70 °C)

and then at RT for 21 hours. Zinc chloride (1.4 M in THF, 1.1 mL, 1.5 mmol) was added and stirred at RT for 1 hour. The reaction mixture was transferred to a stirring solution of $Pd(PPh_3)_4$ (69 mg, 0.06 mmol) and degassed 3-bromopyridine (0.15 mL, 1.5 mmol) in THF (5 mL) and refluxed at 85 °C for 24 hours. The reaction mixture was allowed to cool to RT, poured into water (50 mL) and extracted with EtOAc (4× 50 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was by column chromatography using 1% Et_3N, 20% EtOAc in hexane over silica followed by 5% EtOAc in hexane over silica to afford the title compound as a pale yellow oil (106 mg, 0.27 mmol, 27%).

GC (AP40L):	Rt 11.19 mins.
^{1}H-NMR:	δ_H ppm (400 MHz, $CDCl_3$) 8.42 (1 H, dd, *J* 4.6, 1.8 Hz, Ho), 8.23 (1 H, dd, *J* 2.1, 0.7 Hz, Hp), 7.36 – 7.27 (4 H, m, ArH), 7.22 (1 H, m, ArH), 7.08 (1 H, m, Hm), 7.04 (1 H, ddd, *J* 7.9, 4.7, 0.9 Hz, Hn), 5.67 (1 H, t, *J* 2.3 Hz, He), 4.80 (1 H, q, *J* 7.2 Hz, Hg), 3.79 (2 H, t, *J* 7.0 Hz, Ha), 2.63 (2 H, td, *J* 7.0, 2.3 Hz, Hb), 1.41 (3 H, d, *J* 7.2 Hz, Me), 0.90 (9 H, s, *t*Bu), 0.07 (6 H, s, $SiMe_2$).
^{13}C-NMR:	δ_C ppm (101 MHz, $CDCl_3$) 153.32 (C, Cf), 148.80 (CH, Co), 148.72 (CH, Cp), 142.75 (C, Cl/h), 135.91 (C, Cl/h), 134.99 (CH, Cm), 128.54 (2 CH, Ci), 127.49 (2 CH, Cj), 126.54 (CH, Ck), 122.61 (CH, Cn), 110.69 (CH, Ce), 93.32 (C, Cc/d), 79.04 (C, Cc/d), 62.01 (CH_2, Ca), 41.19 (CH, Cg), 26.01 (3 CH_3, *t*Bu), 24.32 (CH_2, Cb), 18.45 (C, tBu), 17.14 (CH_3, Me), -5.14 (2 CH_3, $SiMe_2$).
LRMS (ESI$^+$):	*m/z*: 392 ($[M+H]^+$, 100%).
HRMS (ESI$^+$):	Found *m/z*: 392.2493 $[M+H]^+$. Calculated 392.2404 Da.
IR (ATR):	ν_{max}/ cm^{-1} 3085w (=C-H), 3027w (=C-H), 2954m (C-H), 2928m (C-H), 2897m (C-H), 2881m (C-H), 2856m (C-H), 2215w (C≡C), 1600w (Ar), 1583w (Ar), 1563w (Ar), 1495m (Ar), 1471m (Ar), 1462m (Ar), 1448m (Ar), 1409m (Ar), 1100s (C-O), 834s, 774s, 698s.

Enantiopurity from NMR chiral solvating agent:

^{1}H-NMR (400 MHz, $CDCl_3$, 298K) of **436.1** (0.03 M) showed enantiodifferentiation of 5.67 ppm (1 H, t, *J* 2.3 Hz, He) signal to 5.65 ppm (t, *J* 2.2 Hz) and 5.63 ppm (t, *J* 2.2 Hz) in 1:1.1 ratio using (*R*)-(+)-1,1'-bi(2-naphthol) (0.21 M).

References

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