Rhodium-Catalysed [(m+2+2)] Carbocyclisation Reactions

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Thesis submitted in accordance with the requirements for the degree of

Doctor of Philosophy

Department of Chemistry

Sept 2011

Acknowledgement

The completion of my doctorate would not have been possible without the support, advice and collaboration of several people. I would like to take this opportunity to acknowledge and thank them for their help.

I am grateful to Professor P. Andrew Evans for providing me with the opportunity to work within his research group. His unwavering encouragement and plentiful advice has helped shape both the project and my development as a scientist.

I would like to thank all members of the Evans' group whom I have worked alongside over the past four years. In particular, I would like to acknowledge Doctor Steven Atkinson for the initial guidance at the onset of my studies and Ryan O'Conner for proofreading my completed thesis.

I am eternally indebted to my loving parents for being a constant pillar of support and guidance.

Abstract

Rhodium-catalysed [m+n+o] carbocyclisation reactions represent a powerful and expedient means of constructing complex polycyclic systems which would generally not be accessible through classical polycyclic reactions. The research described in this thesis focuses on diastereo- and enantioselective rhodium-catalysed [(m+2+2)] carbocyclisation reactions. In particular, we are interested in obtaining understanding of the operative catalytic cycle and exploiting this understanding to maximize selectivity.

Chapter one will provide a comprehensive review of the seminal rhodium-catalysed [m+n+o] research, focusing on the advances within the fundamental areas of selectivity. The examples described within the chapter have been specifically selected to illuminate the factors that lead to high levels of chemo-, regio-, stereo- and enantiocontrol. Additionally, the concept of diastereoinduction is scrutinised. Analysing the research topic in this unusual manner serves to highlight the areas of rhodium-catalysed [m+n+o] carbocyclisations which require further investigation.

Chapter two of this document delineates our contributions to the rhodium-catalysed cycloisomerisation of dienynes. The cycloisomerisation of dienynes is a worthy endeavour as it allows the installation of up to four stereocentres in a single transformation. Such complex architecture is abundant in naturally occurring compounds; several pertinent examples will be delineated within the text. The chapter begins by describing the seminal examples of rhodium-catalysed *intra*molecular [(2+2+2)] carbocyclisations of triynes, diynes and dienynes. The

incorporation of rhodium-catalysed cycloisomerisation in target direct synthesis is also described. This leads to the development of a stereodivergent diastereoselective [(2+2+2)] dienyne carbocyclisation and the investigation of the scope of this transformation. In an attempt to garner insight in to this novel transformation two possible mechanisms are proposed and their plausibility is investigated through a series of experiments. The proposed catalytic cycle is further scrutinised in an attempt to understand the observed levels of diastereoinduction in this transformation. The chapter concludes by describing the development of the enantioselective [(2+2+2)] dienyne carbocyclisation variant.

Chapter 3 of this thesis illustrates our progress toward the synthesis of (+)-epoxydictymene, a highly functionalised medium sized sesquiterpene. The chapter details the previous synthesis of the natural product and delineates the development of the key ring forming reactions. A novel retrosynthetic analysis will be described based on the temporary silicon-tethered rhodium-catalysed (TST) [(4+2+2)] cycloisomerisation reaction previously disclosed within the Evans group. The historic developments of this transformation will be described and the reaction critiqued against the requirement of the synthesis. A series of experiments will be described which are devised to investigate the validity of this approach. The chapter will conclude with a description of our progress towards the synthesis of the natural product.

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List of Abbreviations

Ac	acetyl
ACP	alkenylidenecyclopropanes
Ar	aryl
BDPP	2,4-bis(diphenylphosphino)pentane
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BMS	borane-methyl sulfide complex
Bn	benzyl
Calcd	calculated
Cat.	catalytic
CBS	2-methyl-CBS-oxazaborolidine
COD	1,5-cyclooctadiene
Cy	cyclohexyl
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DFT	Density functional theory
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DIOP	2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphine)butane
DMAP	4-dimethylaminopyridine
DMP	Dess-Martin periodinane
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane

dppf	1,1'-bia(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
*d*s	diastereoselectivity
ee	enantiomeric excess
ESI	electrospray ionization
FCC	Flash Column Chromatography
FTIR	Fourier transform infrared spectroscopy
g	grams
GC	gas chromatograpy
H8-BINAP	2,2′-bis(diphenylphospino)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl
HPLC	High-performance liquid chromatography
Hz	hertz
IR	infrared
*i*Pr	isopropyl
J	J-coupling
L	ligand
M	metal
mmHg	millimetres of mercury
N	normality
NBD	norbornadiene
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMP	*N*-methyl-2-pyrrolidone

NMR	Nuclear magnetic resonance
Np	naphthyl
PCC	pyridinium chlorochromate
PDC	pyridium chlorochromate
PKR	Pauson-Khand reaction
PMB	*para*-methoxybenzly
ppm	parts per million
QUINAP	1-(2-diphenylphosphino-1-naphthyl) isoquinoline
Segphos	4,4'-bi-1,3-benzodioxole-5,5'-diylbis (diphenylphosphane)
Solphos	7,7′-bis[di(3,5-xylyl)phosphino]-3,3′,4,4′-tetrahydro-4,4′-dimethyl-8,8′-bi(2*H*-1,4-benzoxazine
Tf	triflate
rt	room temperature
TBDMS	*tert*-butyldimethylsilyl-
TIPS	triisopropylsilyl-
TEA	Triethanolamine
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl-
TBHP	*tert*-butyl hydroperoxide
*t*Bu	*tert*-butyl
TES	triethylsilyl

Temp	temperature
Tf	trifluoromethanesulfonyl
TLC	Thin Layer Chromatography
TMS	trimethylsilyl
Tol-BINAP	2,2'-bis(di-p-tolylphosphino)-1,1'-binaphthyl
tppts	3,3',3''-phosphinidynetris(benzenesulfonic acid) trisodium salt
Ts	toluenesulfonyl
UV	ultra-violet
Xyl	3,5-dimethylphenyl

Chapter 1

Conceptual Advances within Rhodium-Catalysed [m+n+o] Carbocyclisations

1.1. Introduction

Rhodium-catalysed [m+n+o] carbocyclisation reactions provide an expedient route to cyclic compounds which would not be accessible either *via* traditional methods or utilising an alternative transition metal catalyst.[1] Indeed, the selective formation of compounds analogous to those prepared *via* alternative transition-metal catalysed transformations is one of the striking features of rhodium-catalysed cycloadditions. The modular nature of carbocyclisation reactions permits the selective and systematic construction of libraries of analogues. The relatively mild reaction conditions make rhodium-catalysis an elogant stratagem for the efficient construction of complex polycyclic natural products in the presence of sensitive moieties.

This chapter will examine the topic of rhodium-catalysed [m+n+o] carbocyclisation through the examination and explication of the conceptual advances within the fundamental areas which govern the selectivity of *every* transformation of this type. This will complement and contrast with previous reviews in this area which provide a historic overview of the field. We hope that examining the field in this manner will serve to highlight the areas in which this discipline remains in its infancy.

1.1.1 Historic Overview

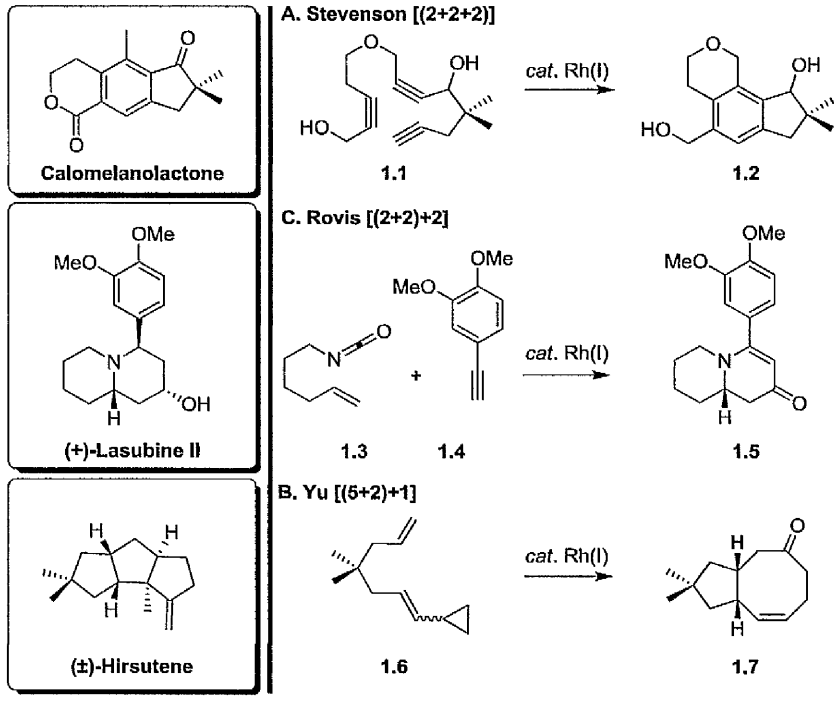


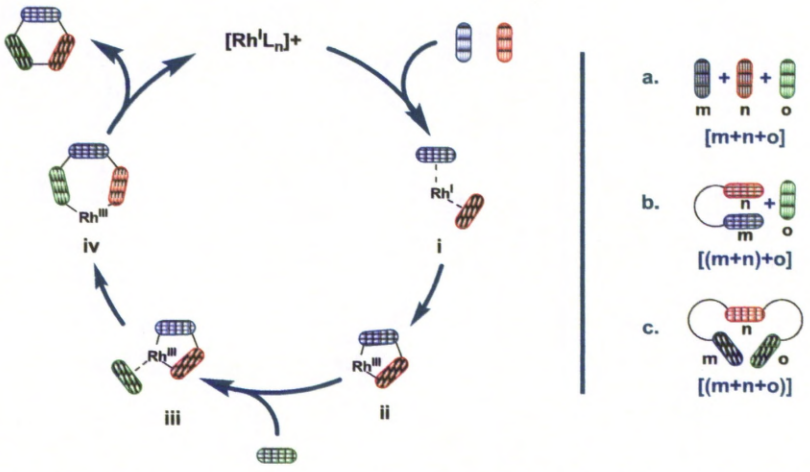
Figure 1.1 Examples of rhodium-catalysed [m+n+o] carbocyclisation in the total synthesis of natural compounds[4]

In 1948, Reppe and Schweckendiek depicted the first *metal*-catalysed [m+n+o] carbocyclisation.[2] This study outlined the *nickel*-catalysed [2+2+2] cyclotrimerisation of monosubstituted alkynes to furnish 1,3,5- and 1,2,4-trisubstituted arenes with no observed chemoselectivity. The first employment of rhodium catalyst in the manifold was reported in 1982, by Grigg *et al.*[3] Since this seminal work the development of new rhodium-catalysed [m+n+o] carbocyclisation has allowed for bond disconnections which would otherwise have been both unfeasible and inconceivable. Figure 1.1 demonstrates three natural product syntheses by rhodium-catalysed [m+n+o] carbocyclisation reactions.[4] Regardless of the progress made within this field, it is important to note that the majority of

rhodium-catalysed [m+n+o] carbocyclisations in natural product synthesis utilise an *intra*molecular [(2+2+2)] trimerisation of three alkynes.

1.1.2 Mechanism, Classification and Considerations

A clear understanding of the mechanism of carbocyclisation transformations can illuminate a number of key difficulties associated with controlling selectivity and help us garner insight into how these challenges have been surmounted. Scheme 1.1 illustrates a generic mechanism for rhodium-catalysed [m+n+o] carbocyclisation reactions.[1c] The initial coordination of a rhodium(I)-complex with two unsaturated motifs (**i**) and oxidative addition provides metallacycle **ii**. The subsequent coordination of a third π–component (**iii**) and resulting carbometallation, affords the final key metallacycle (**iv**). Reductive elimination yields the cyclic product and regenerates the active catalytic complex.



Scheme 1.1 Catalytic cycle and classes of rhodium-catalysed [m+n+o] carbocyclisation reactions

This strategy provides almost unlimited versatility, since the π-moieties can be readily interchanged to facilitate the construction of cyclic adducts with variable ring size, ring number and install different atoms to the cyclic product. For example, utilising carbon monoxide serves to install a single sp^2 carbon into the cyclic adduct.[5] Conversely, dienes and nitriles allow the installation of 4 carbons and a nitrogen-carbon motif into cyclic products, respectively.[6] This stratagem has allowed the formations of 5,[7] 6,[1b,8] 7[9] and 8-membered[10] carbo- and heterocycles, along with rings decorated with amidine[11] and ketone[7,12] functionality.

Rhodium-catalysed [m+n+o] carbocyclisation are further subdivided into three categories depending on the environment of the three unsaturated motifs (Scheme 1.1).

a. *Inter*molecular carbocyclisations ([m+n+o]) - where none of the π-components are tethered.

b. Semi-*inter*molecular carbocyclisations ([(m+n)+o]) - where two of the π-moieties are tethered.

c. *Intra*molecular carbocyclisations ([(m+n+o)]) - where the system is fully tethered.

Carbocyclisations in each category provide mono-, bi- and tricyclic ring motifs respectively. In addition, they often share similar reactivity and experience comparable selectivity issues. For example, *intra*molecular [m+n+o] carbocyclisations often proceed with high levels of chemoselectivity when undertaken at high dilution. It is important to note that universally applicable reaction conditions for each subcategory have not yet been disclosed; interchanging π-motifs requires reaction re-optimisation.

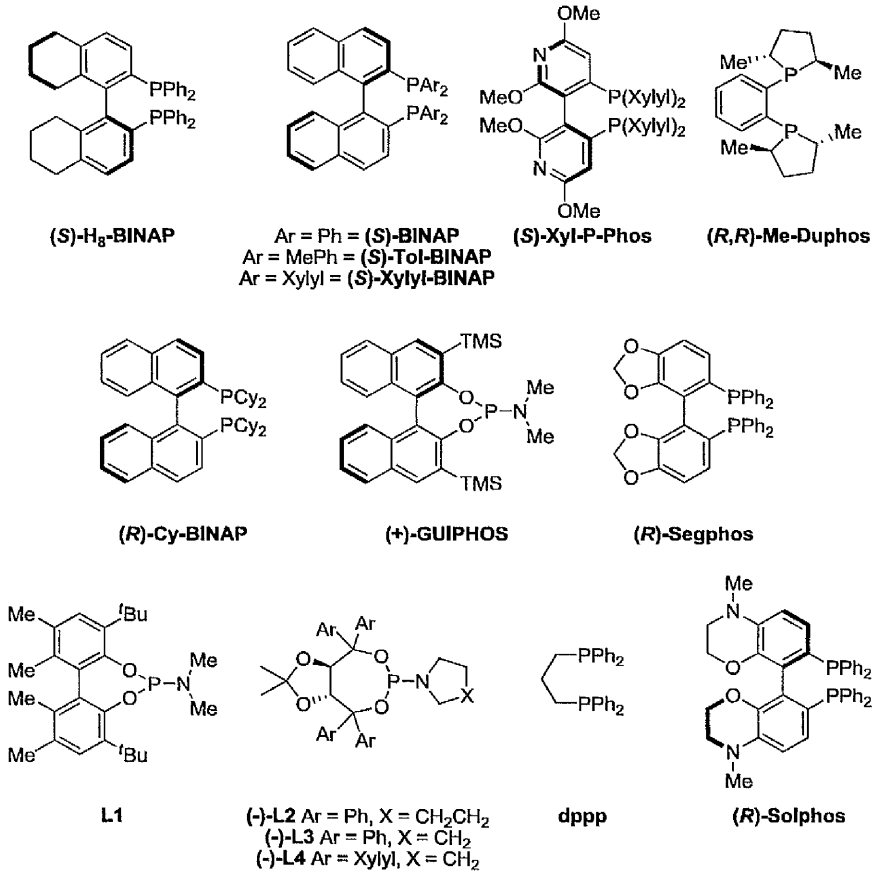


Figure 1.2 Summary of the various ligands utilised in rhodium-catalysed carbocyclisation transformations

Rhodium is known to bind a number of different classes of ligands. Figure 1.2 illustrates a selection of the ligands found to catalyse rhodium [m+n+o] carbocyclisation transformations. Manipulation of electronics and bite/cone angle, along with interchanging mono *vs.* bidentate ligands is necessary to furnish the required cyclic adducts. In addition, the temperature, reaction solvent and pressure have all been shown to have a profound influence on the selectivity outcome of a carbocyclisation event.

The ability to selectively access a single product is the primary goal of all organic transformations. A number of different cyclic products can arise during

every carbocyclisation event; this perspective will examine the factors which govern these outcomes and control the selectivity. Figure 1.3 provides a pictorial example of each category. This review will scrutinize the developments with rhodium-catalysed carbocyclisation under each of these topics. The value of rhodium-catalysed higher order cycloadditions is extended when successfully combined with one of a plethora of additional rhodium-catalysed reactions.

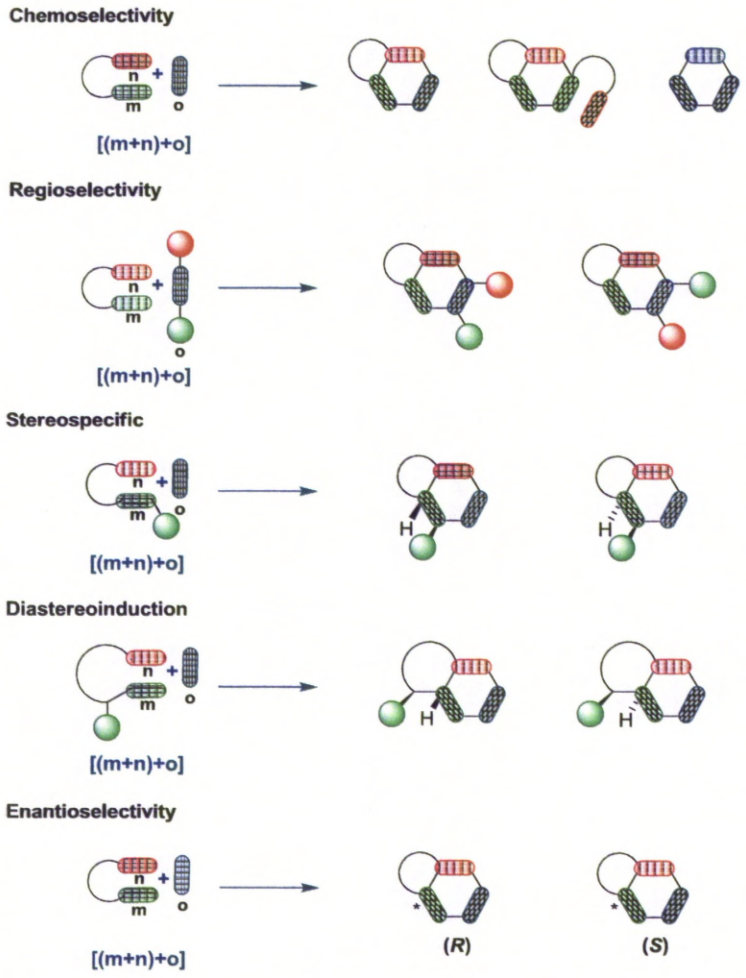


Figure 1.3 Selectivity considerations during rhodium-catalysed [m+n+o] carbocyclisation reactions

1.2 Chemoselectivity in Rhodium-Catalysed [m+n+o] Carbocyclisation Reactions

Subjecting multiple types of π-components to carbocyclisation conditions may result in the formation of several constitutional isomers. The trimerisation of the most reactive π-moiety is the most frequently observed by-product in reactions of this type. The *most reactive π-moiety* is the motif which most readily coordinates to the rhodium centre, as such, this moiety is then incorporated into the cyclic adduct three times. Controlling the ratio in which the unsaturated moieties are incorporated has been the focus of much study. In order to suppress undesired trimerisation reaction it is necessary either to reduce the affinity of rhodium to the most reactive π-moiety, increase the affinity of rhodium to the other unsaturated unit, or increase concentration of the less reactive moieties.

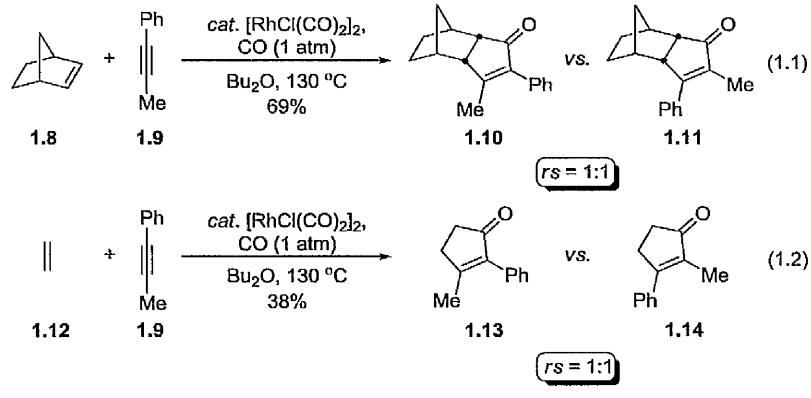
For *intra*molecular carbocyclisations the trimerisation incident can be obviated through dilution, whilst for *inter*molecular and semi-*inter*molecular transformations, chemoselectivity remains a challenging endeavour with several groups undertaking research to address this. During fully *inter*molecular [m+n+o] carbocyclisation reactions of three different components there are 10 different products possible.

There are many rhodium-catalysed [m+n+o] carbocyclisation examples that exhibit chemoselectivity which will not be described within this section; we have selected several examples which serve to illuminate the topic. In addition, many of

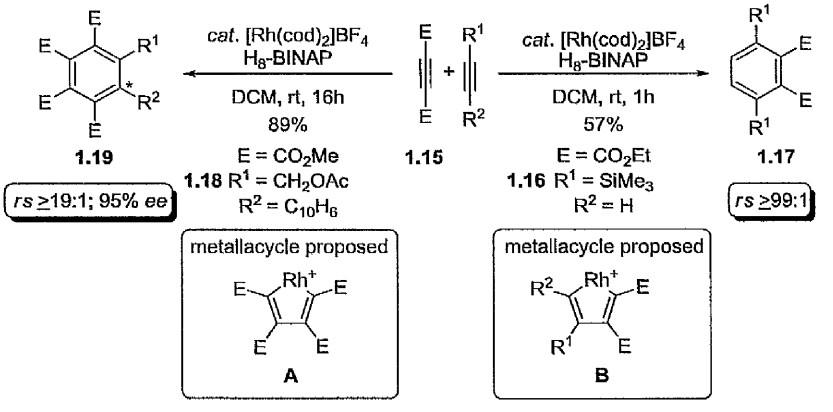
the examples in the following sections will exhibit chemoselectivity as well as demonstrating other selectivities.

1.2.1 Chemoselectivity in Rhodium-Catalysed *Inter*molecular Carbocyclisations

The first example of an *inter*molecular rhodium-catalysed Pauson-Khand reaction (PKR) was reported in 2001 by Narasaka for the construction of cyclopentenones.[13] Treatment of norbornene **1.8** and 1-phenylpropyne **1.9** with $[RhCl(CO)_2]_2$ under an atmosphere of carbon monoxide provided cyclic enones **1.10** and **1.11** in 69% yield and as a 1:1 mixture of regioisomers (eqn. (1.1)). The use of a more reactive alkene was found to be crucial for the success of the chemoselective *inter*molecular PKR. In addition, the authors demonstrated that under 10 atmospheres of ethylene gas **1.12** and one atmosphere of carbon monoxide, 1-phenylpropyne **1.9** underwent a Pauson-Khand annulation to provide cyclopentenones **1.13/1.14**, albeit in modest yield and also as a mixture of regioisomers (38%, *rs* = 1:1, eqn. (1.2)).



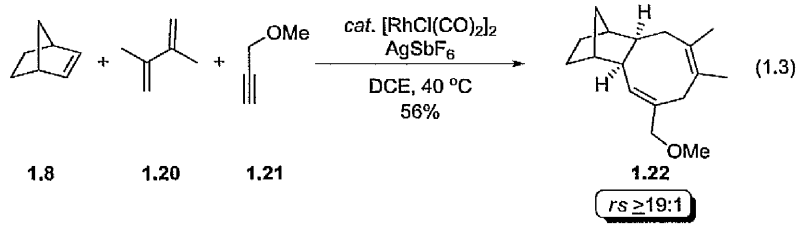
In 2003, the Tanaka group disclosed the co-trimerisation of two electronically different alkynes for the chemo- and regioselective synthesis of arenes.[14] Upon treatment with the requisite cationic rhodium-catalyst, mono-substituted alkyne **1.16** undergoes co-trimerisation with alkyne **1.15** to afford arene **1.17** in good yield and complete regiocontrol (57%, *rs* ≥99:1, scheme 1.2). Subsequent work within the Tanaka group described the chemoselective carbocyclisation of two equivalents of an electron poor alkyne with one equivalent of an electron rich alkyne for the synthesis of non-racemic biaryls.[15] Methyl ester **1.15** and unsymmetrical alkyne **1.18** were reacted with a chiral rhodium-H_8-BINAP complex to provide biaryl **1.19** in excellent yield and with excellent regio- and enantiocontrol (*rs* ≥19:1, 95% *ee*, scheme 1.2).



Scheme 1.2 Chemodivergent synthesis of arenes

The same catalyst is utilised in both transformations, as such we can conclude that it is the terminal substitution of the more electron rich alkyne which determines the chemoselective incorporation. During the carbocyclisation of a mono-substituted alkyne metallacycle **B** is favoured, with the transformation taking one hour to go to completion. Conversely, subjecting an internal alkyne to the reaction conditions results in the formation of metallacyclopentene **A** and the reaction is complete after 16 hours. As alkyne **1.15** is utilised in both transformations, metallacycle **A** can form

during both reactions. From this we can conclude that for mono-substituted alkynes the formation of metallacycle **B** is faster than the formation of metallacycle **A**, whilst the converse can be said for 1,2 disubstituted alkynes.

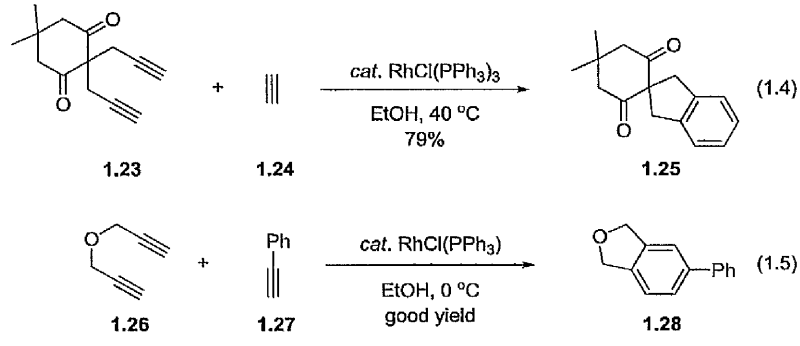


(1.3)

In 2006, Wender *et al.* developed the first example of an *inter*molecular *metal*-catalysed [4+2+2] carbocyclisation reaction to chemoselectively provide a cyclooctadiene with complete diastereocontrol.[4] They demonstrated that upon treatment with the requisite rhodium-catalyst, cyclic norbornene **1.8**, butadiene **1.20** and acetylene **1.21**, will react in a chemoselective manner to provide compound **22** in good yield and excellent diastereocontrol (56%, *ds* ≥19:1 eqn. (1.3)). The highly strained nature of the alkene in norbornene **1.8** increases the reactivity of the alkene moiety, encouraging incorporation into the metallacycle. To further promote the chemoselective coordination of norbornene **1.8** and butadiene **1.20** to the rhodium centre these components are supplied in large excess, six and five equivalents respectively. It is worthy to note, that the generality of this reaction has not been disclosed.

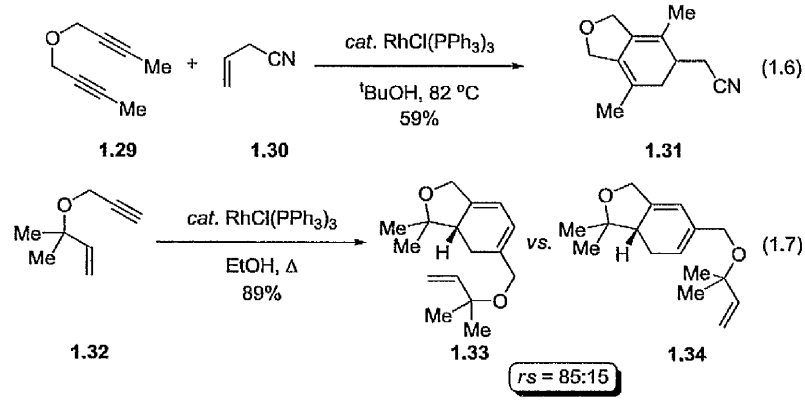
1.2.2 Chemoselectivity in Rhodium-Catalysed Semi-*Inter*molecular [(m+n)+o] Carbocyclisations

In 1982, Grigg *et al.* developed a chemoselective rhodium-catalysed semi-*inter*molecular [(2+2)+2] carbocyclisation.[3] Utilising Wilkinson's catalyst a series of 1,6-diynes were reacted with alkynes to chemoselectively provide benzene derivatives in good yield. Treatment of diyne **1.23** and acetylene **1.24** to Wilkinson's catalyst provided spiro-adduct **1.25** in 79% yield (eqn. (1.4)). It is worth noting that the reaction conditions had to be tailored for each substrate, with the temperature and catalyst loading ranging between 0 – 79 °C and 0.5 – 2 mol%. For example, phenyl acetylene **1.27** is known to trimerise under these conditions at temperatures greater than 25 °C, hence the formation of this undesired product was suppressed by performing the reaction at 0 °C, to afford the desired adduct **1.28** in good yield (eqn. (1.5)).



Subsequent work within the Grigg group disclosed the first semi-*inter*molecular rhodium-catalysed [(2+2)+2] reaction of a 1,6-diyne and an alkene.[17] Subjection of 1,6-diyne **1.29** and acrylonitrile **1.30** to Wilkinson's catalyst afforded diene **1.31** in 59% yield (eqn. (1.6)). Crucial to the success of this transformation was

utilising 1,6-diyne with terminal substitution in order to suppress the undesired dimerisation of compound **1.29**. The same paper reported the first example of a rhodium-catalysed semi-*inter*molecular [(2+2)+2] dimerisation of a 1,6-enyne. Treatment of compound **1.32** with Wilkinson's catalyst at reflux provided bicyclic dienes **1.33/1.34** in 89% as an 85:15 ratio of regioisomers (eqn. (1.7)). Interestingly, the conditions found to be optimum for the 1,6-diyne failed to furnish the desired bicycle, with ethanol solvent proving optimal.



1.2.3 Chemoselectivity Final Remarks

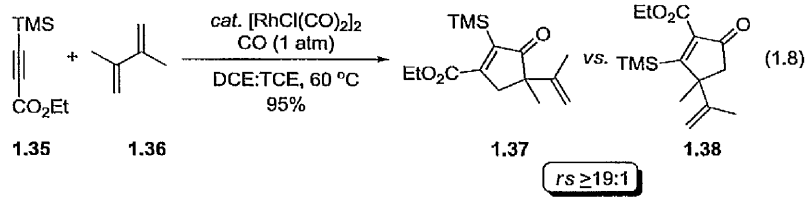
Despite the advances specified above, controlling the chemoselective outcome of rhodium-catalysed [m+n+o] carbocyclisation reactions remains a challenging obstacle. The *inter*molecular rhodium-catalysed [2+2+2] of three different units remains elusive. In addition, the successful incorporation of alkenes is often restricted to highly strained or conjugated moieties. This serves to significantly limit the current synthetic utility of these reactions. Nevertheless, the pursuit of *inter*molecular [m+n+o] carbocyclisations remains a beneficial endeavour since they provide a direct route to hetrocyclic compounds from commercially available materials. In contrast, *intra*molecular carbocyclisations, which circumvent

chemoselectivity issues through dilution, often require lengthy multi step synthesis to obtain substrates.

1.3 Regiocontrol in Rhodium-Catalysed [m+n+o] Carbocyclisation Reactions

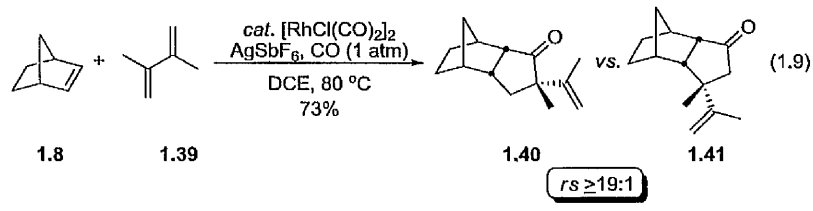
A variety of regioisomers can arise from carbocyclisations which involve the reaction of two or more unsymmetrical moieties. The ratio of these products can be a result of mathematical probability or one regioisomer may dominate through judicious choice of reaction conditions. Factors governing the orientation of an unsaturated motif upon insertion include minimisation of steric hindrance, the dipole moment of the π-moiety and restricted rotation of the σ-motif, either resulting from the tethering or the coordination of the metal centre to an adjacent directing group.

1.3.1 Regiocontrol in Rhodium-Catalysed *Inter*molecular [m+n+o] Carbocyclisation Reactions

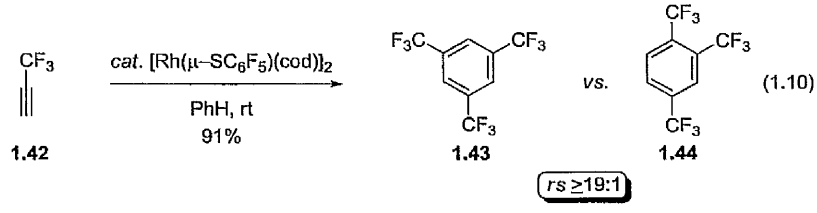


Wender and co-workers reported the first example of a rhodium-catalysed regioselective PKR for the synthesis of cyclopentenones.[18] Under an atmosphere of carbon monoxide, treatment of unsymmetrical alkyne **1.35** and diene **1.36** with $[RhCl(CO)_2]_2$ to provide adduct **1.37** in excellent yield and regioselectivity (95%, *rs* ≥19:1, eqn. (1.8)). Several unsymmetrical alkynes were reacted to give a series of cyclopentenones with yields and regioselectivities depending on the substitution of

the alkyne. Significantly, any modification of the diene resulted in diminished reaction yields or halted the reaction completely.



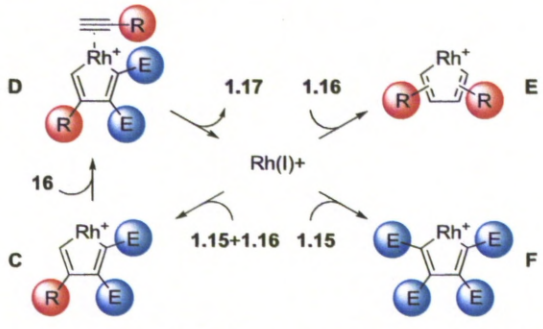
The group also described the first example of a regioselective *inter*molecular rhodium-catalysed PKR involving the reaction of a diene, an alkene and carbon monoxide.[19] Treatment of the highly strained norbornene **1.8** and two equivalents butadiene **1.39** with the requisite rhodium-complex under one atmosphere of carbon monoxide afforded cyclic enone **1.40** in 73% yield with excellent regiocontrol (*rs* ≥19:1 eqn. (1.9)). Interestingly, utilising the diene is again crucial to the success of the reaction; the analogous semi-*inter*molecular reaction with a bis-ene fails to furnish the desired product. The scope of the transformation was not investigated further.



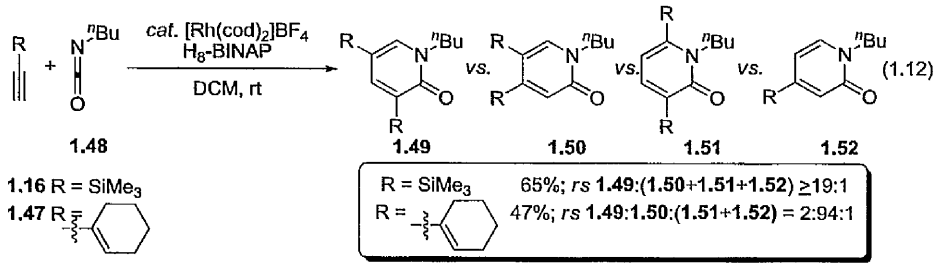
Garcia and co-workers outlined the first example of a regioselective *inter*molecular rhodium-catalysed carbocyclisation in 1996.[20] In a single example, they demonstrated that a rhodium-catalysed *inter*molecular [2+2+2] cycloaddition of fluoroalkylacetylenes would provide selective access to symmetrical 1,3,5-

trisubstituted arenes. Treatment of acetylene **1.42** with the requisite rhodium-catalyst furnished the desired trisubstituted aromatic **1.43** in excellent yield and regiocontrol (91%, *rs* ≥19:1, eqn. (1.10)).

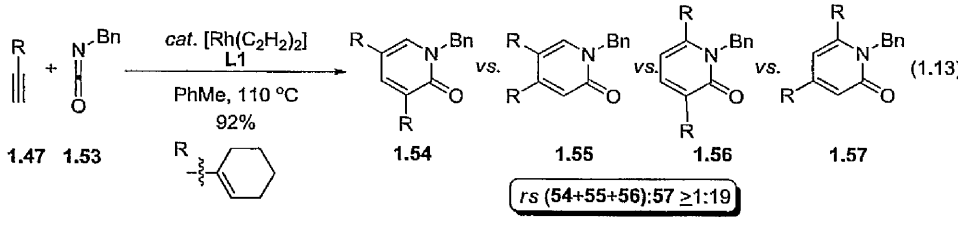
In section 1.2.1, we described the regio- and chemoselective *inter*molecular [2+2+2] carbocyclisation the Tanaka group disclosed for the construction of substituted arenes.[14] The trimerisation of alkynes **1.15** and **1.16** provided arene **1.17** in good yield and excellent regiocontrol (57%, *rs* = 99:1:0 eqn. (1.11)). Scheme 1.3 describes the plausible mechanism that the authors proposed to account for the high levels of selectivity in this transformation. The preferential formation of metallacycle **C** over metallacycle **E** and **F** accounts for the high levels of chemo- and regioselectivity observed in this transformation. The coordination of terminal alkynes results in the formation complex **D**; subsequent reductive elimination furnishes **1.17** and regenerates the active rhodium-catalyst. They demonstrated that whilst alkyl-acetylene and aryl-acetylene are suitable substrate for this transformation, sterically hindered alkynes suffer from reduced reactivity.



Scheme 1.3 Proposed mechanism for the co-trimerisation of alkynes **1.15** + **1.16**

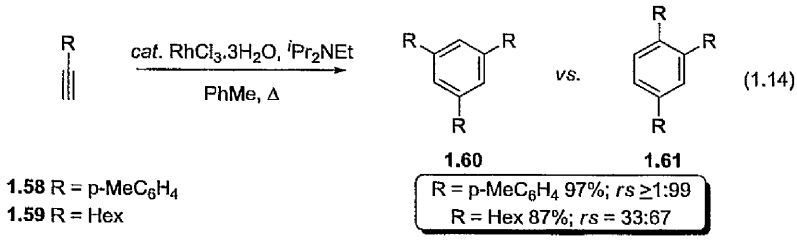


Tanaka went on to expand this rhodium-catalysed *inter*molecular [2+2+2] methodology to the synthesis of nitrogen heterocycles by replacing the 2π dialkyl acetylenedicarboxylate component **1.15** with an isocyanate moiety.[21] They demonstrated that under the same catalytic conditions isocyanate **1.48** reacted with two equivalents of alkyne **1.16** to afford pyridone **1.49** in good yield and excellent regiocontrol (*rs* **1.49**:(**1.50**+**1.51**+**1.52**) ≥19:1, eqn. (1.12)). The regioselectivity observed was shown to be highly dependent on the substitution of the alkynes, for example when cyclohexene **1.47** is subjected to the same reaction conditions complementary pyridone **1.50** is obtained as the major regioisomer in moderate yield (47%, *rs* **1.49**: **1.50**:(**1.51**+**1.52**) = 2:97:1).



Interestingly, Rovis later reported a rhodium-catalysed *inter*molecular [2+2+2] carbocyclisation for the construction of an alternative pyridone regioisomer.[22] They demonstrated that treatment isocyanate **1.53** and two equivalents of alkyne **1.47** with the requisite neutral rhodium-phosphoramidite complex

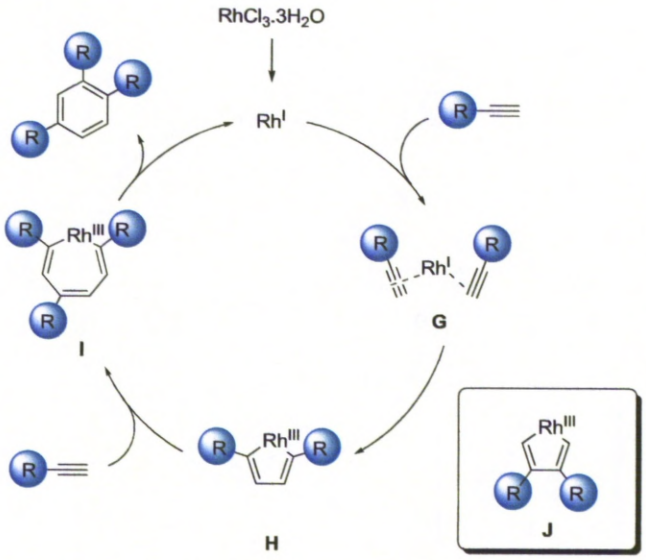
furnishes pyridone **1.57** in 92% and excellent regiocontrol (*rs* (**1.54**+**1.55**+**1.56**): **1.57** ≥19:1, eqn. (1.13)). Significantly, the high levels of selectivity observed are independent of the electronics and sterics of the alkyne.



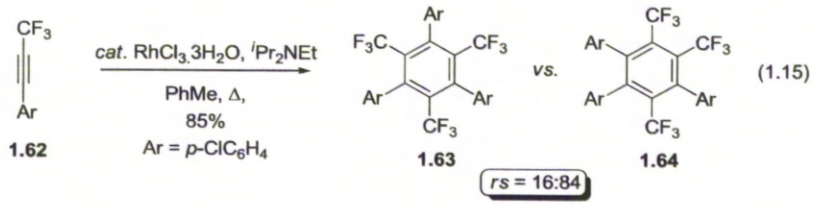
In 2007, H. Tanaka described the regioselective rhodium-catalysed [2+2+2] trimerisation of a series of mono-substituted and internal alkynes for the construction of substituted arenes in moderate to high yields.[23] For example, in the presence of $RhCl_3.3H_2O$ and $^iPr_2NEt$, alkyne **1.58** underwent trimerisation to give trisubstitued arene **1.61** in excellent yield and regioselectivity (97%, *rs* ≥1:99, eqn. (1.14)). The regioselectivity was demonstrated to be highly influenced by substituents on the alkyne, with aryl groups reacting with high levels of regiocontrol and less sterically hindered alkyl-acetylenes suffering from reduced selectivity (**1.59**, 87%, *rs* ≥33:67, eqn. (1.14)).

In a subsequent paper, the authors proposed the mechanism outlined in scheme 1.4 to account for the varying degrees of regiocontrol.[24] The active catalyst is formed by reduction of $RhCl_3.3H_2O$ by the amine to afford an electron-rich rhodium(I)-species. Coordination of two alkynes and oxidative addition provides rhodacyclopentadiene **H**. Carbometallation of the final alkyne (intermediate **I**) and reductive elimination furnishes the arenes and regenerates the active catalyst. They postulated that higher levels of regiocontrol are observed for aromatic-aryl moieties

as a result of the preferential formation of di(α-aryl)-rhodacyclopentadienes (**H**, R = Ar) over di(β-aryl) rhodacyclopentadienes (**J**).



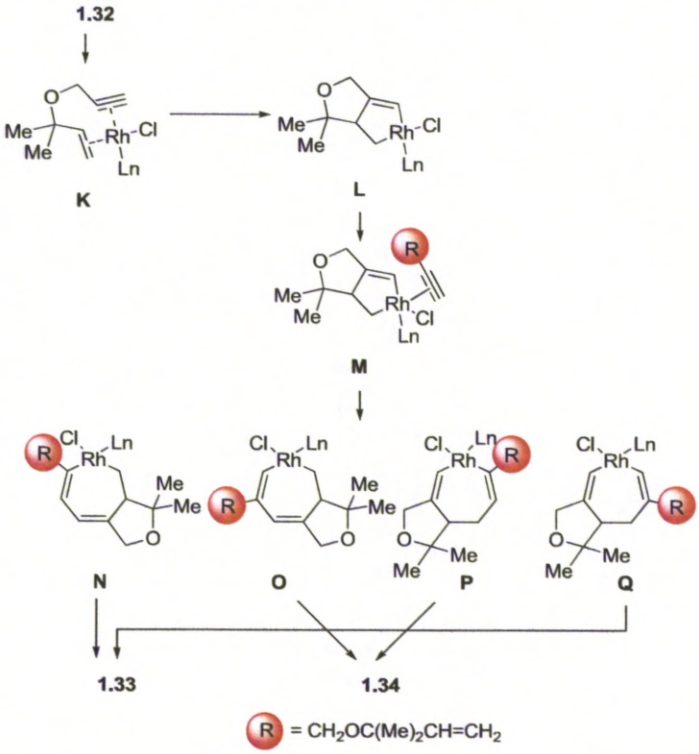
Scheme 1.4 Proposed mechanism for the [2+2+2] trimerisation of alkyne **1.58** and **1.59**



Recently, Konno *et al.* reported that the complementary 1,2,5-CF_3-trisubstituted arenes could be accessed *via* a rhodium-catalysed [2+2+2] trimerisation reaction.[25] For example, acetylene **1.62** underwent carbocyclisation with rhodium chloride and $^{i}Pr_2NEt$ amine additive to afford fluoroalkylated aromatics **1.63** and **1.64** in 85% yield and a 16:84 ratio of regioisomers favouring arene **1.64** (eqn. (1.15)). The reaction is tolerant of electron rich and deficient aromatic substituents, however the trimerisation of alkyl-alkenes proved unsuccessful. Aryl alkenes and alkynoates were shown to be suitable substrates for this transformation, although

they suffer from marginally reduced yields and regioselectivity. It is worthy to note that this methodology provides complementary CF_3-substituted arenes to those previously reported by Garcia (section 1.3.1, eqn (1.10)).

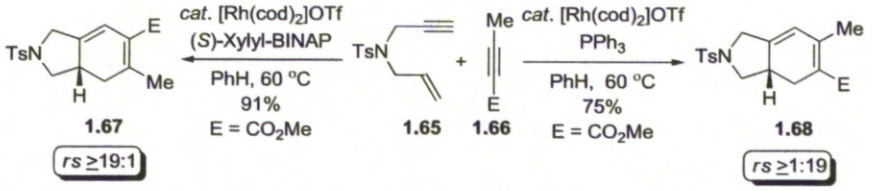
1.3.2 Regiocontrol in Rhodium-Catalysed Semi-*Inter*molecular [(m+n)+o] Carbocyclisation Reactions



Scheme 1.5 Proposed mechanism for the formation of bicyclic diene **1.33**

In section 1.2.2, (eqn. (7)) we described the regioselective rhodium-catalysed [(2+2)+2] dimerisation of 1,6-enynes.[17] Scheme 1.5 delineates the mechanism that the authors proposed to account for the selectivity in the formation of dimer **1.33** over **1.34**. The initial coordination of the 1,6-enyne to the rhodium centre and subsequent oxidative addition provide metallacycle **L**. Coordination of a further alkyne moiety, followed by insertion, gives a rhodacycloheptadiene intermediate.

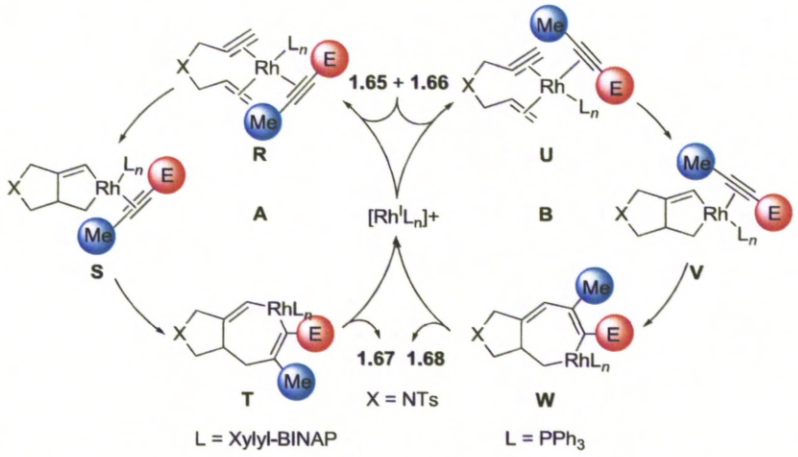
Four different rhodacycloheptadienes can arise depending on whether the insertion step involves the alkyl-rhodium bond or the vinyl-rhodium bond and the orientations of the alkyne upon insertion. Subsequent reductive elimination then furnishes **1.33** and **1.34**; the major product **1.33** arises either by insertion of the alkyne into the vinyl-rhodium bond with the R group adjacent to rhodium (metallacycle **N**) or by insertion of alkyne into the alkyl-rhodium bond with R oriented away from rhodium (metallacycle **Q**). The authors postulate that the regiospecific insertion into the vinyl-rhodium σ-bond to give **N** is the most likely route to **1.33**. Interestingly, carbocyclisation is suppressed by terminal substitution of the alkene; it was suggested that this is a consequence of less effective co-ordination of the terminal alkene, *i.e.* rhodacyclopentene formation is suppressed.



Scheme 1.6 Regiodivergent rhodium-catalysed [(2+2)+2] carbocyclisation for the construction of bicyclohexadiene

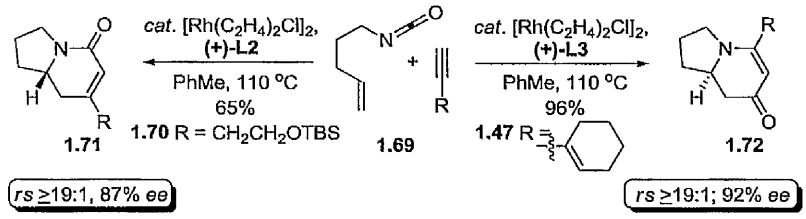
Evans *et al.* delineated the first example of a regiodivergent rhodium-catalysed [(2+2)+2] carbocyclisation.[26,27] They demonstrated that through the judicious choice of ancillary ligand it is possible to selectively construct complementary bicyclohexadiene regioisomers in a manner analogous to the way in which Nature utilises enzymes to construct analogues of compounds from a small range of starting materials. For example, treatment of 1,6-enyne **1.65** and methyl-2-butynoate **1.66** with a cationic rhodium-Xylyl-BINAP complex prepared *in situ*, furnishes the desired diene **1.67** in good yield and excellent regiocontrol (91%, *rs*

≥19:1, scheme 1.6). Conversely, subjecting the same substrates to a cationic rhodium-PPh_3 complex prepared *in situ,* provides the corresponding bicyclohexane **1.68**, also in excellent regiocontrol and 75% yield.



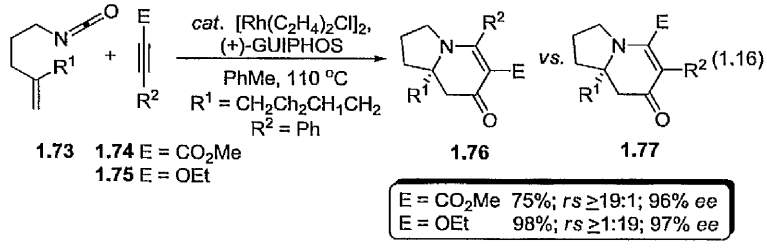
Scheme 1.7 Proposed catalytic cycles for the regiodivergent rhodium-catalysed [(2+2)+2] cycloaddition reaction

The authors postulated that the observed regiodivergency can be accounted for by the mechanistic dichotomy delineated in Scheme 1.7. The initial coordination of the 1,6-enyne (**1.65**) and subsequent oxidative addition affords metallabicyclopentenes **S** and **V**. The mechanistic dichotomy arises from the migratory insertion of the alkyne into either the rhodium–alkyl bond of **S** (**Cycle A**), or the rhodium–vinyl bond in metallacycle **N** (**Cycle B**). The resulting metallabicycloheptadiene **T** and **W** then undergo reductive elimination to furnish bicyclohexa-1,3-dienes **1.67** and **1.68,** respectively. The preferential migration of the rhodium–alkyl *vs.* the rhodium–vinyl bond arises as a result of obstruction of the necessary *cis*-alignment with the vinyl group in **S** due to the bidentate ligand; this in turn promotes the generally less-favourable alkyl migration.

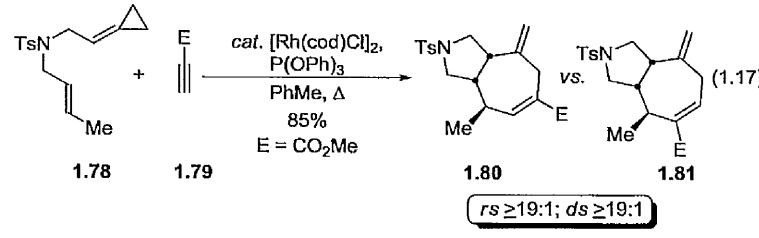


Scheme 1.8 Regiodivergent [(2+2)+2] carbocyclisation of tethered isocyanate-alkenes with alkynes

In 2006, Rovis investigated the semi-*inter*molecular rhodium-catalysed [(2+2)+2] cycloadditions for the synthesis of nitrogen containing heterocycles.[28] They demonstrated that the nature of the terminal alkyne (aryl/conjugated or alkyl) controls the regioselectivity of the transformation. For example, treatment of alkenyl isocyanate **1.69** and alkyl acetylene **1.70** with the requisite neutral rhodium-phosphoramidite (**(+)-L2**) complex, yields cyclic lactam **1.71**, as a single regioisomer in excellent enantioselectivity (65%, *rs* ≥19:1, 87% *ee*, scheme 1.8). Whilst the reaction of **1.69** and **1.47** in the presence of the same catalyst modified with phosphoramidite **(+)-L3**, underwent an atypical [(2+2)+2] cycloaddition to furnish the bicyclic vinylogous amide product **1.72**, in 96% yield and excellent regio- and enantiocontrol (*rs* ≥19:1, 92% *ee*). This unique rhodium-catalysed [(2+2)+2] transformation includes two C-C and C-N bond-forming events and results in fragmentation of the isocyanate moiety.

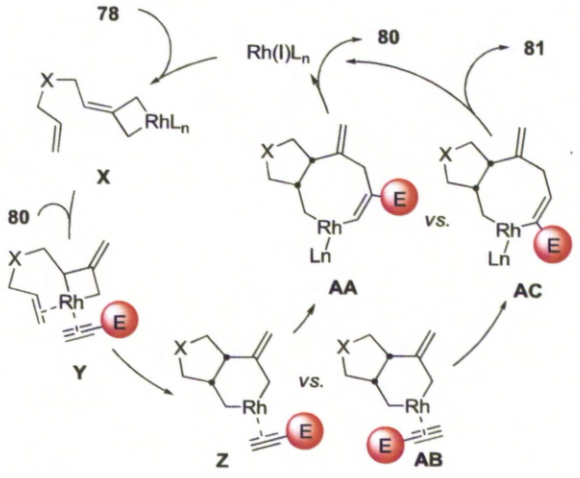


Rovis later went on to expand this methodology for the regioselective incorporation of internal unsymmetrical alkynes.[29] They demonstrated that by varying the electronic substituents on the alkyne they could manipulate the orientation of the alkyne upon insertion. For example, upon treatment with the requisite rhodium-complex, isocyanate **1.73** undergoes cycloaddition with unsymmetrical alkyne **1.74** (containing an electron withdrawing R-substituent) to provide bicyclic vinylogous amide **1.76** in 75% yield and excellent regio- and enantiocontrol (*rs* ≥19:1, 96% *ee,* eqn. (1.16)). Conversely, under the same reaction conditions alkyne **1.75**, (containing an electron-donating substituent on the acetylene) provides the analogous vinylogous amide **1.77** in excellent yield, regio- and enantioselectivity (98%, *rs* ≥1:19, 97% *ee*). Diminished reaction rates were observed upon cycloaddition of electron deficient aryl alkynoate and alkynes with sterically bulky substituents.



The first rhodium-catalysed semi-*inter*molecular [(3+2)+2] carbocyclisation for the construction of the bicycloheptenes was reported by Evans in 2008.[9] They demonstrated that an alkenylidenecyclopropane (ACP) tethered to an alkene would undergo cycloaddition with activated alkynes in a highly regio- and diastereoselective manner. For example, treatment of ACP **1.78** and alkyne **1.79** with a rhodium-phosphite complex furnished bicyclic **1.80** in 85% yield, in excellent regio- and diastereocontrol (eqn. (1.17)). Diminished regioselectivity was observed

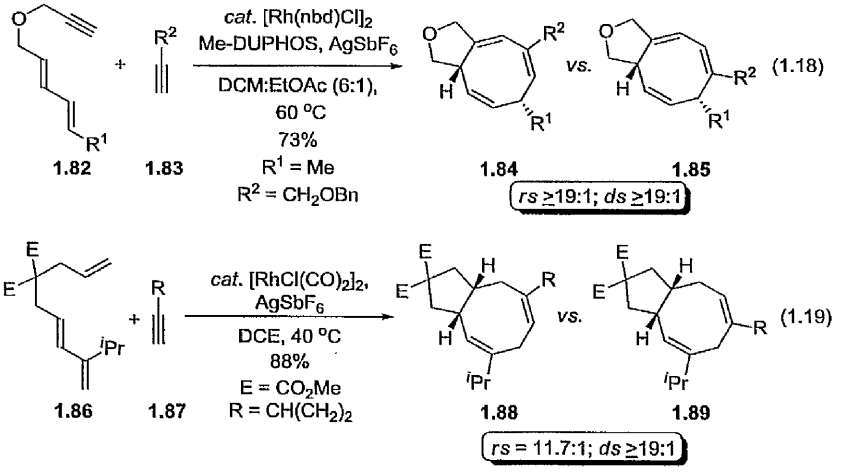
with terminal alkenes leading the authors to conclude that the catalytic cycle delineated in scheme 1.9 is prevalent within this transformation. Oxidative addition of rhodium into the distal bond of the ACP **1.78** provides metallacyclobutene **X**, which upon rearrangement and an *intra*molecular carbometallation of the pendent alkene, results in metallacyclopentene **Z**. During this step the two stereogenic centres are installed. A second carbometallation of the alkyne moiety provides either **AA** or **AC** depending on the orientation of the alkyne upon insertion. Hence 1,2-substituted alkene experience greater degrees of regioselectivity due to greater steric hindrance promoting the preferential formation of metallacycle **AA** from **Z**. Finally a reductive elimination results in compound **1.80** or **1.81** and regeneration of the active catalyst.



Scheme 1.9 Postulated catalytic cycle for the semi-*inter*molecular [(3+2)+2] cycloaddition

The Gilbertson group described a regioselective rhodium-catalysed semi-*inter*molecular [(4+2)+2] carbocyclisation for the construction of bicyclooctatrienes (eqn. (1.18)).[30] Subjecting compound **1.82** and alkyne **1.83** to the requisite rhodium-catalyst affords the bicyclic adduct **1.84** in 73% yield and excellent regio- and

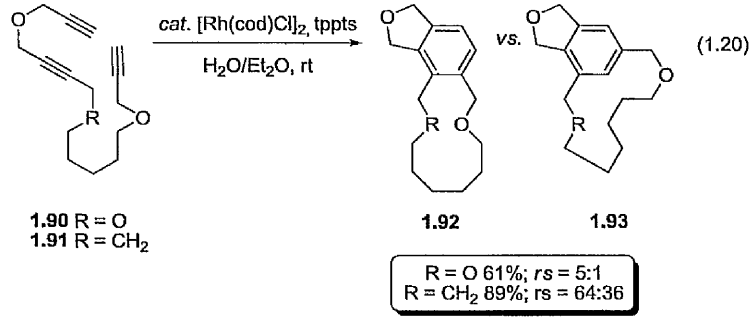
diastereocontrol (*rs* ≥19:1, *ds* ≥19:1). Interestingly, internal dienes underwent carbocyclisation with diminished yield and furnished a mixture of regioisomers.



Wender *et al.* reported a rhodium-catalysed semi-*inter*molecular [(4+2)+2] carbocyclisation for the construction of bicyclooctenes.[31] Previous work within the group outlined that substrates of the type **1.86** undergo a rhodium-catalysed [4+2] isomerisation to provide 5,6-bicyclic compounds. It was demonstrated that compounds of this type are also suitable substrates for semi-*inter*molecular [(4+2)+2] with alkynes, providing 5,8-bicyclic adducts in good regiocontrol and excellent diastereoselectivity. For example, treatment of **1.86** and acetylene **1.87** with the requisite cationic rhodium-complex afforded bicyclooctadienes **1.88** and **1.89** in excellent diastereocontrol and as an 11:7 mixture of regioisomers, favouring **1.88** (eqn. (1.19)). The transformation was shown to be tolerant of a range of acetylenes including alkyl, ether, ester and ketone substituents. In addition 1,1-disubstituted alkenes were shown to undergo carbocyclisation facilitating the introduction of quaternary carbon stereogenic centres.

1.3.3 Regiocontrol in Rhodium-Catalysed *Intra*molecular [(m+n+o)] Carbocyclisation Reactions

In 2003, Oshima and co. delineated a rhodium-catalysed [(2+2+2)] cycloisomerisation transformation for the synthesis of arenes.[32] Treatment of trieyne **1.90** with the requisite rhodium-catalyst provides arenes **1.92** and **1.93** in 61% yield as a 5:1 mixture of regioisomers, favouring **1.92** (eqn. (1.20)). These findings represent seminal work within the field, despite the moderate regiocontrol, since they represent the first example of regiocontrol within the *intra*molecular manifold. Significantly, the ether tether was crucial to the regiocontrol obtained, with trieyne **1.91** undergoing carbocyclisation to provide arenes **1.92** and **1.93** in 89% yield as a 64:36 mixture of regioisomers.



1.3.4 Regiocontrol Final Remarks

Much work has been undertaken within this arena. To maximise the utility of regioselective carbocyclisations high levels of regiocontrol must be attainable for a large range of substrates, allowing the researcher to anticipate the outcome of the transformation. The pinnacle of regiocontrol within [m+n+o] carbocyclisations is the

ability to select complementary regioisomers through modification of the catalytic system. This has been exemplified by the [(2+2)+2] work undertaken by Evans and Rovis. The work of Garcia and Konno serves as an additional example.

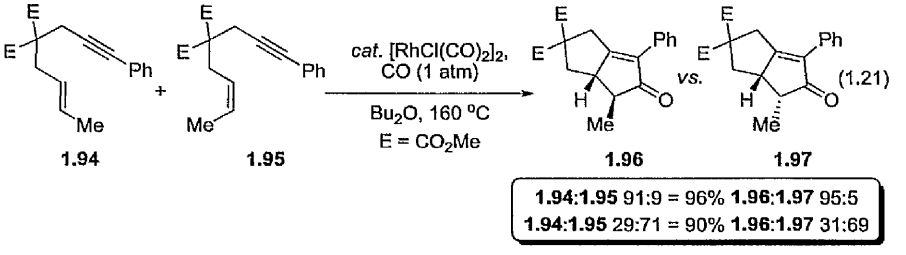
1.4 Stereospecific Rhodium-Catalysed [m+n+o] Carbocyclisation Reactions

A large degree of success has been achieved within the field of diastereoselective rhodium-catalysed [(m+n+o)] carbocyclisations and consequently this topic has been comprehensively reviewed previously.[1c] As such, we felt it unnecessary to further highlight this topic within this article, rather, we have chosen to delineate the concepts of the expanding field of stereospecific carbocyclisations; as a group we have an ongoing interest in the ability to selectively access complementary diastereoisomers. Such dichotomy is conceptually appealing since it has the potential to allow access to families of natural products or libraries of analogues *via* late stage manipulations.

1.4.1 Stereospecific Rhodium-Catalysed Semi-*Inter*molecular [(m+n)+o] Carbocyclisation Reactions

In 2001, Narasaka *et al.* reported the first example of stereoincorporation within a rhodium-catalysed carbocyclisation.[13] This study outlined the Pauson-Khand annulation of 1,6-enynes under one atmosphere of carbon monoxide, to provide cyclopentenone in good to excellent yield. Significantly, the reaction was found to be tolerant of disubstituted alkenes, with the geometry of the alkene determining the sterochemical outcome of the reactions. For example, subjecting the predominately (*E*)-isomer **1.94** (**1.94**: **1.95** 91:9) to the reaction conditions allowed access to

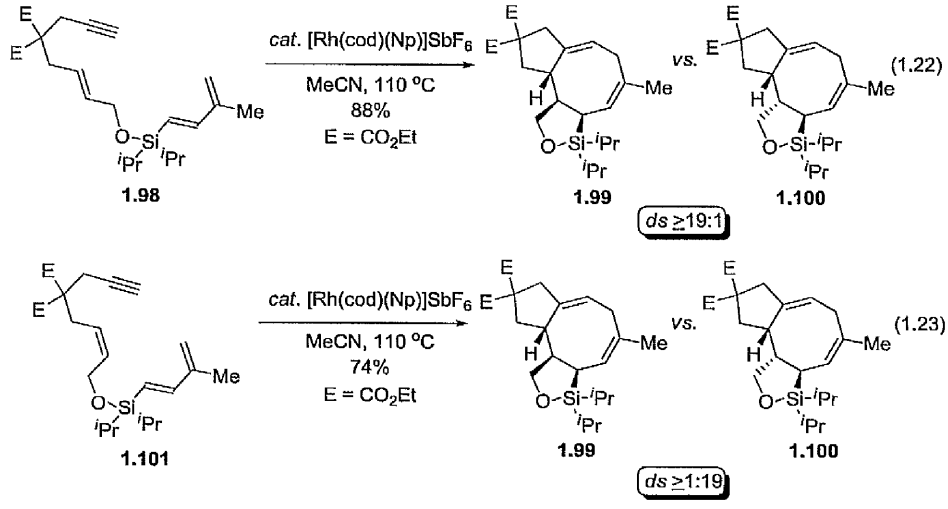
cyclopentenone **1.96** in excellent yield and with almost complete stereoincorporation (96%, **1.96**: **1.97** = 95:5, eqn. (1.21)). Conversely, treatment of the analogous (*Z*)-isomer **1.95** (**1.94**: **1.95** 29:71) with the requisite rhodium catalyst furnish cyclopentenone **1.97** with comparable stereoincorporation and yield (90%, **1.96**: **1.97** 31:69). Interestingly, it was demonstrated that electron withdrawing groups are also tolerated at this position; significantly, electron deficient alkenes are not suitable substrates in cobalt catalysed PK reactions. Crucial to the success of carbocyclisation of these substrates was the reduction in concentration of carbon monoxide (0.1 atm) to eliminate a subsequent decarboxylation reaction.[33]



1.4.2 Stereospecific Rhodium-Catalysed *Inter*molecular [(m+n+o)] Carbocyclisation Reactions

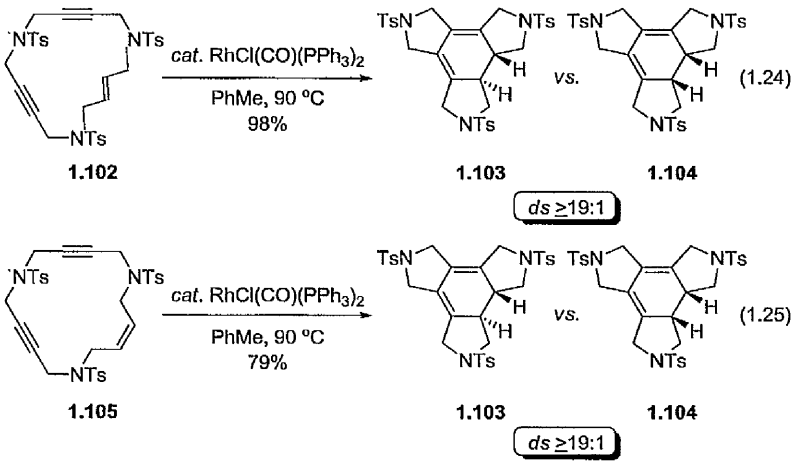
Evans *et al.* reported a temporary silicon-tethered *intra*molecular rhodium-catalysed [(4+2+2)] carbocyclisation which was shown to exhibit an intriguing alkene based dichotomy.[34] During the reaction the (*E*)- and (*Z*)-olefins are stereospecifically incorporated, to afford the diastereomeric tricyclic octanoids with excellent selectivity. For example, treatment of diene-yne-ene **1.98** with the requisite cationic-rhodium catalyst provided octanoid **1.99** in 88% yield as a single diastereoisomer (*ds* ≥19:1, eqn. (1.22)). Isomerisation of **1.101** occurs under the

same reaction conditions to provide tricyclic adduct **1.100** in good yield and excellent diastereoselectivity (74% yield, *ds* ≥19:1, eqn. (1.23)). The silicon-tethered [(4+2+2)] cycloisomerisation reaction addressed the underlying limitations of the previously reported semi-*inter*molecular variant, with carbon tethered enynes successfully undergoing cycloisomerisation and the tethering of the 1,3-disubstituted dienes circumventing regiochemical problems. Significantly, this widens the synthetic utility of the transformation allowing expedient access to a number of natural products.



Roglans *et al.* described the carbocyclisation of macrocyclic enediynes providing access to tetracycles with complete stereospecificity with respect to the regioincorporation of the initial macrocyclic alkene bond.[35] This research demonstrated that the treatment of macrocyclic enediynes **1.102** and **1.105** with the requisite rhodium-catalyst furnishes the resultant tetracycle **1.103** and **1.104**, in excellent yield and stereospecificity (eqn. (1.24) & (1.25)). The authors postulate a mechanism involving either the initial coupling of the two alkyne groups, followed by the incorporation of the olefin *via* a carbometallation or a Diels-Alder type

cycloaddition. Both mechanisms account for the high levels of stereospecificity. Interestingly, none of the analogous aromatic tetracycle was observed despite the presence of an active transition metal.



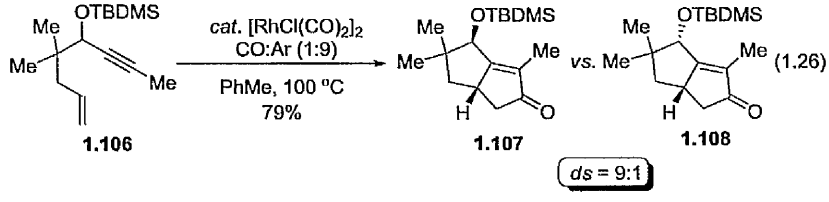
1.4.3 Stereospecific Final Remarks

In order to observe high levels of stereoincorporation, it is imperative that the carbocyclisation conditions are tolerant to incorporating 1,2-disubstitued alkenes (section 1.2.1) and mild enough to prevent isomerisation of the internal olefin. This phenomenon has yet to be described within the fully intermolecular manifold. This is probably a consequence of the problems associated with chemo- and regioselective incorporation of the requisite olefin moiety into the metallacycle (section 1.2).

1.5 Diastereoinduction in Rhodium-Catalysed [m+n+o] Carbocyclisation Reactions

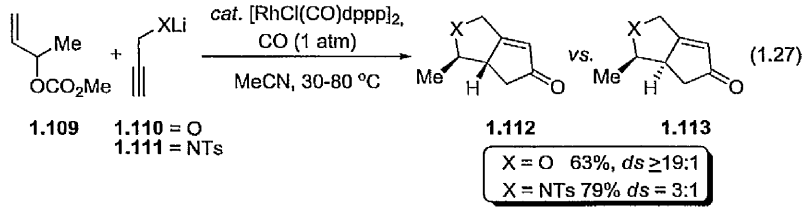
Through the judicious choice of chiral substrate it is possible to influence the stereochemistry of the cyclic products of a carbocyclisation transformation. A chiral centre situated adjacent to an unsaturated motif can have a profound impact upon the metallacycles formed; if coordination of the unsaturated moiety to the metal centre occurs preferentially on the less sterically encumbered face of the molecule, diastereocontrol is observed. When the substrate is enantiomerically enriched, the inherent chirality of the substrate is relayed into the product; this allows access to enantiomerically enriched metallacycles without modification of the catalytic system with chiral ligands which can alter the reactivity profile of the reaction.

1.5.1 Diastereoinduction in Rhodium-Catalysed Semi-*Inter*molecular [(m+n)+o] Carbocyclisation Reactions

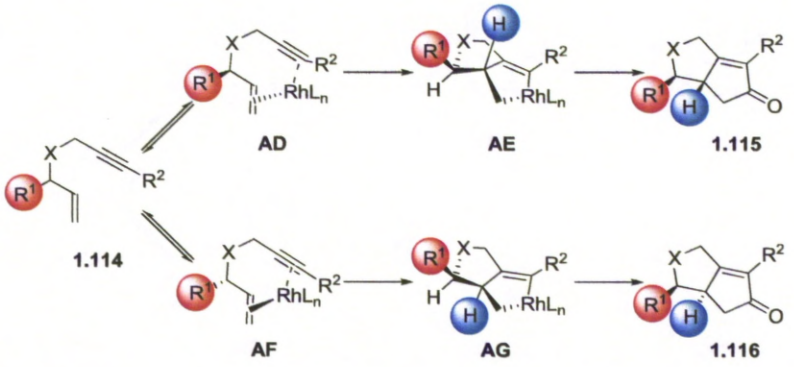


The Narasaka group demonstrated the first example of stereoinduction within a rhodium-catalysed Pauson-Khand annulation reaction.[13] Their study outlined the carbocyclisations of various 1,6-enynes with $[RhCl(CO)_2]_2$, furnishing the corresponding cyclopentenone in good to excellent yields. In a single example, they found that treatment of racemic enyne **1.106** with the requisite rhodium-catalyst

under 0.1 atmosphere of carbon monoxide furnishes bicyclic compounds **1.107** and **1.108** in 79% yield as a 9:1 ratio of diastereoisomers (eqn. (1.26)). This transformation was the key step in their formal synthesis of *dl*-coriolin, and was performed on a multi-gram scale.

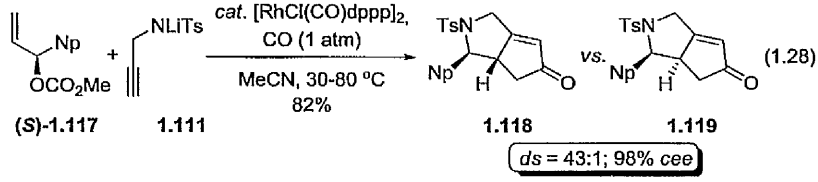


The Evans group demonstrated that stereoinduction in the Pauson-Khand annulation reaction could be extended to a phosphine bound rhodium-catalyst.[36] A series of 1,6-enynes containing a methyl bearing stereogenic centre at the allylic position were prepared *via* an allylic amination reaction. An *in situ* PKR furnished the corresponding cyclopentenones with moderate diastereocontrol and in good yields. As a case in point, allyl carbonate **1.109** and lithium salt **1.110** undergo annulation to give adduct **1.112** in 63% yield as a ≥19:1 mixture of diastereoisomers (eqn. (1.27)). Interestingly, the levels of stereocontrol were found to be variable, for example when tosyl **1.111** was subjected to the same reaction conditions bicyclic adducts **1.112** and **1.113** were obtained in 79% yield as a 3:1 mixture of diastereoisomers.

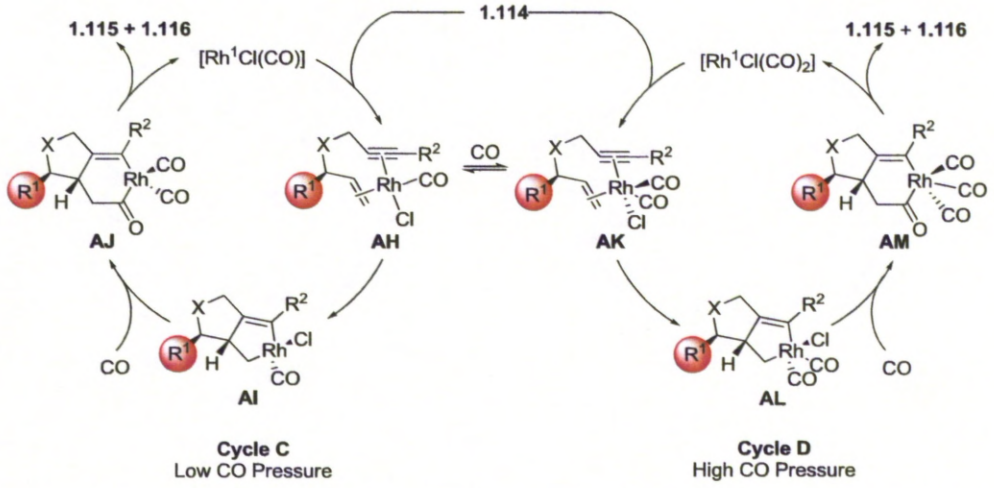


Scheme 1.10 Proposed mechanism for the diastereoselective Pauson-Khand reaction

Scheme 1.10 outlines the mechanistic hypothesis the authors proposed to account for the observed diastereoselectivity during the PK annulation. The initial coordination of enyne **1.114** with the rhodium-catalyst can proceed from either faces resulting in two diastereoisomers (**AD/AF**); the relative population of **AD** and **AF** is influenced by the steric bulk of the substituent at the allylic position of the 1,6-enyne (R^1). Oxidative addition then leads to the irreversible formation of the diastereomeric metallacycles **AE/AG**, subsequent migratory insertion of metal bound carbon monoxide, followed by reductive elimination to furnish bicyclic cyclopentenones **1.115** and **1.116**. Based on this mechanism the authors rationalised that *if* the initial coordination is reversible, increasing the steric hindrance exhibited by the substituent R^1 should significantly improve the diastereoselectivity of the transformation. To test this hypothesis, the methyl group was replaced with a 2-naphthyl substituent. Gratifyingly, allyl carbonate **(*S*)- 1.117** and tosyl compound **1.111** underwent allylic substitutions followed by carbocyclisation under the optimised reaction conditions to furnish adducts **1.118/1.119** in a good yield and excellent diastereoselectivity (82%, *ds* = 43:1, eqn. (1.28)). It was shown that the allylic amination proceeds with retention of absolute chemistry (98% *cee*).

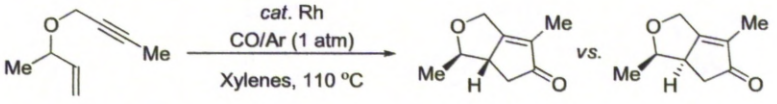


In a collaboration between Evans and Baik, high-level density functional theory was utilised to garner further insight into the high levels of stereocontrol observed during rhodium-catalysed PK annulations reactions.[37] Two plausible mechanistic scenarios were identified depending upon the exact composition of the catalytic rhodium-catalyst. A square planar complex would result from π-bonding of a 1,6-enyne with 16 electron Rh(I)Cl(CO) catalyst (**Cycle C**); a trigonal-bipyrimidal complex would result from interaction with 18 electron $Rh(I)Cl(CO)_2$ catalyst (**Cycle D**). Computational analysis suggested that a trigonal-bipyramidal coordination geometry of rhodium is required to promote a highly stereoselective Pauson-Khand reaction. At relatively high CO concentrations, the most prevalent species will be **AK**, while **AH** is expected to be the dominant species at low CO concentration. Thus, it was hypothesised that a substantial loss in diastereoselectivity would result from a reduction in CO concentration, arising from a shift of the equilibrium in favour of complex **AH**. In addition, the presence of a strongly binding spectator ligand, such as phosphine, is likely to enforce a trigonal-bipyramidal geometry and thereby afford high levels of diastereoselectivity, regardless of CO pressure. The hypothesis was explored experimentally through varying the CO concentration and screening phosphine ligands (Table 1.1). Gratifyingly, these findings are in accordance with the previous work of Narasaka and Evans in this area.



Scheme 1.11 Proposed competing pathways for the rhodium-catalysed pauson-khand reaction under high and low CO pressure

Table 1.1 Effect of CO pressure on the diastereoselectivity of the rhodium-catalysed PKR



120 1.121 1.122

Entry	Rhodium Complex	Presure [atm] CO	Ar	Yield [%]	*ds* 1.121:1.122
1	$[RhCl(CO)_2]_2$	1.00	00	81	22:1
2	"	0.10	0.90	64	10:1
3	"	0.05	0.95	57	6:1
4	$[RhCl(CO)(dppp)]_2$	1.00	0.00	88	≥99:1
5	"	0.10	0.90	51	58:1
6	"	0.05	0.95	44	57:1

Additional computation analysis revealed that the key transition state in the reaction is highly charge-polarised, with the different diastereoisomers exhibiting dramatically different polarisation configurations (Figure. 1.5). The groups postulated that improved diastereocontrol would be obtained through preferentially lowering the activation barrier of the favoured metallacycle through manipulation on the polarisation. Experimentally, the alkyne was polarised by addition of a chloride. Significantly, the reaction now proceeds under ambient conditions and is independent of the nature of the group at the allylic position. For example, chloro-

enyne **1.124** proceeded to give bicyclic adduction **1.125** in excellent yield and diastereocontrol (80%, *ds* = 97:3, eqn. (1.29) compare with 79% and *ds* = 3:1 eqn. (1.27)).

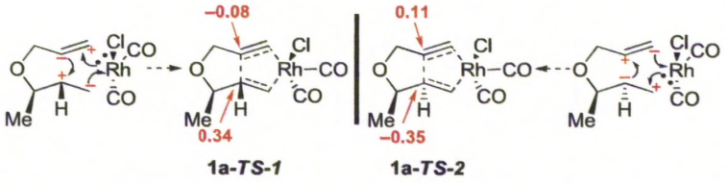


Figure 1.4 Computed partial charges at the oxidative addition transition states (in red) and a conceptual view of the oxidative addition invoking heterolytic π-bond cleavage

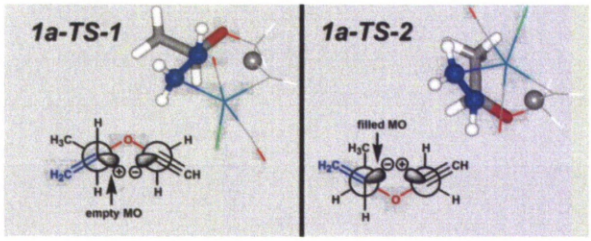
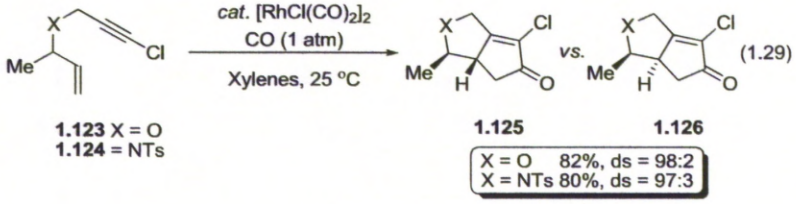
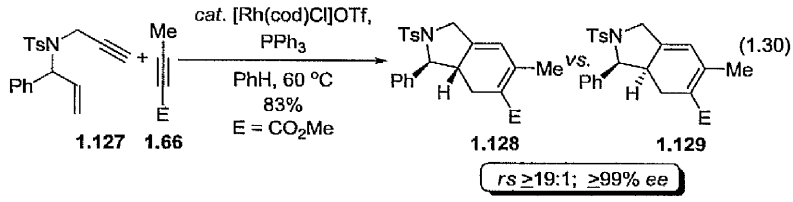


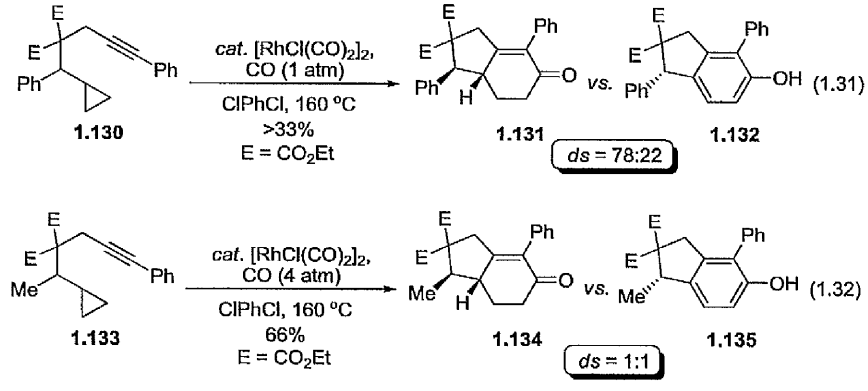
Figure 1.5 Structures of **1a-TS-1** and **1a-TS-2**

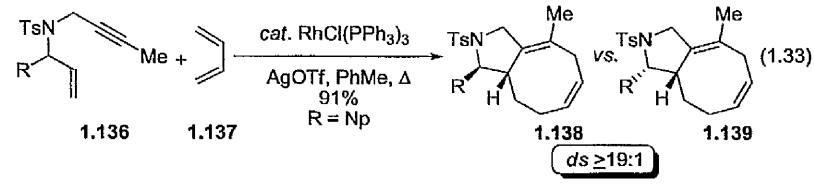


The Evans group went on to report the first example of stereoinduction in a combined regio- and diastereoselective [(2+2)+2] reaction.[27] Phenyl substituted 1,6-enyne **1.127** was selected to facilitate the direct comparison with previous diastereoselective rhodium-catalysed carbocyclisation reactions. Treatment of 1,6-enyne **1.127** and unsymmetrical alkyne **1.66** with the salt free rhodium-catalyst afforded **1.128** in 83% yield with ≥19:1 regio- and diastereoselectivity (eqn. (1.30)). Interestingly, subjection of 1,6-enyne **1.127** and alkyne **1.66** to the optimum conditions for the [4+(2+2)] carbocyclisations (*vide infra*) provided a mixture of bicyclohexadienes **1.128** and **1.129** with poor regio- and stereocontrol.

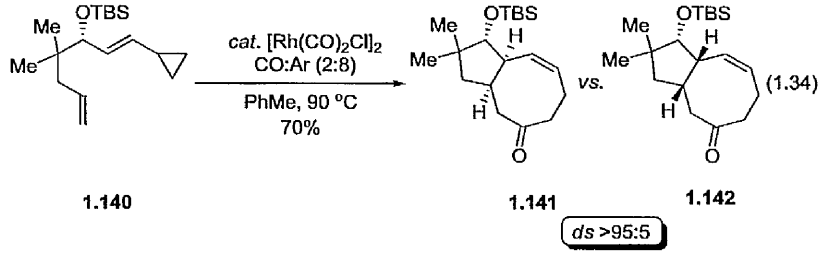


In 1999, Narasaka described the first example of stereoinduction in a rhodium-catalysed carbocyclisation, demonstrating the validity of this concept.[39] Cyclopropane compounds were shown to undergo [(3+2)+1] cycloisomerisation to furnish cyclic enones in good to moderate yield. Treatment of cyclopropane **1.130**, which contains a phenyl group adjacent to the cyclopropane moiety, with the requisite rhodium-catalyst at one atmosphere of carbon monoxide, furnished bicyclic compounds **1.131** and **1.132** as a 78:22 mixture of diastereoisomers (favouring **1.131**), albeit in a poor yield (>33%, eqn. (1.31)). Interestingly, on an analogous substrate they demonstrated the yield could be improved through increasing the pressure to four atmospheres of carbon monoxide, however this had a detrimental effect on the levels of stereoinduction (66%, *ds* = 1:1, eqn. (1.32)).





The Evans group also reported the first example of stereoinduction within a rhodium-catalysed semi-*inter*molecular [(4+2)+2] carbocyclisation.[6a] This demonstrated that a 1,6-enyne containing substitution at the allylic position undergoes cycloaddition with a diene to provide bicyclic octanoids with complete diastereocontrol. For example, treatment of the enyne **1.136** and diene **1.137** with silver triflate modified Wilkinson's catalyst, furnished the azabicycle **1.138** in 91% yield and in excellent diastereoselectivity (*ds* ≥19:1 eqn. (1.33)). Disappointingly, this reaction was found to be intolerant of any alternative substitution at the allylic position. The group went on to disclose a more general reaction utilising rhodium-NHC complex, which provided a remarkable improvement in the overall efficiency and is tolerant of functional groups such as esters, other olefins, and aryl groups.[40]



Recently, Yu *et al.* reported a diastereoselective rhodium-catalysed [(5+2)+1] carbocyclisation which they utilised in the synthesis of (+)-asteriscanolide.[41] Under an atmosphere of carbon monoxide and argon, ene-vinylcyclopropane **1.140** was transformed into cyclooctenone **1.141** in 70% yield (*ds* >95:5, eqn. (1.34)). The synthesis was completed in 19 steps and 3.8% overall yield.

1.5.2 Diastereoinduction Final Remarks

Utilising carbocyclisation reactions that proceed with high levels of stereoinduction is a highly efficient route to enantiomerically enriched cyclic compounds. This provides a complementary strategy to the modification of rhodium-metals with chiral ligands (section 1.6). This is particularly useful tool to have in your arsenal, when modification of catalyst with chiral ligands results in reduced catalytic activity. Nevertheless, the synthesis of enantiomerically enriched substrates can make this stratagem cumbersome. One efficient route to 1,6-enynes is *via* an allylic substitution reaction. In several instances allylic substitution reactions and carbocyclisation which demonstrate stereoinduction have been combined in 'one-pot'.

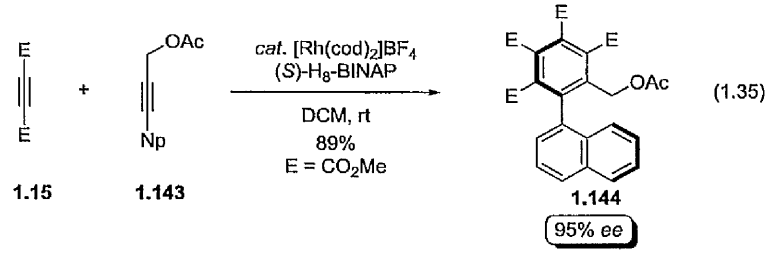
1.6 Enantioselective Rhodium-Catalysed [m+n+o] Carbocyclisation Reactions

Over the few past decades there has been a steady increase in the number of articles published addressing the synthesis of enantiomerically enriched compounds. The driving force of this focus can been found within Nature.[42,43] When designing molecules to interact with natural compounds it is important to consider the absolute configuration of the compound since it has long been established that different enantiomers can interact with natural compounds in very different manners.[44] As such, the development of methodology to access enantiomerically pure compounds is of the upmost importance. It has been demonstrated that the modification of a

rhodium-centre with chiral ligands allows expedient access to enantiomerically enriched compounds.

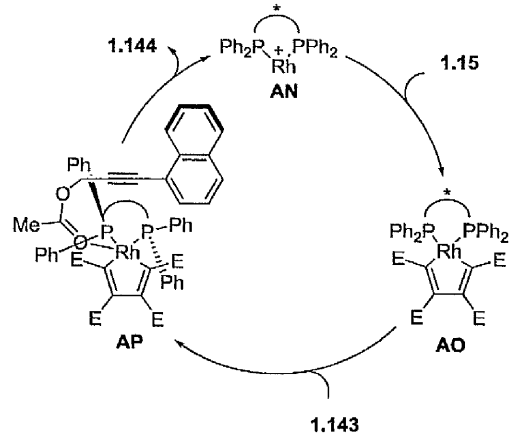
Chirality within a molecule can be the product of several different events. Inherent chirality arises as a consequence of the presence of a curvature in a molecule that would be devoid of symmetry axes in a two-dimensional depiction; axial chirality and planar chirality are two examples. Conversely, point chirality originates from the formation of a stereogenic element within a structure.

1.6.1 Enantiocontrol in Rhodium-Catalysed *Inter*molecular [m+n+o] Carbocyclisations



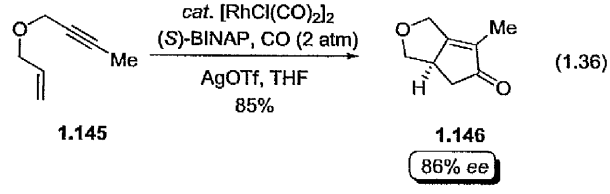
In 2005, Tanaka reported the first example of an enantioselective rhodium-catalysed [m+n+o] carbocyclisation for the construction of axially chiral biaryl compounds.[15] A series of biaryl compounds were synthesised *via* a chemoselective cycloaddition of two equivalents of an electron deficient symmetrical alkyne, and one molecule of an unsaturated electron rich alkyne (as delineated in section 1.2.1). The experiment produced biaryl compounds with excellent enantioselectivities and good yields. An example of Tanaka's work involved the treatment of alkynes **1.15** and **1.141** with the requisite cationic rhodium-(*S*)-H_8-BINAP complex to provide biaryl complex **1.142**, in good yield and excellent enantiomeric excess (89% 95% *ee*,

eqn. (1.35)). The authors postulated that the high levels of enantiomeric excess were a consequence of minimisation of the steric repulsion between the biphenyl phosphine group of the chiral ligand and the naphthalene rings of metallacyclopentene **AP** (scheme 1.12)



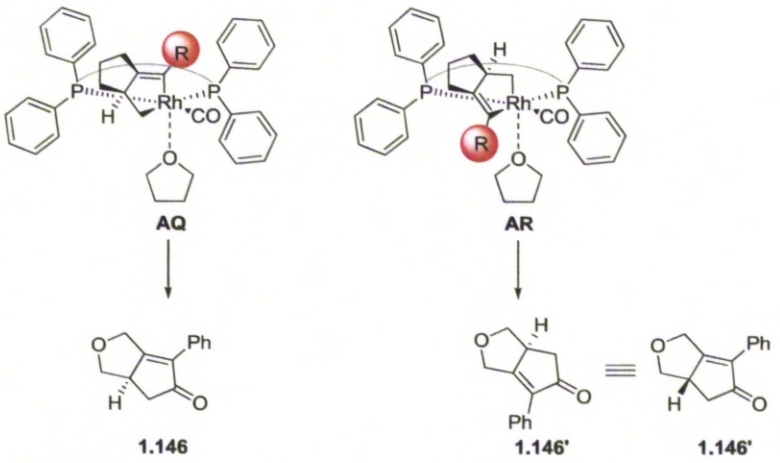
Scheme 1.12 Possible catalytic cycle for the formation of axially chiral biaryl arenes

1.6.2 Enantiocontrol in Rhodium-Catalysed Semi-*Inter*molecular [m+n+o] Carbocyclisations



Despite a plethora of research into the PKR, it was not until 2000 that Jeong disclosed the first asymmetric rhodium-catalysed Pauson-Khand reaction.[45] They employed $[RhCl(CO)_2]_2$ and (*S*)-BINAP as the catalytic system for the enantioselective synthesis of cyclopentenones. Treatment of 1,6-enyne **1.143** with the requisite rhodium-catalyst modified with (*S*)-BINAP yielded the desired carbonylative cycloadduct **1.144** in good yield and enantiomeric excess (85%, 86%

ee, eqn. (1.36)). Several factors were found to be critical for the success of this reaction including the *in situ* preparation of catalyst, utilisation of coordinating solvents, the addition of a silver salt and balancing the carbon monoxide pressure.

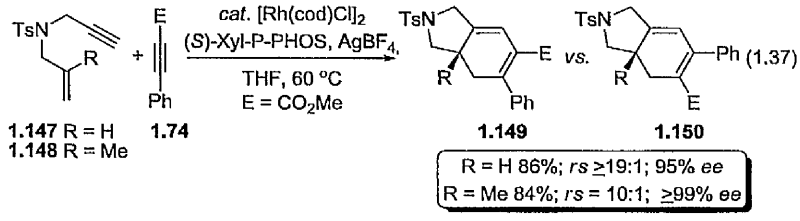


Scheme 1.13 Proposed transition states during the mechanism for the formation of cyclopentenones

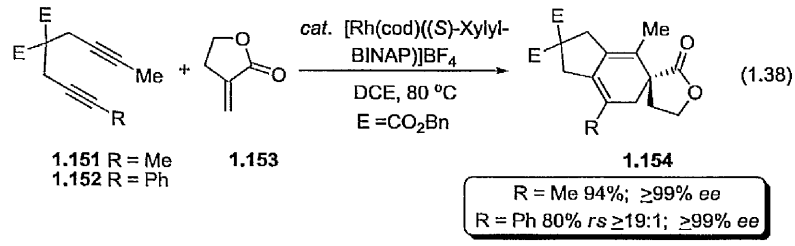
The authors postulated a mechanism involving a cationic pathway is prevalent with the 1,6-enyne binding to the [Rh(CO)(*S*)-BINAP] complex to furnish an octahedral rhodium-metallacyclopentene intermediate. Transition state **AR** is prevalent due to diminished steric interactions between the R group and the diphenyl groups of the ligand. The succeeding migratory insertion of carbon dioxide and reductive elimination provides the bicyclic cyclopentenone.

In a collaboration with Eun Kim, Jeong went on to explore this research further by delineating the effect of varying the electronic and steric properties of chiral biaryl diphosphine ligands in the rhodium-catalysed asymmetric PKR.[46] It was demonstrated that the enantioselectivity and reaction yield were significantly influenced by varying the electron density on phosphorus and the dihedral angle of

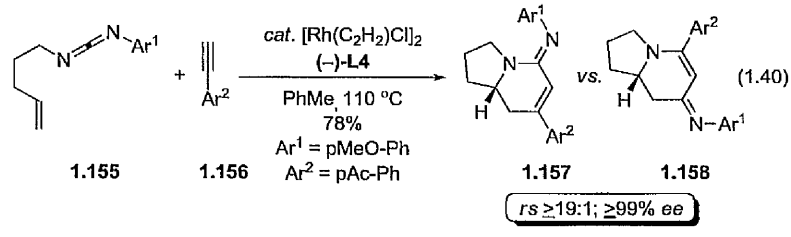
the chiral bidentate phosphine ligands. For most substrates, the highest enantioselectivities were obtained utilising ligands bearing a narrower dihedral angle than BINAP. Furthermore, ligands with a deshielded phosphine provided better enantioselectivity with a reduced formation of side products; however these catalytic systems suffered from slower reaction rates.



Evans *et al.* disclosed the first regioselective asymmetric semi-*inter*molecular [(2+2)+2] cycloaddition of 1,6-enynes with unsymmetrical 1,2-disubstituted alkynes.[26] Bidentate phosphine ligands with a narrow dihedral angle and a large degree of steric hindrance provided the highest levels of selectivity. For example, treatment of 1,6-enyne **1.145** and arylpropiolate **1.74** with the $[Rh(cod)Cl]_2$ catalyst modified with (*S*)-Xyl-P-PHOS, provided bicyclohexadiene **1.147** in good yield and excellent regio- and enantioselectivities (86%, *rs* >19:1, 95% *ee*, eqn. (1.37)). Curiously, whilst it was demonstrated that enantioselectivity remained consistently high independent of the electronic properties of the arylpropiolate and the nature of the 1,6-enyne tether (O, NTs, $C(CO_2CH_3)$), these parameters had a marked effect on both the yield and regioselectivity. This transformation was also tolerant to internal substitution of the alkene, facilitating the formation of quaternary carbon stereogenic centres in excellent enantioselectivities (84%, *rs* = 10:1, 99% *ee*, eqn. (1.37)).

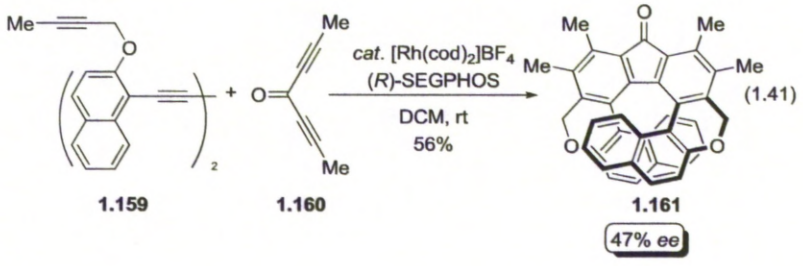


In 2006, Shibata *et al.* reported the enantioselective semi-*inter*molecular [(2+2)+2] carbocyclisation of diynes with exocyclic methylene ketones and lactones to provide a series of optically active spirocyclic derivatives.[47] They employed a chiral [Rh(cod)(*S*)-Xylyl-BINAP]BF_4 catalytic system to afford tricycle **1.154** in good yield and enantiomeric excess (94%, 99% *ee*, eqn. (1.38)). They also demonstrated that this reaction could proceed with regiocontrol, subjecting unsymmetrical 1,6-diyne **1.152** to the optimised reaction conditions furnished lactone **1.154** as a single regioisomer in 80% yield and excellent enantiomeric excess (*rs* ≥19:1, 99% *ee*, eqn. (1.38)).

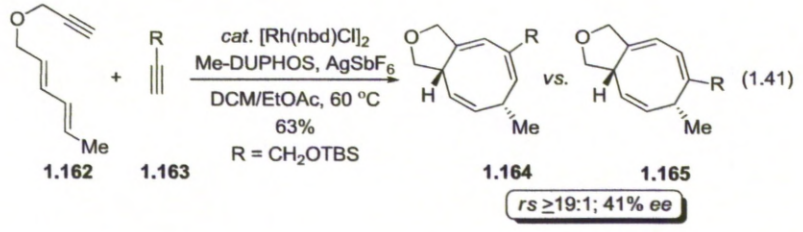


In 2006, Rovis and co-workers reported an asymmetric rhodium-catalyst [(2+2)+2] carbocyclisation for the synthesis of bicyclic amidines.[11] The incorporation of carbodiimides as the 2π moieties allows for the formation of compounds containing a bridging nitrogen in excellent enantioselectivities. The *in situ* modification of the $[Rh(C_2H_2)Cl]_2$ dimer with phosphoramidite ligand **(–)-L4** provided a chiral complex that facilitated the carbocyclisation of carbodiimide **1.155**

and aryl acetylene **1.156**, to afford amidine **1.157** in good yield with excellent regio- and enantioselectivity (78%, *rs* ≥19:1, 99% *ee,* eqn. (1.40)). In some cases compound of the type **1.158** were observed as a minor regioisomer; in the analogous reaction with isocyanate a similar compound is isolated as the major regioisomer and is believed to result from a carbon monoxide migration process (Scheme 1.8). The authors postulated that in this transformation, the migration process is repressed as a result of the bulky imido moiety being located further away from the rhodium centre.

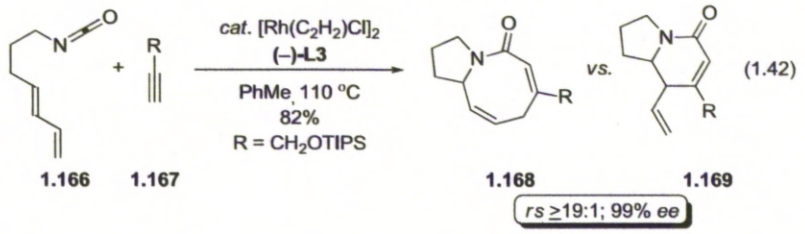


Tanaka reported the synthesis of [9]-helicene-like structures *via* two semi-*inter*molecular rhodium-catalysed [(2+2)+2] carbocyclisations.[48] Treatment of diyne **1.160** and two equivalents of 1,7-diyne **1.159** with the requisite (*R*)-Segphos modified rhodium-catalyst, provided helical **1.161** (56%, 47% *ee*, eqn. (1.41)). This transformation generates five new carbocycles in a single step, albeit in modest yield and enantioselectivity



In 2002, Gilbertson reported the first example of a rhodium-catalysed enantioselective [(4+2)+2] carbocyclisation.[30] Treating 1,6-dienye-yne **1.162** and

alkyne **1.163** with a chiral Me-DuPhos rhodium-complex provided the desired bicyclic adduct **1.164** in good yield and moderate enantioselectivity (63%, *rs* ≥ 19:1, 41% *ee,* eqn. (1.41)). The authors stated that for all other substrates lower levels of enantioselectivity were obtained, however, this data was not disclosed.



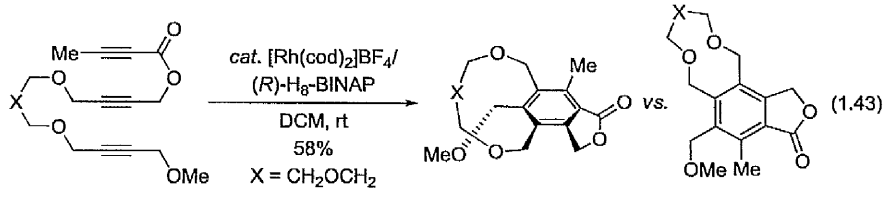
(1.42)

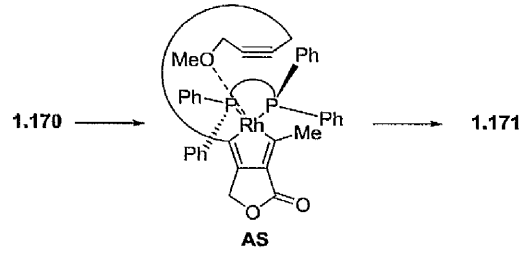
In 2006, Rovis and co-workers reported an asymmetric [(4+2)+2] semi-*intra*molecular carbocyclisation for the construction of azocines.[49] The incorporation of the isocyanate moiety as a 2π motif allowed access to enantiomerically enriched bicyclic ε-lactams. Treatment of isocyanate **1.166** and alkyne **1.167** with the requisite rhodium-complex provided bicyclic lactam **1.168** in good yield and excellent regio- and enantioselectivity (82%, *rs* ≥19:1, 99% *ee,* eqn. (1.42)). The authors hypothesised that the mechanism of this transformation is distinct to the earlier report [(2+2)+2] carbocyclisations of isocyanate and carbidiimides (Scheme 1.8). The levels of enantioselectivity remained consistently high regardless of the acetylene substitution.

1.6.3 Enantiocontrol in Rhodium-Catalysed *Intra*molecular [(m+n+o)] Carbocyclisations

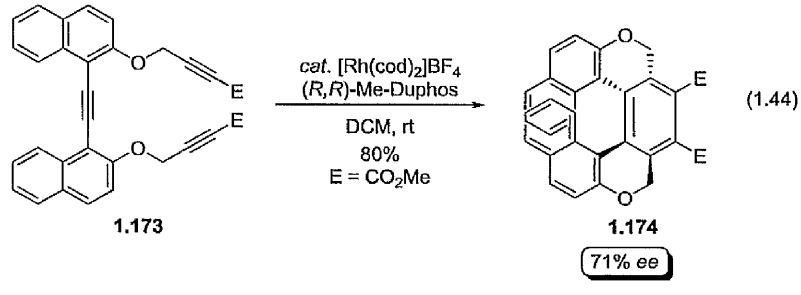
The Tanaka group reported an enantioselective rhodium-catalysed *inter*molecular [(2+2+2)] cycloisomerisation for the synthesis of cyclophanes.[50]

Triyne **170** underwent cycloisomerisation upon treatment with the *in situ* generated rhodium-(*R*)-BINAP catalyst, to provide tricycle **1.171** in >98% enantiomeric excess, albeit as a 1:1 mixture of diastereoisomers (eqn. (1.43)). The authors accounted for the high degrees of enantioselectivities by postulating that the catalytic cycle involved the preferential coordination and subsequent oxidative addition of rhodium to the 1,6-diyne; this results in metallacyclopentene **AS**. High levels of enantioselectivity result from coordination of the terminal methoxy group to the cationic rhodium, and the steric interaction between the ansa chain of **1.170** and diphenyl phosphine groups of chiral ligand (Scheme 1.12).

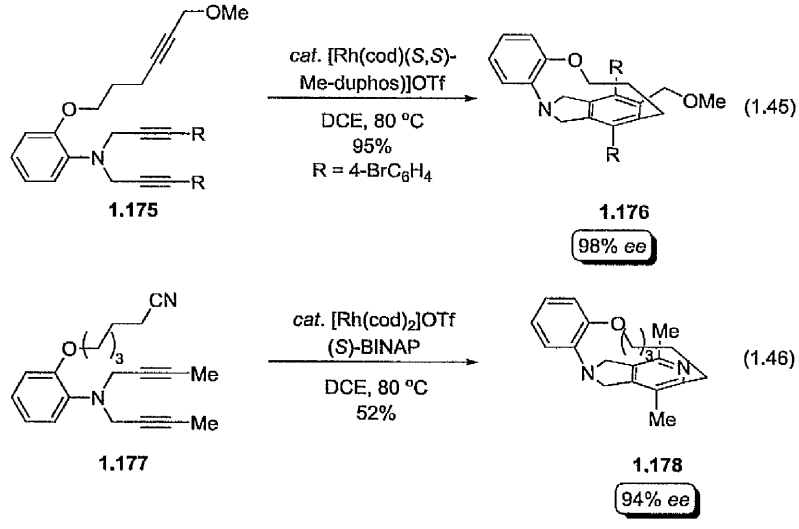




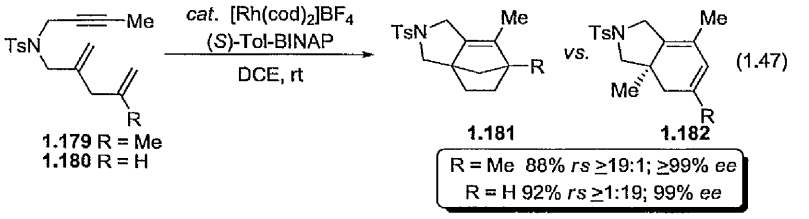
Scheme 1.14 Plausible mechanism for the formation of cyclophanes



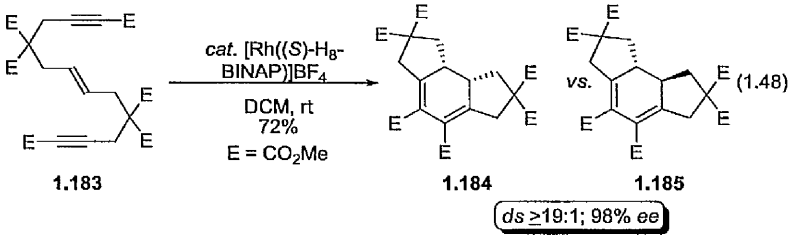
Subsequent work described the rhodium-catalysed [(2+2+2)] carbocyclisation of triynes to provide functionalised helically chiral molecules.[51] Treatment of triyne **1.173**, with a rhodium-BF_4 catalyst modified with (*R,R*)-Me-Duphos, provides helicene-like **1.174** in excellent yield and good enantiomeric excess (80%, 71% *ee*, eqn. (1.44)). The electronics of the triyne have a considerable influence on the yield and enantioselectivity of this transformation, for example, electron rich triynes experience an increase in both reactivity and enantiomeric excess.



In 2009, Shibata *et al.* described the rhodium-catalysed [(2+2+2)] cyclotrimerisation of 2-aminophenol triynes to yield asymmetric caged compounds in high yields and enantiomeric excess.[52] Treatment of triyne **1.175** with the rhodium-(*S,S*)-Me-Duphos complex furnished 1,2,4-trisubstituted arene **1.176** in 95% yield and 98% enantiomeric excess (eqn. (1.45)). The transformation is tolerant of various tether lengths and R groups, for example diyne-nitrile **1.177** undergoes carbocyclisation to furnish pyridinophane **1.178** in moderate yield and excellent enantiomeric excess, albeit requiring modification of catalyst conditions (52%, 94% *ee*, eqn. (1.46)).



The Shibata group further described the first *intra*molecular [(2+2+2)] cycloisomerisation of dienynes for the construction of bridged tricyclic compounds with two new quaternary carbon stereocenters.[53] Subjecting dienyne **1.179** to the chiral catalyst derived from $[Rh(cod)_2]BF_4$ and (*S*)-Tol-BINAP, provided tricycle **1.181** in 88% yield with excellent regio- and enantiocontrol. Notably, subjecting dienyne **1.180**, lacking 1,1-disubstituted alkene, to the optimised reaction conditions results in the formation of bicyclic **1.182** in excellent enantiomeric excess (92%, *rs* ≥19:1, 99% *ee*, eqn. (1.47)).



The Shibata group also disclosed the first asymmetric *intra*molecular rhodium-catalysed [(2+2+2)] cycloisomerisation of dienynes, providing chiral tricyclic dienes in excellent enantioselectivities.[54] Subjecting diyne **1.183** to the $[Rh((S)\text{-}H_8\text{-}BINAP)]BF_4$ catalyst at room temperature, provided the C2-symmetrical tricycle **1.184** in good yield and with excellent enantiomeric excess (72%, 98% *ee*, eqn. (1.48)). The authors postulated that excellent levels of enantioselectivity results from the preferential formation of metallacycle **AT** over **AU** (Figure 1.6) due to minimisation of steric interaction between R group of the substrate and the phenyls

on the phosphorus atoms of H_8-BINAP. Intriguingly, it was demonstrated that the nature of the tether is crucial for obtaining high selectivity, with the analogous sulfonamide tethered diynene undergoing cycloaddition to yield tricyclic compounds with diminished enantiomeric excess (21% *ee*). The authors postulated that this discrimination in enantiomeric excess is a result of alternative mechanistic pathways for the tethers.

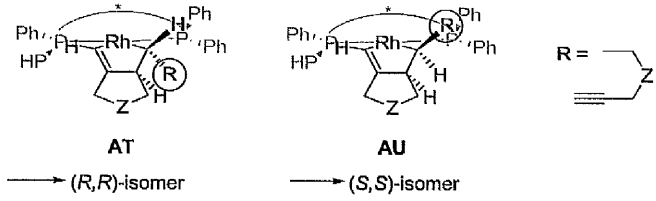
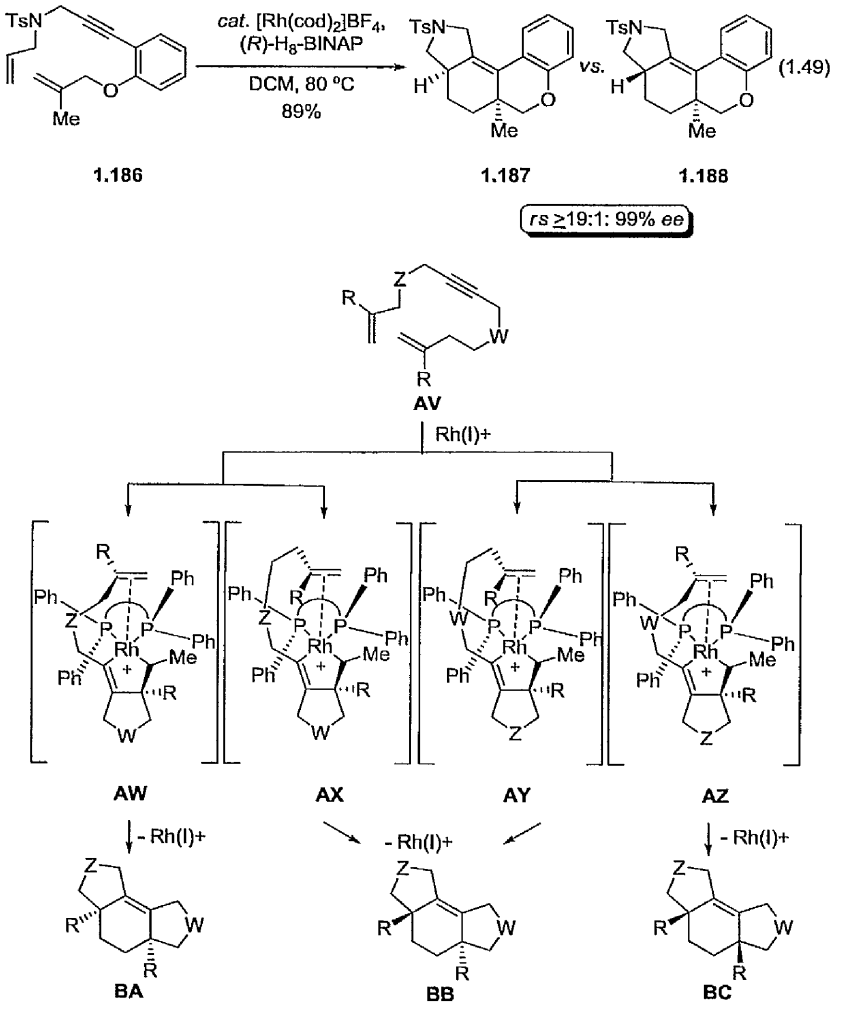


Figure 1.6 Metallacycles in the formation of tricyclic dienes

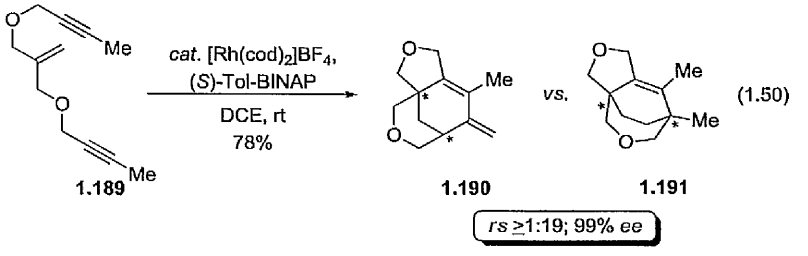
In 2008, Tanaka *et al.* described the asymmetric *intra*molecular [(2+2+2)] carbocyclisation of unsymmetrical dienynes.[55] Utilising a cationic rhodium-(*R*)-H_8-BINAP complex, a series of fused tri- and tetracyclic cyclohexenes were synthesised in varying yields and levels of enantio- and diastereoselectivity. Treatment of the phenol **1.186** under the optimum conditions furnished tetracycle **1.187** in 89% yield, as a single diastereoisomer and in excellent enantiomeric excess (99% *ee*, eqn. (1.49)). Crucial to controlling the diastereo- and enantioselectivity was selecting unsymmetrical dienynes. Specifically, dienyes with tethers of different lengths and with alkenes with differing reactivates furnish ter- and tetracycles with higher selectivities.



Scheme 1.15 Proposed mechanisms for the formation of *cis*- and *trans*-tricyclic cyclohenenes

Scheme 1.15 described the mechanism the authors proposed to account for the selective formation of tetracyclic compound **1.187**. The coordination and oxidative addition can occur between two different enynes resulting either in intermediates **AW** and **AX** or **AY** and **AZ**. The selective formation of a pair of intermediates is prevalent in substrates containing two dienyne moieties which have a large difference in the reactivity. In the case of **1.186**, it is known that the 1,7-enyne moiety is less reactive to rhodium than 1,6-enynes; the difference in reactivities results in the preferential formation of intermediates **AW** and **AX**. The

second stereocenter is constructed during the coordination of rhodium to the final alkene moiety. A large degree of steric repulsion between the tether or R group and the axial P–Ph group of (*R*)-H_8-BINAP, results in a highly diastereoselective reaction. The *trans*-selective coordination of the final bond (shown in intermediate **AX** or **AY**) furnishes the same enantiomer **BB** of the trans-fused cyclohexene. Conversely, *cis*-selective coordination results in the formation of intermediates **AW** and **AZ**, which in turn furnish an enantiomeric pair of *cis*-fused cyclohexenes **BA** and **BC**. As the aryl group of **1.186** provides an excellent template to control facial discrimination in the migratory insertion of the pendant alkene, it was postulated that the phenol linked double bond does not coordinate to rhodium with *trans*-selectivity due to the rigid structure of the phenol-linked tether. Hence, it was rationalised that the carbocyclisation of phenol-lined dienyne proceeds via intermediate **AW**.



Shibata delineated the enantioselective synthesis of bridge tricyclic adducts containing two chiral centres and an *exo*-methylene group *via* the isomerisation of diynenes containing a central 1,1-disubstituted alkene.[53b] Isomerisation of the diynene **1.189** occurred upon treatment with requisite chiral rhodium-complex to afford diene **1.190** in good yield and excellent regio- and enantiocontrol (78%, *rs* ≥1:19, 99% *ee*, eqn. (1.50)). This transformation provides complementary bridge tricyclic compounds to the dineyne variant Shibata previously reported (eqn. (1.47)).

1.6.4 Enantioselective Carbocyclisation Final Remarks

Enantioselectivity is the current bench mark new carbocyclisations are measured against. The vast array of commercially available chiral ligands makes screening a relatively simple task. Regardless, obtaining enantiomerically enriched adduct can be challenging. For example, often in reactions that require a high carbon monoxide pressure or acetonitrile as a solvent, these groups can ligate to the metal preventing the modification of the rhodium-centre with chiral ligands.

1.7 Conclusions

We have illustrated the fundamentals of rhodium-catalysed [m+n+o] carbocyclisations, and in doing so have also described the current limitations within this domain and the areas which are prime for future development. An array of 5, 6, 7 and 8 membered carbo- and heterocycles have been synthesised by incorporating carbon monoxide, alkynes, alkenes, alkenyldenecyclopropane, dienes, isocyantes and carbodiimides motifs into the rhodium-catalysed [m+n+o] carbocyclisation manifold. The utility of these reactions is highlighted by the application of [m+n+o] carbocyclisations in the synthesis of biologically active compounds including viridin[56] and alcyopterosin E.[57] Undoubtedly, this field represents a fertile ground for further research and development.

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Chapter 2

Intramolecular Rhodium-Catalysed [(2+2+2)] Cycloisomerisation Reaction of Dienynes

2.1 Introduction

Transition metal-catalysed [2+2+2] carbocyclisations encompass a highly important subcategory within [m+n+o] transformations. Indeed, after the Pauson-Khand reaction,[1,2] the largest degree of research has been undertaken within this arena. A plethora of substrates have been employed and an array of transition-metals utilised;[3] It is therefore unsurprising that this transformation has proved to be a reliable tool towards the realisation of natural product synthesis.[4] Regardless of the extent of research undertaken, the most frequently incorporated moieties remain alkynes, with the inclusion of alkene less forthcoming.

*Intra*molecular cyclisation reactions, also known as cycloisomerisation reactions, are a useful tool to circumvent issues associated with poor reactivity, often facilitating transformations that are unachievable in the *inter*molecular reaction manifold. Moreover, the tethering of three π-components is advantageous for the assembly of tricyclic skeletons in a single transformation, proving to be a regioselective and atom economical strategy. The installation of olefins into the rhodium-catalysed [(2+2+2)] carbocyclisation manifold provides complex polycyclic systems encumbered with up to two stereocentres per alkene, in a single step (Figure 2.1). Such architecture features in a range of complex natural and non-natural

products. Nevertheless, the pursuit of such methodology remains a challenging endeavour, partly due to the directional constraint during coordination of the metal species with the single olefin π-bond, coupled with the lack of back bonding from a second orthogonal π-orbital.

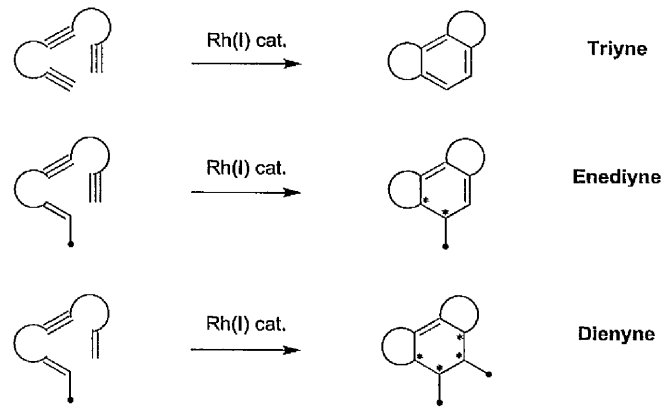


Figure 2.1 *Intra*molecular [(2+2+2)] carbocyclisations of triynes, enediynes and dienynes

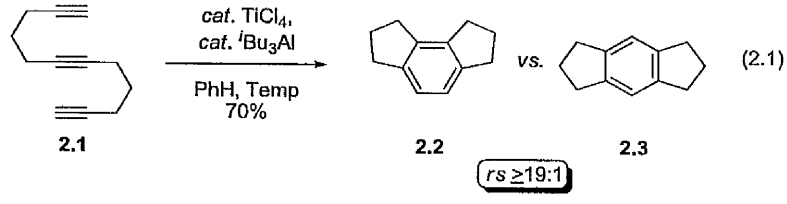
As a result of the magnitude of work executed within this area, the following discussion will be limited to the seminal rhodium-catalysed *intra*molecular [(2+2+2)] carbocyclisations. The succeeding chapter will commence with an historic overview of the research undertaken within rhodium-catalysed [(2+2+2)] cycloisomerisation reactions for triynes, endiynes and dienynes. Subsequent focus will describe our current contributions within the rhodium-catalysed cycloisomerisation of dienynes.

2.2 Transition Metal-Catalysed [(2+2+2)] Cycloisomerisation

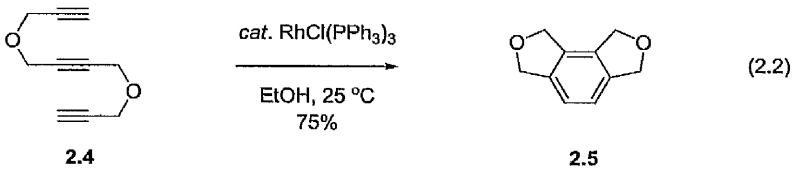
2.2.1 Transition Metal-Catalysed [(2+2+2)] Cycloisomerisation of Triynes

The rhodium-catalysed [(2+2+2)] cycloisomerisations of triynes is a reliable and efficient route to substituted arenes. The construction of complex medium-sized compounds in a single transformation is inconceivable utilising classic transformations. The reliable and predicable behaviour of this transformation has made this an attractive tool toward the synthesis of a number of natural products.

Figure 2.2 The *intra*molecular [(2+2+2)] carbocyclisation of triynes

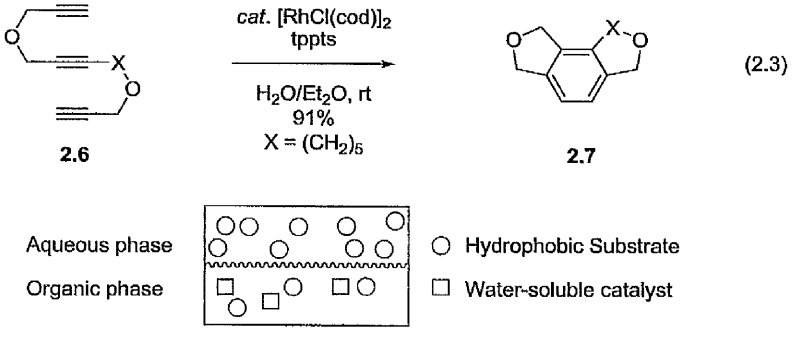


The primary example of a transition-metal catalysed *intra*molecular [(2+2+2)] carbocyclisation was described in 1967 by the Hubert group.[5] Upon exposure to Ziegler's catalyst, triyne **2.1** isomerised to afford the analogous indacene **2.2** in 70% yield (eqn. (2.1)). Changing the length of the tethers had a profound effect on the reaction course, with the analogous 1,7,13- triyne furnishing a 1:1 mixture of regioisomers.



2.4 2.5 (2.2)

It was not until 1982 that this transformation was explored with a late transition-metal catalyst, wherein, *Grigg et al.* disclosed the cycloisomerisation of triynes for the construction of substituted arenes.[6] This seminal reaction utilised Wilkinson's catalyst to provide the requisite tricyclic heterocycle **2.5** from the linear triyne **2.4** in 75% yield (eqn. (2.2)).[7] In addition, this work also documented the first example of a rhodium-catalysed semi-*inter*molecular carbocyclisation reaction, demonstrating that a series of 1,6-diynes undergo dimerisation with substituted acetylenes to provide bicyclic arenes in good yields.



2.6 2.7 (2.3)

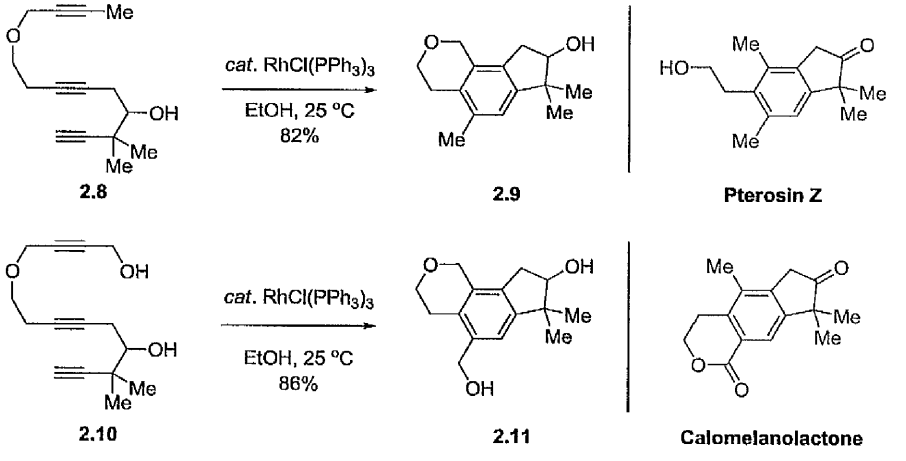
Figure 2.3 Schematic of the biphasic system controlling the concentration of substrate in the reaction medium

*Intra*molecular cycloisomerisations are often performed at high dilutions in order to overcome the undesired *inter*molecular [2+2+2] side reactions; this can result in large quantities of solvent waste which can be costly to dispose of. In 2003, Oshima *et al.* developed an aqueous-organic biphasic system which overcame this limitation through regulating the concentration of hydrophobic substrate in the aqueous reaction medium.[8] The water-miscible catalyst was prepared *in situ* from $[RhCl(cod)]_2$ and 3,3′,3″-phosphinidynetris(benzenesulfonic acid) trisodium salt.

Subjecting triyne **2.6** to the biphasic system for 22 hours provided tricyclic **2.7** in 91% yield (eqn. (2.3)). Substrates with longer length tethers (10/11 atoms) also undergo cycloisomerisation, albeit with diminished regioselectivity.

2.2.2 Rhodium-Catalysed Triyne Cycloisomerisation in Total Synthesis

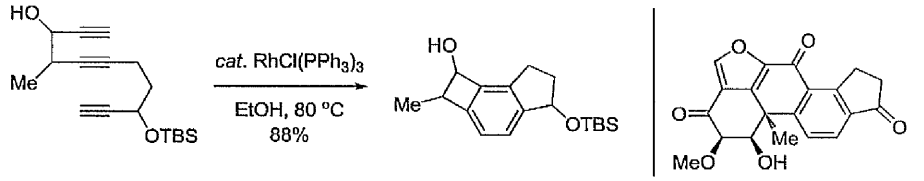
Rhodium-catalysed [(2+2+2)] cycloisomeration reactions have attracted interest from the synthetic chemistry community as a useful tool for the synthesis of naturally occurring molecules.[4] In addition to being an atom economical process, the relatively mild reaction conditions allows the incorporation of sensitive moieties in the substrates. Finally, the ability to construct complex skeletons from simple linear substrates in an expedient manner makes this methodology appealing.



Scheme 2.1 Key step in the total synthesis of calomelanolactone and pterosin Z

In 1989, Stevenson and Neeson utilised a triyne cycloisomerisation to complete the total synthesis of a pair of natural products belonging to the illudalane family, pterosin Z and calomelanolactone (Scheme 2.1).[14] Treatment of triyne **2.8** with Wilkinson's catalyst provided arene **2.9** in 82% yield. Likewise, subjecting

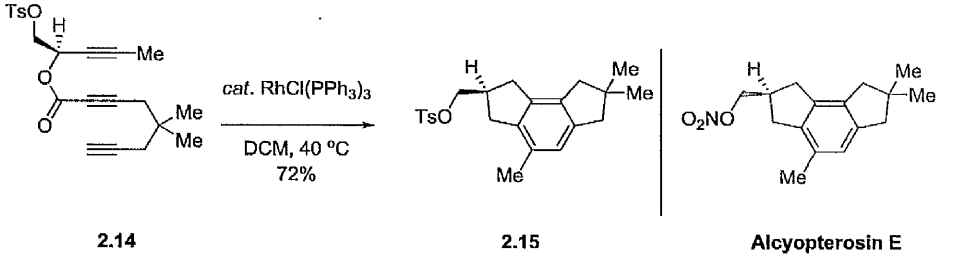
triyne **2.10** to the same reaction conditions provided diol **2.11** in 86% yield. The total syntheses of the natural products were reported in 6 and 9 steps respectively.



2.12 **2.13** **(±)Viridin**

Scheme 2.2 Key step in the total synthesis of viridin

In 1998, the Sorensen group delineated the total synthesis of (±)-viridin (Scheme 2.2), a naturally occurring furanosteroidial antibiotic.[15] To install the 5,6-bicyclic ring skeleton they utilised a rhodium-catalysed triyne cyclotrimerisation reaction. Significantly, the reaction tolerated a TBS protecting group, an unprotected alcohol, as well as the necessary two carbon tether to provide the 4,6,5-tricycle **2.13** in 88% yield (Scheme 2.2). In addition to the cycloisomerisation, the synthesis included a thermal electrocyclic rearrangement. The natural product was synthesised in 23-steps and 5% overall yield.



2.14 **2.15** **Alcyopterosin E**

Scheme 2.3 Key step in the total synthesis of alcyopterosin E

In 1989, Witulski *et al.* exploited a cyclotrimerisation as the principal transformation in the first total synthesis of the naturally occurring alcypterosin E (Scheme 2.3).[16] Treatment of 1,6,11-triyne **2.14** with Wilkinson's catalyst provided

functionalised tricycle **2.15** in 72% yield. The synthesis was completed in one additional step to provide the naturally occurring illudalane sesquiterpenoid in 10 steps.

2.2.3 Rhodium-Catalysed [(2+2+2)] Cycloisomerisation of Enediynes

Tricyclic dienyes with up to two stereogenic centres can be accessed *via* higher-order carbocyclisations by incorporating an olefin into the cycloisomerisation substrate. Exposure of the enediynes to asymmetric catalysts now facilitates the formation of enantiomerically enriched stereogenic centres, with 1,2-disubstituted alkenes providing a route to quaternary centres. There are three different categories of tricyclic-dienes accessible from the cycloisomerisation of enyndienes depending upon the connectivity of the three π-components in the substrate (Figure 2.4).[17] Such architecture features in a range of complex natural and non-natural products.

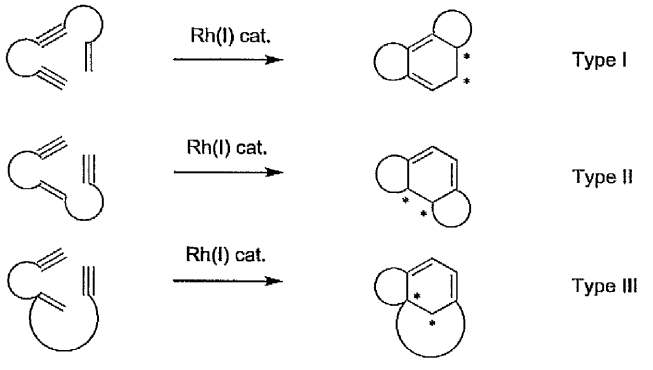
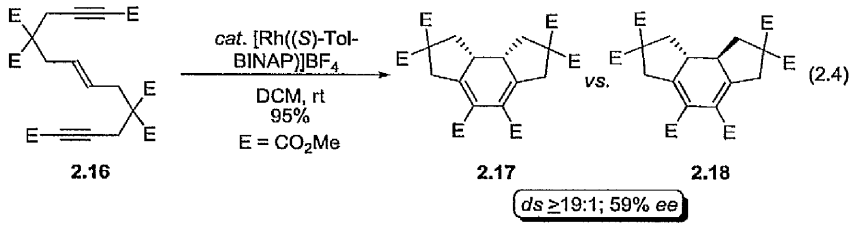


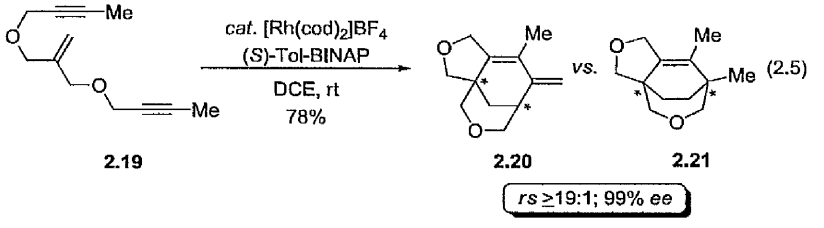
Figure 2.4 Classes of enyndienes and the products of the *intra*molecular [(2+2+2)] carbocyclisation

2.2.3.1 Rhodium-Catalysed [(2+2+2)] Cycloisomerisation of Enediynes: *Type II*



The Tanaka group disclosed the first example of an asymmetric *intra*molecular rhodium-catalysed [(2+2+2)] cycloisomerisation of enediynes.[18] Subjecting enediyne **2.16** to the rhodium-((*S*)–Tol–BINAP)]BF_4 complex, prepared *in situ*, provided the C2-symmetrical tricycle **2.17** in excellent yield and with moderate enantiomeric excess and excellent diastereocontrol (95%, 59% *ee*, eqn. (2.4)). Independently, the Shabata group reported that utilising an isolated [Rh(H_8-BINAP)]BF_4 catalyst provides increased enantioselectivities (72%, 98% *ee*).[19] They also examined the scope of the reaction in greater detail, demonstrating that various tethers can be incorporated and the substituent on the terminal acetylene varied.

2.2.3.2 Rhodium-Catalysed [(2+2+2)] Cycloisomerisation of Enediynes: *Type III*



Subsequent work within the Shibata group delineated the enantioselective cycloisomerisation of *type III* enediynes for the construction of bridged tricyclic adducts.[20] For example, treatment of enediyne **2.19** with the requisite chiral rhodium-(*S*)-Tol-BINAP complex furnished diene **2.20** in 78% yield and with excellent regio- and enantiocontrol (*rs* ≥19:1, 99% *ee*, eqn. (2.5)). The analogous nitrogen tethered enediyne was also found to furnish bridged dienes, however adjustment of the reaction temperature was required.

2.2.4 Transition Metal-Catalysed [(2+2+2)] Cycloisomerisation of Dienynes

The incorporation of two olefins into rhodium-catalysed [(2+2+2)] carbocyclisations would provide an efficient route to complex polycyclic systems encumbered with up to four stereocentres. As illustrated in Figure 2.5, there are three different classes of dienynes.[21] The first group encompasses dienyes with the 3 π-components tethered through the terminal positions of a central alkyne (*type I*). Cycloisomerisation of *type I* dienyes provide tricyclic adducts with an alkene moiety situated between the three rings. Tethering the three components through the terminal positions of the alkene (*type II*) provide the analogous tricyclic compounds. Finally, connecting the three π-components together *via* a 1,1-disubstitued alkene facilitates the formation of bridged tricyclic products of the *type III*.

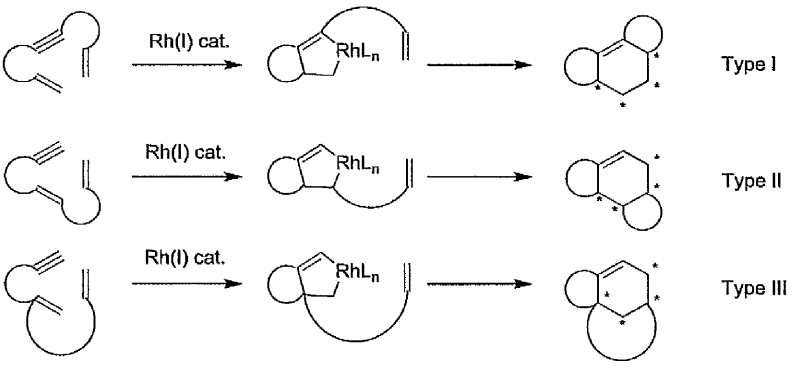
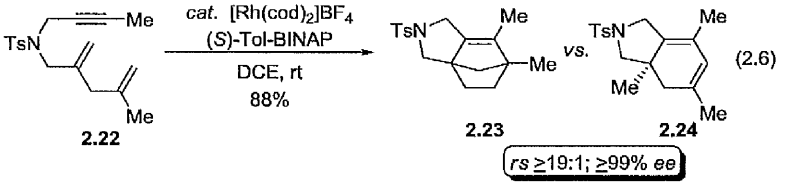


Figure 2.5 Classes of dienyne and the tricyclic products of the *intra*molecular [(2+2+2)] carbocyclisation.

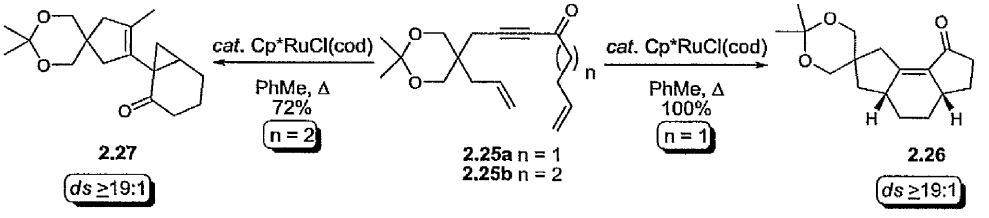
2.2.4.1 Rhodium-Catalysed [(2+2+2)] Cycloisomerisation of Dienynes: *Type III*



In 2006, Shibata *et al.* disclosed an asymmetric *intra*molecular [(2+2+2)] cyclisation of *type I* dienynes, for the construction of optically active bridged tricyclic products.[22] Subjecting dienyne **2.22** to the cationic rhodium-(*S*)-Tol-BINAP complex, prepared *in situ*, affords tricycle **2.23** in good yield and excellent enantiomeric excess (88%, rs ≥19:1, ≥99% *ee*. eqn. (2.6)). The transformation was shown to tolerate carbon, nitrogen, and oxygen tethers, producing the polycyclic products in good yield and with excellent enantioselectivity in all cases. The internally substituted 1,1-alkene is crucial for the construction bridge tricyclic adducts.

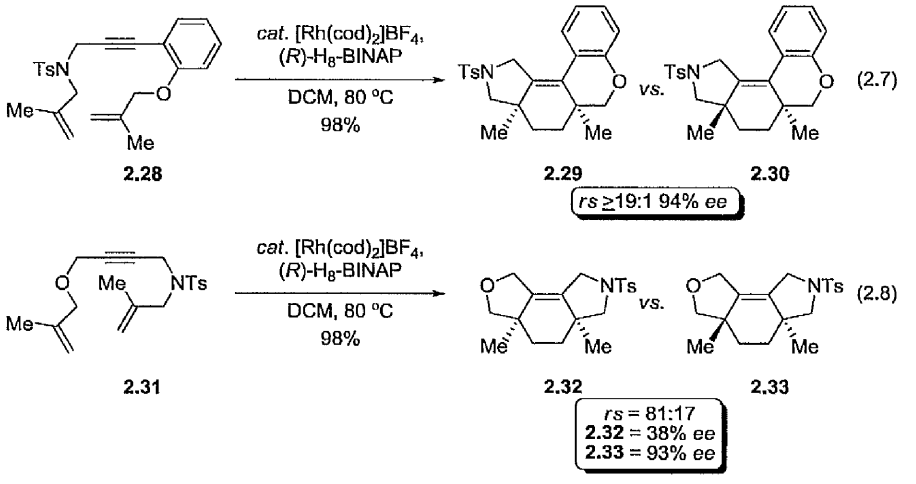
2.2.4.2 *Ruthenium*-Catalysed [(2+2+2)] Cycloisomerisation of Dienynes: *Type I*

Mori and co-workers published an alternative *ruthenium*-catalysed [(2+2+2)] cycloisomerisation of *type I* dienynes, for the construction of tricyclohexenes.[23] Treatment 1,11-diene-6-ynes **2.25a**, with (Cp*)RuCl(cod) provided acetal **2.26** in excellent yield and as single diastereoisomers (100%, *ds* ≥19:1, Scheme 2.4). Interestingly, the length of the tether is crucial to the success of the cyclisation with substrates containing a five carbon tether undergoing cycloisomerisation to provide the alternative carbocycle **2.27** in 72%. Significantly, the reaction is also tolerant of substitution at the internal position of the alkene, facilitating the construction of adducts with two quaternary centres.



Scheme 2.4 *Ruthenium*-catalysed [(2+2+2)] cycloisomerisation of dienynes of the *type I*

2.2.4.3 Rhodium-Catalysed [(2+2+2)] Cycloisomerisation of Dienynes: *Type I*



Tanaka *et al.* disclosed an asymmetric rhodium-catalysed cycloisomerisation of dienynes (*type I*) for the construction of tri- and tetracyclic scaffolds.[24] Subjecting aryl-dienyne **2.28** to the chiral rhodium-complex, prepared *in situ*, provides the adduct **2.29** in 98% yield in excellent diastereo- and enantiomeric excess (*ds* ≥19:1, 94% *ee*, eqn. (2.7)). It is important to note, that the degrees of diastereo- and enantiocontrol observed during the isomerisation are substrate dependant. For example, subjecting dienyne **2.31** to the optimised reaction conditions affords tricyclic adducts **2.32** and **2.33** as an 81:17 ratio (eqn. (2.8)). In this case, high levels of enantiocontrol are only observed for the minor diastereoisomer (**2.32** = 38% *ee vs.* **2.33** = 93% *ee*). The rationale proposed to account for the substrate controlled diasteoselectivity is described in greater detail in Section 1.6.4. Arguably the necessity to tailor the substrates significantly limits the utility of this reaction.

2.2.4.4 Rhodium-Catalysed [(2+2+2)] Cycloisomerisation of Dienynes: *Type I*

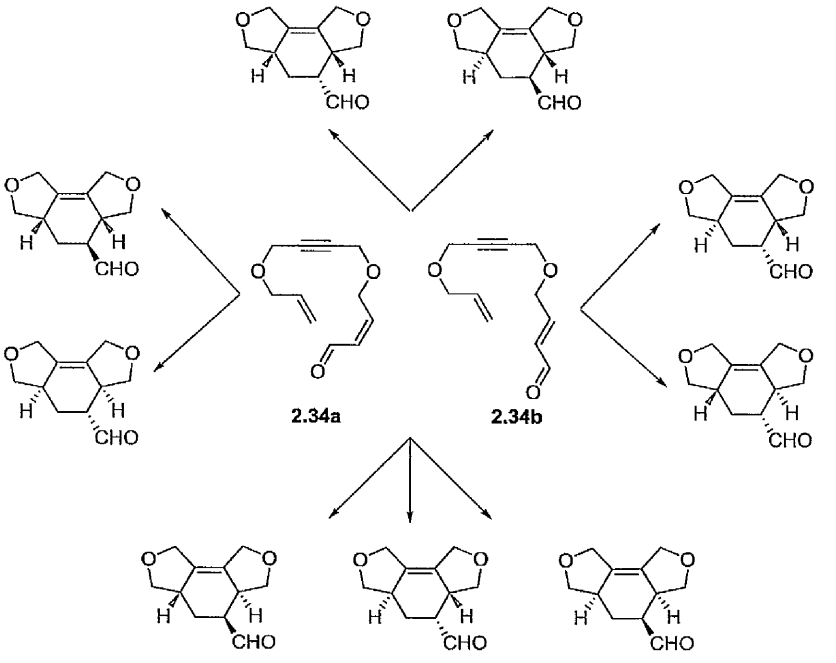


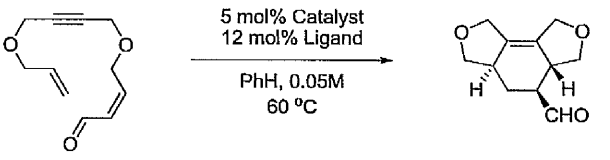
Figure 2.6 Possible tricyclohexene products from the [(2+2+2)] cycloisomerisation of enals-**2.34a** and **2.34b**

Independently, the Evans group developed a rhodium-catalysed [(2+2+2)] cycloisomerisation of dienynes for the synthesis of tricyclic cyclohexene products (Table 2.1).[25] Previous work disclosed the construction of diastereomeric octanoids *via* rhodium-catalysed [(4+2+2)] carbocyclisation reactions. Importantly, during the transformation the central 1,2-disubstituted alkene moiety was stereoselectively incorporated into the 5,8-bicyclic adduct, thus manipulating the geometry of the olefin provides a handle to access complementary diastereomeric products.[26] The ability to selectively access stereodivergent products was identified as a welcome addition to the [(2+2+2)] dienyne cycloisomerisation reactions. Enals-**2.34a/b** were selected as promising substrates for this transformation since the successful

cycloisomerisation would install three new stereogenic centres onto the tricyclic scaffold, with the aldehyde providing a means for further fuctionalisation post reaction. Figure 2.6 depicts the six possible diastereoisomers which could arise from this transformation.

Table 2.1 summarises the primary examination of this transformation; the principal exploration was undertaken by Dr. James R. Sawyer.[25] The initial investigation utilising Wilkinson's catalyst failed to provide the desired tricycle, with only starting material recovered post reaction. Treatment of dienyne **2.34a** with $[RhCl(cod)]_2$ and bidentate phosphine bis(1,2-diphenylphosphino)ethane (dppe) proved more successful, furnishing tricyclic **2.35a** in 66% yield and as a single diastereoisomer. The influence of the ligand on the reaction was investigated, with all other ligands screened impeding the reaction.[27] The optimum catalyst system for this transformation was found to be 5 mol% $[RhCl(cod)]_2$ dimer, modified *in situ* with 12 mol% bis(1,2-diphenylphosphino)propane (dppp) ligand (entry 3), providing **2.35a** in good yield and excellent diastereocontrol (entry 3, 82%, *ds* $\geq$19:1).

Table 2.1 Optimisation of the [(2+2+2)] cycloisomerisation reaction of (*Z*)-α,β-unsaturated aldehyde **2.34a**[a]



2.34a **2.35a**

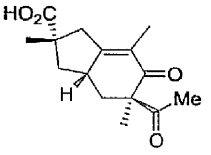
Entry	Catalyst	Ligand	Additive	Yield (%)	*ds*
1	$RhCl(PPh_3)_3$	-	-	0	-
2	$[RhCl(cod)]_2$	dppe	-	66	≥19:1
3	"	dppp	-	82	"
4	"	dppb	-	1	"
5	"	dppp	AgOTf (2eq)	4	"

[a] All reactions were carried out on a 0.25 mmol scale. [b] Isolated yields. [c] Diasterioselectivity was determined by ^1H NMR of the crude reaction mixture.

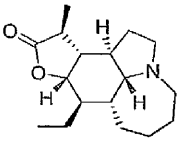
The addition of silver additives has previously proven to be effective in increasing the efficiency of transition metal-catalysed higher-order carbocyclisations.[28] The silver additive removes the chloride counter-ion from the rhodium-centre, creating a more reactive cationic species. Interestingly, in this transformation the modification of the catalytic system by the addition of silver triflate resulted in drastically diminished yield (entry 5, 4%). This is indicative that the active catalytic species of the reaction is a neutral rather than a cationic rhodium-complex.

The unanticipated stereochemistry of structure **2.35a** was determined *via* X-ray analysis. Intriguingly, the geometry of the enal is *not* conserved during the course of transformation, with a *cis*-relationship between the aldehyde and adjacent proton observed in the product. In addition, a *trans*-relationship exists between the two ring hydrogens. This is unprecedented for rhodium-catalysed carbocyclisations (Chapter

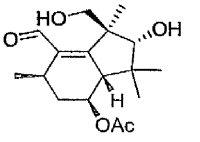
1, Section 1.4.2). It is plausible that epimerisation of the aldehyde occurs after the carbocyclisation event.



Paneolic Acid



Stenine



7α-Hydroxybotryenalol

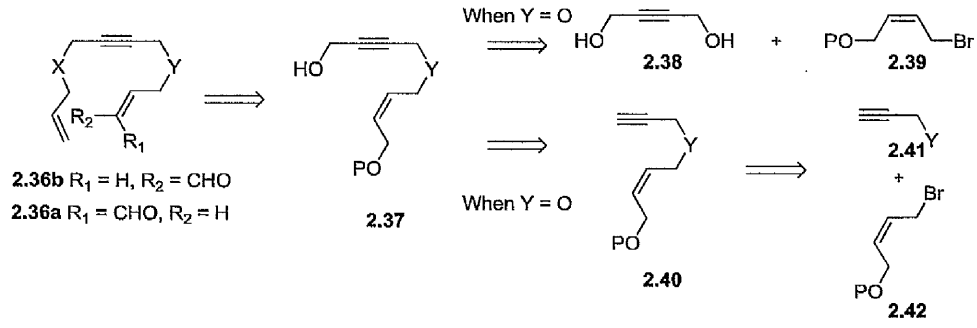
Figure 2.7 Natural products accessible *via* the [(2+2+2)] cycloisomerisation of enals-**2.34a** and **2.34b**[29-31]

This transformation could be fundamental in the expeditious construction of complex natural and non-natural products, with the aldehyde acting as a handle for additional functionalisation post carbocyclisation. Indeed, a literature search identified natural products **paneolic acid**,[29] **stenine**[30] and **7α-hydroxybotryenalol**[31] (amongst others) as plausible targets which could be synthesised efficiently *via* this transformation (Figure 2.7).

2.3. Investigating the Scope of the Rhodium-Catalysed *Intra*molecular [(2+2+2)] Cycloisomerisation

Having established the optimum reaction conditions, we turned our attention to the exploration of the range of substrates compatible with this reaction. Previous research in this field utilised sulphonamide and malonates as tethers;[22-24] installation of these pendant groups would allow direct comparison with related carbocyclisation methodology. In addition, carbon and nitrogen atoms occur frequently in natural and non-natural products. Through variation of the nature of the substituents at the X and

Y positions, combined with altering the enal geometry, 18 substrates can be envisaged to probe the scope of this reaction.



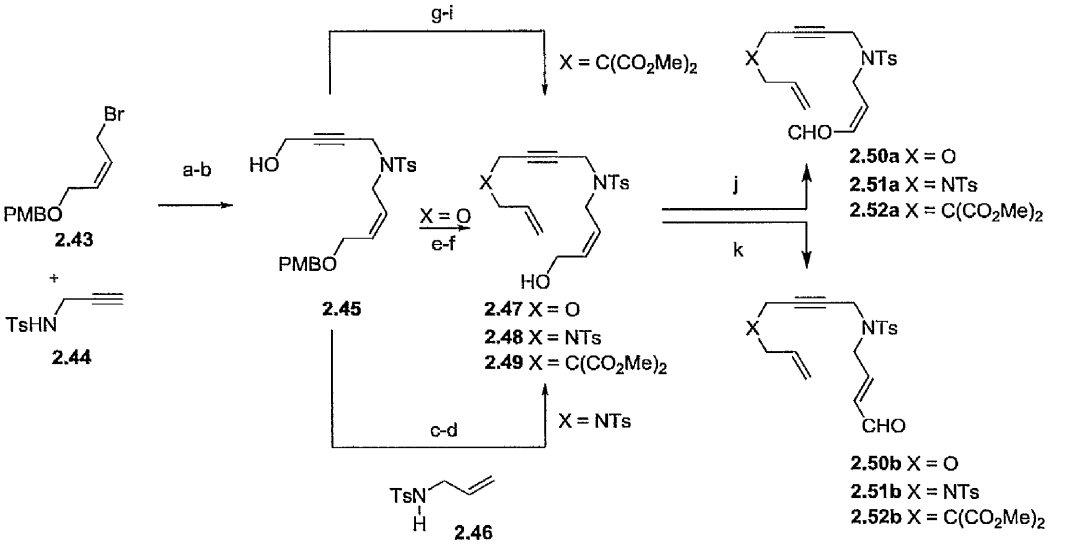
Scheme 2.5 Retrosynthetic analysis of the [(2+2+2)] cycloisomerisation substrates

Scheme 2.5 outlines the retrosynthetic analysis of the substrates. The 18 substrates are synthesised most efficiently through a divergent synthesis. Retrosynthetic disambiguation reveals that a late stage oxidation would allow access to both *cis*- and *trans*-enals, depending upon the reaction condition employed. Alcohol **2.37** provides a means of varying the nature of the tether X at a late stage in the synthesis. In the forward direction, this could be realised *via* deprotonation and reaction with allyl bromide (X = O), a Mitsunobu reaction[32] (X = NTs) or through a two-step sequence involving bromination and addition of the deprotonated methyl malonate (X = $C(CO_2Me)_2$). In turn, it was envisaged that alcohol **2.37** could be prepared from the monoprotection of 2-butyn-1,4-diol **2.38** (when Y = O) or by a one carbon homologation of terminal alkyne **2.40** (when Y = NTs, $C(CO_2Me)_2$).

2.3.1 Synthesis of Substrate with Sulfonamide Tethers at the Y Position

Our studies began with the synthesis and subsequent cycloisomerisation of the six substrates containing a sulfonamide at the Y tether. The substrates exhibiting

oxygen and malonate substituents at this position were synthesised and investigated by other members of the Evans' group.[33] In order to examine the transformation accurately, these results will be presented and analysed postliminary.



a. NaH, THF, 0 °C→rt, then **2.44**, THF, rt, 16 hr (98%); b. *n*BuLi, THF, –78 °C, 6 hr, then $(CH_2O)n$, –78 °C→rt, 14 h (55%); c. DIAD, PPh_3, **2.46**, THF, rt, 16 hr (64%); d. DDQ, DCM/pH 7 buffer (10:1), 0 °C, 1 hr (85%); e. NaH, DMF, 0 °C→rt, then allyl bromide, DMF, rt, 16 hr (87%); f. DDQ, DCM/pH 7 buffer (10:1), 0 °C, 1 hr (83%); g. NBS, PPh_3, DCM, –78 °C→–40 °C (83%); h. Dimethyl allylmalonate, NaH, DMF, 0 °C→rt, then substrate, DMF, rt, 16 hr (91%); i. DDQ, DCM/pH 7 buffer (10:1), 0 °C, 1 hr (90%); j. DMP, $NaHCO_3$, DCM, rt, 1 hr (67-75%); k. PCC, $MgSO_4$, NaOAc, rt, 2 hr (58-67%).

Scheme 2.6 Divergent synthesis of aldehydes **2.50-2.52a/b**

Scheme 2.6 described the syntheses of aldehydes **2.50-2.52a/b**. The deprotonation of sulfonamide **2.44** with sodium hydride and coupling with bromide **2.43** proceeded to provide the desired terminal alkyne in 98% yield. Homologation of the alkyne of the resulting compound through deprotonation with *n*-butyl lithium and subsequent reaction with an excess of paraformaldehyde, furnished key alcohol **2.45** in a 55% yield. Undertaking the deprotonation at –78 °C is crucial to the

success of this reaction, as it minimises the competing deprotonation of the sulfonamide group.[34]

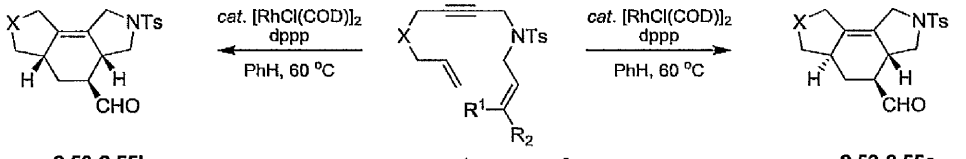
To install the oxygen substituent at position Y, alcohol **2.45** was deprotonated and treated with allyl bromide to provide the requisite allyl ether in 87% yield. To synthesise the bis-sulfonamide substrates, a Mitsunobu reaction was utilised under standard conditions with *N*-allyl-4-methylbenzenesulfonamide **2.46** (64% yield). Alternatively, bromination of **2.45** with PPh_3 and NBS followed by an alkylation reaction with dimethyl allylmalonate installed the carbon tether in 75% yield (2 steps).[35] Treatment with DDQ in the presence of pH 7 buffer, cleaved the PMB protecting groups to afford alcohols **2.47-2.49** in 83-90% yield. Oxidation of alcohols **2.47**, **2.48** and **2.49** with Dess-Martin periodinane or PCC provided the *cis*-(**2.50-2.52a**) and *trans*-aldehydes (**2.50-2.52b**) in 67-75% and 58-80% yields, respectively.[36,37]

2.3.2 Substrate Scope

The results of the carbocyclisation studies of substrates **2.50-2.52a/b** (Y = sulfonamide) are presented in Table 2.2. Under the optimised reaction conditions *cis*-enals, **2.50a** (X = O) and **2.51a** (X = NTs) were found to furnish the corresponding cycloadducts **2.53a** and **2.54a** in 76% and 73% yield, respectively (entries 1 & 3). In both cases the reaction proceeds with excellent diastereoselectivity in keeping with the initial reaction observation. Disappointingly, the *cis*-enal malonate bearing substrate (**2.52a**) failed to undergo carbocyclisation, with the isomerised product **2.52b** isolated after the designated reaction time (entry 5).[38]

The sulfonamide-oxgyen tethered containing *trans*-enal **2.50b** underwent carbocyclisation to afford tricycles **2.53b**: **2.53a** in 76% yield, as a 4:1 mixture of diastereoisomers, favouring **2.53b** (entry 2).[39] We can conclude that the decrease in diastereocontrol does not result from olefin isomerisation prior to the carbocyclisation event, as it is widely known that upon exposure to acid α,β-unsaturated *cis*-aldehydes isomerise to the analogous *trans-enals.*[40] In keeping with the *cis*-enal **2.52a**, *trans*-malonate tethered **2.52b** failed to undergo cycloisomerisation (entry 6). Surprisingly, *trans-bis*-sulfonamide substrate **2.51b** also suffered the same fate with starting material isolated post-reaction (entry 4).

Table 2.2 Substrate scope for the [(2+2+2)] cycloisomerisation reaction of a range of (*E*)/(*Z*)-α,β-unsaturated aldehydes[a]



2.53-2.55b | **2.50-52a** = R^1 = CHO, R^2 = H; **2.50-52b** = R^1 = H, R^2 = CHO | **2.53-2.55a**

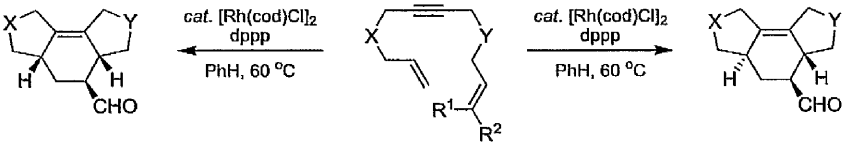
Entry	X	Dienyne	Enal geometry	Product	Yield (%)[b]	*ds*[c]
1	O	**2.50a**	*Z*	**2.53a**	76	≥19:1
2	"	**2.50b**	*E*	**2.53b**	76	4:1
3	NTs	**2.51a**	*Z*	**2.54a**	73	≥19:1
4	"	**2.51b**	*E*	**2.54b**	n/r	-
5	$C(CO_2Me)_2$	**2.52a**	*Z*	**2.55a**	n/r	-
6	"	**2.52b**	*E*	**2.55b**	n/r	-

[a] All reactions were carried out on a 0.25 mmol scale. [b] Isolated yields. [c] diastereoselectivity was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture

In order to garner greater insight into this complex transformation, it is imperative that we examine these findings in conjunction with the carbocyclisation results of the analogous dienynes (Table 2.3). The synthesis and carbocyclisation of the remaining *cis*- and *trans*-dienynes was performed by Dr. Stephen J. Atkinson.[33]

Notably, the initial observations made for substrates containing a sulfonamide at Y position are evident across the whole substrate range.

Table 2.3 Substrate scope for the [(2+2+2)] cycloisomerisation reaction of a range of (*E*)/(*Z*)-α,β-unsaturated aldehydes[a]



2.35/2.53-2.55/2.61-2.65b **2.34/2.50-2.52/2.56-2.60a** *Z* = R^1 = CHO, R^2 = H; **2.34/2.50-2.52/2.56-2.60b** *E* = R^1 = H, R^2 = CHO; **2.35/2.53-2.55/2.61-2.65a**

Entry	X	Y	Enal geometry			Yield (%)[b]	*ds*[c]
1	O	NTs	**2.50a**	*Z*	**2.53a**	76	≥19:1
2	"	"	**2.50b**	*E*	**2.53b**	76	1:4
3	NTs	"	**2.51a**	*Z*	**2.54a**	73	≥19:1
4	"	"	**2.51b**	*E*	**2.54b**	n/r	-
5	$C(CO_2Me)_2$	"	**2.52a**	*Z*	**2.55a**	n/r	-
6	"	"	**2.52b**	*E*	**2.55b**	n/r	-
7	O	O	**2.34a**	*Z*	**2.35a**	76	≥19:1
8	"	"	**2.34b**	*E*	**2.35b**	74	1:6
9	NTs	"	**2.56a**	*Z*	**2.61a**	73	≥19:1
10	"	"	**2.56b**	*E*	**2.61b**	67	1:4
11	$C(CO_2Me)_2$	"	**2.57a**	*Z*	**2.62a**	28	≥19:1
12	"	"	**2.57b**	*E*	**2.62b**	21	1:6
13	O	$C(CO_2Me)_2$	**2.58a**	*Z*	**2.63a**	56	≥19:1
14	"	"	**2.58b**	*E*	**2.63b**	n/r	-
15	NTs	"	**2.59a**	*Z*	**2.64a**	61	≥19:1
16	"	"	**2.59b**	*E*	**2.64b**	n/r	-
17	$C(CO_2Me)_2$	"	**2.60a**	*Z*	**2.65a**	n/r	-
18	"	"	**2.60b**	*E*	**2.65b**	n/r	-

[a]All reactions were carried out on a 0.25 mmol scale. [b]Isolated yields. [c]diastereoselectivity was determined by ^{1}H NMR of the crude reaction mixture

The first conclusion we can draw is that the geometry of the enal has a significant effect on the reaction outcome, with *cis* and *trans*-enals providing access to complementary diastereoisomers. In all cases, the *cis*-isomers react with complete diastereocontrol (*ds* ≥19:1 entries 1, 3, 7, 9, 11, 13 & 15), whilst the corresponding *trans*-isomers show a significantly lower selectivity (*ds* = 1:4 entries 2 & 10: *ds* = 1:6 entries 8 & 12). The reason for the discrepancy in extent of diastereocontrol is not

intuitive. A current collaboration with the Baik group aims to employ DFT calculations to investigate the origin of this phenomenon further.

In addition, in several cases there is a discrepancy between the reactivity of the *trans*- and *cis*-enals, with three examples demonstrating reactivity for cis-substrates, whilst the isomerisation of the trans-substrate is completely retarded (entries 3 *vs.* 4, 13 *vs.* 14 & 15 *vs.* 16). We postulated that this incongruity arises as a result of a greater steric encumbrance in the transition-state of the *trans*-enals, resulting in lower reactivity. Future research will serve to probe this phenomenon further.

Another intriguing aspect to this study is the effect of different tethers on the reactivity of the reaction. Notably, the reaction is most efficient when both tethers are oxygen atoms, such that the reaction proceeds in 76% and 74% isolated yield for the *cis*- and *trans*-enals respectively (entries 7 & 8). As expected the incorporation of a sulfonamide group at the X & Y position is also tolerated (entries 1-2 & 9-10). Replacing the heteroatom tethers with a malonate group has a detrimental effect on the efficiency of the transformation, in many cases, completely impeding the reaction (entries 5-6, 11-12 & 13-18).

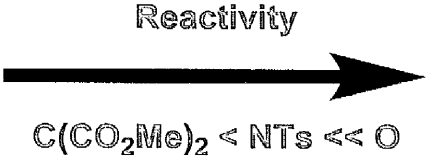


Figure 2.8 Tolerance of the three tethers

Furthermore, there is a disparity in efficiency of locating the malonate at positions X *or* Y. The *cis*-enal dienyne substrates with a malonate tether at the Y

position proceed with greater efficiency than the analogous X = malonate tethered dienynes. For example, whilst dienyne **2.58a** (X = O, Y = C $(CO_2Me)_2$) undergoes carbocyclisation to afford the desired adduct in 56% yield (entry 13), the corresponding dienyne affords cyclic **2.57a** (X = C $(CO_2Me)_2$, Y = NTs) in poor yield (entry 11, 28%). In concurrence, dienyne **2.59a** (X = NTs, Y = $C(CO_2Me)_2$) proceeds with 61% yield (entry 15), whilst the dienyne **2.52a** (X = $C(CO_2Me)_2$, Y = NTs) fails to undergo cycloisomerisation (entry 5).

The only *trans*-enal containing malonate that undergoes carbocyclisations is dienyne **2.57b** (X = $C(CO_2Me)_2$, Y = O). As expected the cycloisomerisation proceeds with moderate diastereocontrol, to provide tricycles **2.62b**:**2.62a** in 21% yield as a 6:1 mixture of diastereoisomers (entry 12). Surprisingly, for this example the analogous dienyne **2.58b** (X = O, Y = $C(CO_2Me)_2$) fails to undergo isomerisation; This result is in direct conflict with the trend observed for the *cis*-malonate tethered enals (entry 14). Nevertheless, we postulate that this result is more reflective of the altered reactivity of the *trans*-enals than the influence of the position of the malonate tether.

2.4 Conformation of the Relative Sterochemistry

At this juncture it was crucial to confirm the relative stereochemistry of the tricyclic products obtained from the carbocyclisation reaction. The relative stereochemistry of the tricycle **2.61a** was confirmed *via* X-ray crystallogrphy by Dr S. J. Atkinson (**2.61a**, Figure 2.9). Notably, a *trans*-relationship exists between the

two bridgehead protons, whilst the aldehyde and adjacent protons are *cis* to each other with the aldehyde occuping a *pseudo*-equatorial position in the tricyclic ring. Interestingly, this shows that the enal geometry has *not* been conserved in the carbocyclisation. It is widly documented that *cis*-enals can isomerise to provide the analogous *trans*-enals. Nevertheless we have demonstrated that *cis*- and *trans*-dienynes undergo cycloisomerisation to provide different diastereoisomers, as such we can conclude that the isomerisation does not occure prior to the cycloisomerisation. It was therefore postulated that the epimerisation event occurs after the carbocyclisation reaction.

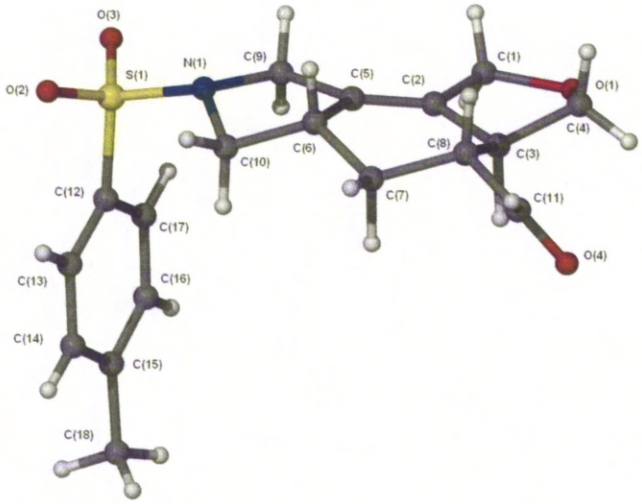
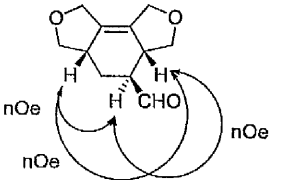


Figure 2.9 X-Ray Crystal of Tricycle **2.61a**

This unexpected result meant that obtaining a crystal structure for the corresponding product from the cyclisation of the *trans*-enal was highly important. Attempts to obtain a crystal from the analogous tricycle **2.61b** and the dervisitisation of compound **2.34b** proved unsuccessful due to disorder in the crystals. We therefore

turned our attention to confirming the relative stereochemistry of the tricycles *via* advanced NMR assignment.

Nuclear Overhauser Effect (nOe) is a useful method to confirm the relative sterochemistry of rigid compounds. Nuclei that are in close spatial proximity to each other can give rise to a nOe, facilitating the assignment of the relative stereochemistry. This method has proved particularly reliable for the stereochemical assignment of six-membered rings.

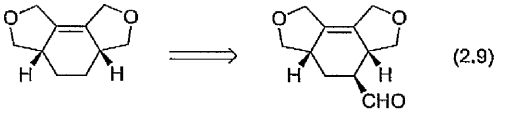


2.35b

Figue 2.10 Possible nOe of dienyne **2.35b**

Iradiation of each of the bridgehead protons of tricycle **2.35b** (2.52 and 2.44 ppm) failed to show a nOe enhancement of the opposite bridgehead proton or the proton adjacent to the aldehyde. Nevertheless, the absence of a nOe signal is not conclusive in the assignment of the realative stereochemistry of a compound. In the case of compounds **2.35b**, **2.53b**, **2.61b** and **2.62b**, the assignment of the ^{1}H NMR reveals that the ring junction protons occur as broad peaks. This is indicative of the tricyclic structure flipping between two different conformations, preventing the observation of reliable nOe signal. It was hoped that increasing the temperature of the NMR would increase the rate at which the compound changes between conformers, however this was not sufficient to sharpen the peaks and nOe data could not be obtained for these compounds.

In the event that the stereochemistry of a compound can not be confirmed through crystallography it is common to convert a molecule into a known substance. Based on the above assumption that the carbocyclisation products of *cis*-dienynes undergo epimerisation post reaction we can also assume that the diastereoisomer obtained from the *trans*-substrate does not have the same relative stereochemistry across the ring, since epimerisation of the aldehyde stereocentre would result in the same diastereoismer. Therefore it was assumed that a *cis* relationship must exist between the ring protons of the *trans*-dienynes products. Tricycle **2.66** is a previously reported product of a ruthenium catalysed carbocyclisation.[23] It was noted the decarbonylation of compound **2.35b** would provide tricycle *meso*-symmetrical **2.66**, providing conformation of the relative stereochemistry across the ring (eq. 2.9).

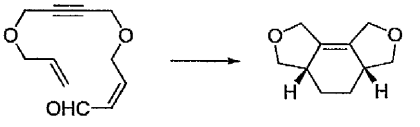


2.66 **2.35b** (2.9)

The decarbonylation reaction of tertiary aldehydes to provide alkanes has been reported with several transition metals including rhodium, ruthenium, iridium and palladium.[41] Frequently a rhodium-complex is used to facilitate this transformation. Due to the stability of the resultant carbonyl-rhodium complex the transformation is undertaken either quantitatively or at high reaction temperature to facilitate the regeneration of the active catalysts.

$$RhCl(PPh_3)_3 + RCHO \rightarrow RhCl(CO)(PPh_3)_2 + RH + PPh_3$$

During the initial optimisation of the [(2+2+2)] carbocyclisation it was observed that increasing the amount of rhodium-catalyst result in lower yields, with complete consumption of the starting material. We hypothesised that in these examples the deminished yield was a consequence of the decarbonylation of the tricyclic product. We further hypothesised that performing the reaction with stoichiometric rhodium will result in the formation of tricycle **2.66** if a *cis* relationship exists between the ring protons of tricyclic compound **2.35b**. The reaction was undertaken in a Young NMR tube in deuterated chloroform to allow the reaction to be monitored by *in situ* NMR. After 30 min the complete consumption of starting material was observed, after filtration through a cotton wool plug tricycle **2.66** was observed as a crude mixture (~34% yield by ^{1}H NMR (eq. 2.10)).



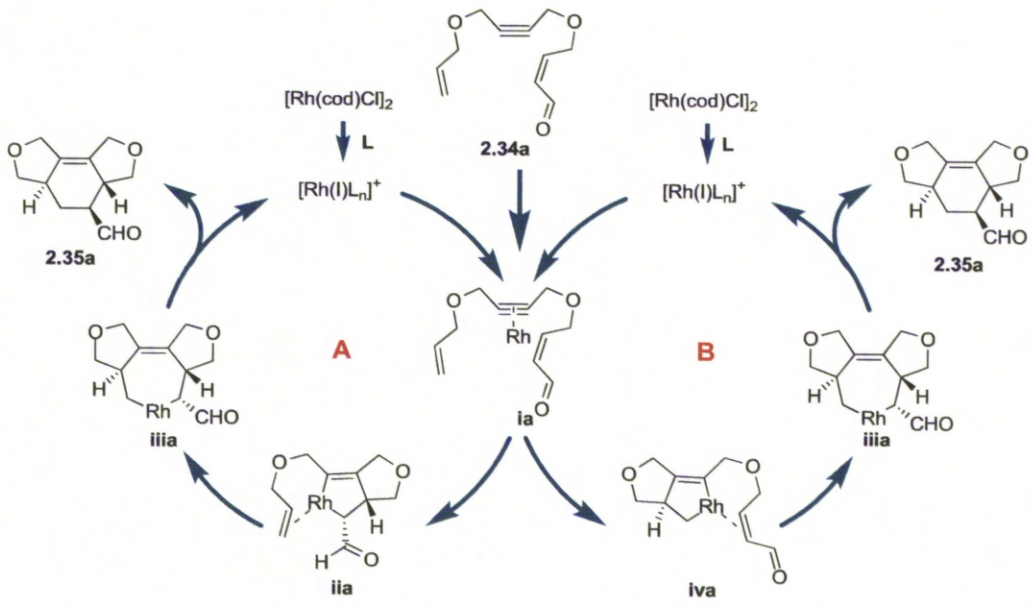
2.34b **2.66** (2.10)

Having shed some light on the stereochemical outcome of this transformation it was important to confirm that all of the carbocyclisation products, resulting from the respective enal geometries, had the same relative configurations. This was undertaken by comparison of the ^{1}H NMR spectra (Appendix 1).

2.5 Proposed Catalytic Cycle

Scheme 2.7 outlines two plausible catalytic cycles for the cycloisomerisation of *cis*-dienyne **2.34a** based on the seminal studies of others.[7] The generation of a key metallacyclopentene intermediate is well documented from 1,6-enyne systems.[6,1,2,42] In this system two 1,6-enyne systems can be considered. If the rhodium preferentially undergoes oxidative addition with the acetylene and the more electron-

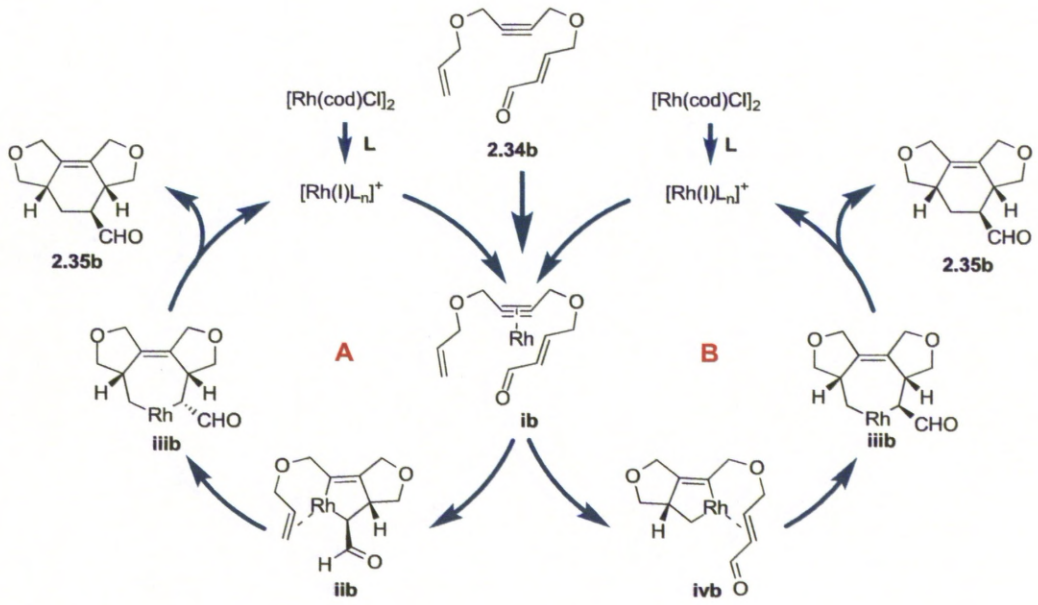
deficient olefin, *cycle A* would proceed. The oxidative addition of a *cis*-enal to the rhodium-centre results in a *trans* relationship between the aldehyde moiety and neighbouring ring junction proton as depicted in rhodacyclopentene **iia**.



Scheme 2.7 Proposed catalytic cycles for the *intra*molecular rhodium-catalysed [(2+2+2)] carbocyclisation of *cis*-dienyne **2.34a**

The subsequent carbometallation of intermediate **iia** is the diastereodetermining step in the depicted cycle. The conformation of intermediate **iia** dictates that the remaining alkene approaches the metal centre selectively from the bottom face. Carbometallation of the remaining alkene would then generate the 7-membered metallacycle **iiia**. Subsequent reductive elimination and epimerisation of the aldehyde stereocenter would furnish the desired tricyclic product and regenerate the active catalyst.

Conversely, *cycle B* will dominate upon the preferential coordination of the acetylene and the terminal olefin. Oxidative addition then results in the formation of the alternative rhodacyclopentene **iva**. Once again the diasterodetermining step in the catalytic cycle is the carbometallation step; with the conformation of intermediate **iva** determining that the *cis*-enal approaches the rhodium-centre from the bottom face. The product of this step is the same 7-membered metallacycle as observer in cycle A (**iiia**). Reductive elimination and epimerisation of the aldehyde stereogenic centre provides tricycle **2.35a**.



Scheme 2.8 Proposed catalytic cycles for the *intra*molecular rhodium-catalysed [(2+2+2)] carbocyclisation of *trans*-dienyne **2.34b**

Two analogous catalytic cycles can be depicted for cycloisomerisation of the *trans*-dienyne **2.34b** (Scheme 2.8). In keeping with the previously proposed catalytical cycles the degree of diastereoselectivity observed in the transformation is determined during the carbometallation step. In table 2.3 we observed that *trans*-

dienynes undergo cycloisomerisation with less diasteriocontrol than the corresponding *cis*-substrates (*ds* = 6:1 *vs. ds* ≥19:1). A greater understanding of the operative catalytic cycle would allow us to compare and contrast the diasterodeterming steps and transition states of the *cis* and *trans* reaction in an attempt to garner insight in to this discrepancy.

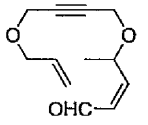
Cycle A describes the oxidative addition of the alkyne and the more electron-deficient olefin. The oxidative addition of a *trans*-enals results in a *cis* relationship between the aldehyde and adjacent proton. Coordination of the pendant olefin to rhodacyclopentene **iib** occurs predominately from the bottom face of the rhodium complex, with carbometallation resulting in rhodacycle **iiib**. From the experimental results we can conclude the ratio of coordination from this trajectory is 6:1, with the minor diastereoisomer occurring the coordination of the olefin from the opposite face of the rhodium complex, followed by carbometallation resulting in rhodacycle **iiia** (scheme 2.7) Reductive elimination of rhodacycle **iiib** provides tricyclic **2.35b**.

In analogy with the catalytic cycles described for the *cis*-dienyne, *cycle B* will occur from the oxidative addition of the acetylene and the terminal olefin, resulting in rhodacyclopentene **ivb** and installing the first stereocenter. The *trans*-enal now primarily approaches the rhodium centre from the bottom face to provide 7-membered **iiib** as the major diastereoisomer. Reductive elimination provides tricycle **2.35b** as the major diastereoisomer.

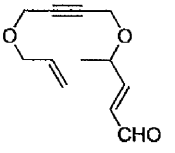
In section 2.6 we will examine the metallacycles in greater detail in order to determine the disparity between the levels of diastereocontrol observed during the carbocyclisation of the *cis*- and *trans*-enals.

2.6 Diastereoinduction within Dienyne [(2+2+2)] Cycloisomerisations Reactions

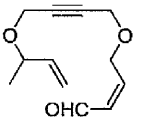
In order to ascertain whether catalytic cycle *A* or *B* is dominant in the cycloisomerisation of the reported dienynes we designed a series of experiments. We postulated that the introduction of a chiral group adjacent to the olefin which undergoes oxidative addition would strongly influence the stereochemistry of the tricycle, since the rhodium would preferentially coordinate to the alkene from the less sterically encumbered face. Conversely, a chiral group remote from the initially coordinated olefin would exhibit no stereocontrol, since the stereochemistry of the newly formed stereocentres is already pre-set before it can exert its influence.



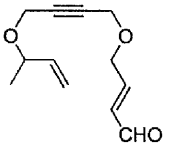
2.67a



2.67b



2.68a

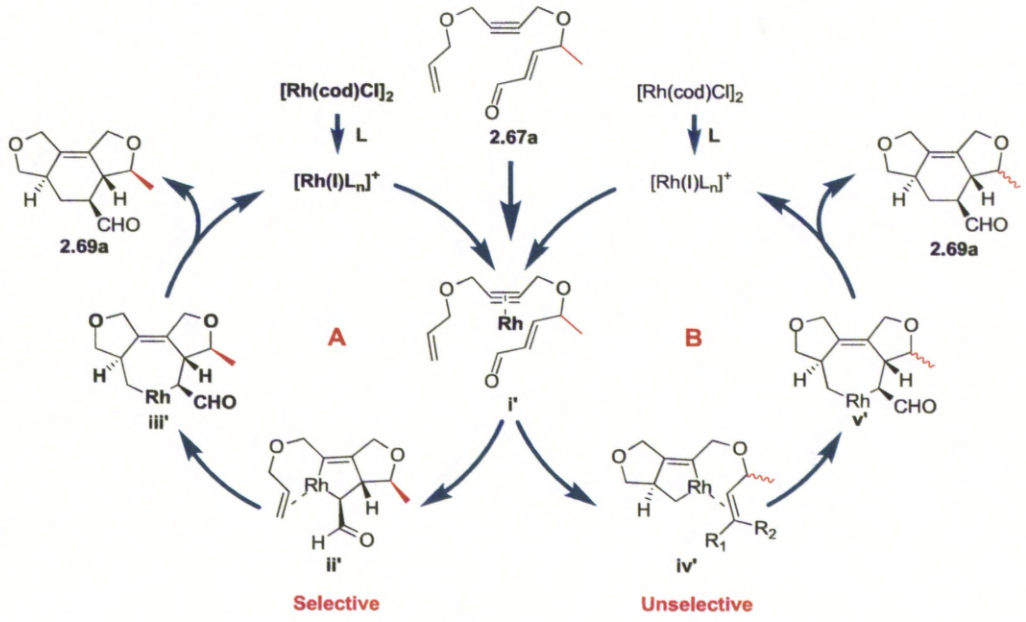


2.68b

Figue 2.11 Dienynes **2.67a/b** and **2.68a/b**

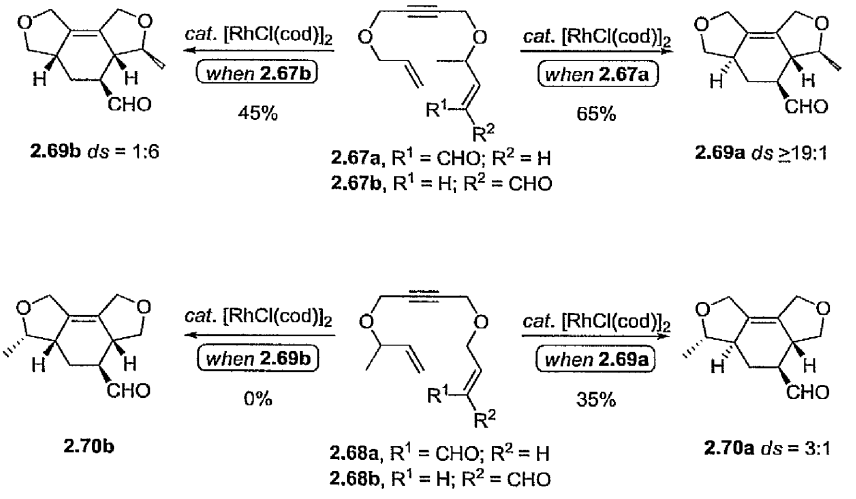
Dienynes **2.67a(*cis*)** + **2.67b(*trans*)** and **2.68a(*cis*)** + **2.68b(*trans*)** were designed to test this hypothesis. Scheme 2.9 describes two plausible catalytic cycles for the carbocyclisation of dienyne **2.67a**. If the transformation proceeds *via* catalytic *cycle A* we would expect to obtain cyclic adduct **2.69a** as a single diastereoisomer as

the 1,6-enyne system undergoing oxidative addition is strongly influenced by the methyl stereocenter.



Scheme 2.9 Rational for stereoinduction in the rhodium-catalysed [(2+2+2)] carbocyclisation

Interestingly, treatment of **2.67a** under the optimal reaction conditions furnished the tricycle **2.69a** in 65% yield, crucially as a single diastereomer (*ds* ≥19:1, by ^{1}H NMR, Scheme 2.9). Carbocyclisation of **2.67b** proceeded in 45% yield with the expected *ds* of 1:6, in accordance with the diastereoselectivity observed for **2.69b** (*vide supra*).[43] Dienynes **2.68a/b** were synthesis by Dr S. Atkinson, and subjected to the optimum carbocyclisations conditions.[33] Treatment of **2.68a** under the optimal reaction conditions furnished the tricycle **2.70a** in 35% yield as mixture of diastereoisomers (*ds* = 3:1, by ^{1}H NMR, Scheme 2.10). Since δ-substitution of the α,β–unsaturated aldehyde is likely to have a greater impact on *cycle A* (Scheme 2.9), through the *stereoselective* formation of **ii'**, (compared to the formation of **iv'**, *cycle B*), it is postulated that *cycle A* is operative in these carbocyclisations.



Scheme 2.10 Stereoinduction in rhodium-catalysed [(2+2+2)] carbocyclisations

The relative stereochemistry the ring protons and aldehyde of compounds **2.69a**, **2.69b** and **2.70a** were assigned though direct comparison of the ^{1}H NMR spectra of the analogous tricycles **2.34a** and **2.35b**.

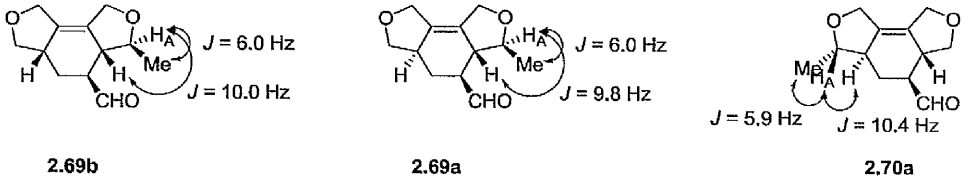
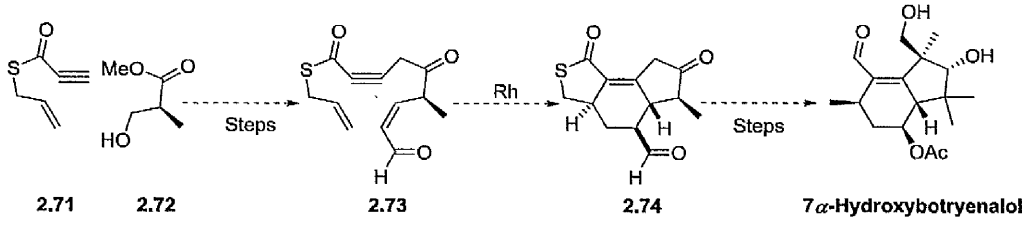


Figure 2.12 ^{1}H NMR J coupling values

The relative stereochemistry of the methyl groups and vincal bridgehead protons was assigned based on the J coupling values (Figure 2.12). In all cases the proton labled H_A appeared as a double quartets with the smaller coupling constant in agreement with the coupling constant observed for the methyl group (**2.69a/b** = 3.51 ppm, **2.70a** dq = 3.45 ppm). For compound **2.69a** the larger coupling constant (J = 9.8 Hz) corresponded to the coupling constant calculated for the adjecent ring proton (2.52 ppm). For all three examples, the larger coupling constant was between 9.8 and

10.4 Hz. The coupling constant of this magnitude are indictive of a *trans*- H-H relationship as predicted by the Karplus equation. This is in keeping with the stereochemistry predicted from the catalytic cycle. Though indicative of the stereochemistry of compounds **2.69a/b** and **2.70a** as predicted by the mechanism in Figure 2.9, without confirmation *via* X-ray crystalography this assignment remains tentative.

Subjecting an enantiomerically enriched dienyne to the reaction conditions provides an efficent route to optically active tricyclic products. Whilst yields remain modest for this transformation, it is plausible that re-optimisation of the reaction conditions for the modified substrate would offer improvement. This could be invaluable in the synthesis of natural products. Specifically, 7α-hydroxybotryenalol could be synthesised *via* a [(2+2+2)] cycloisomerisation, with the desired stereochemistry induced through the δ-methyl group (**2.73**, Scheme 2.11).[31]

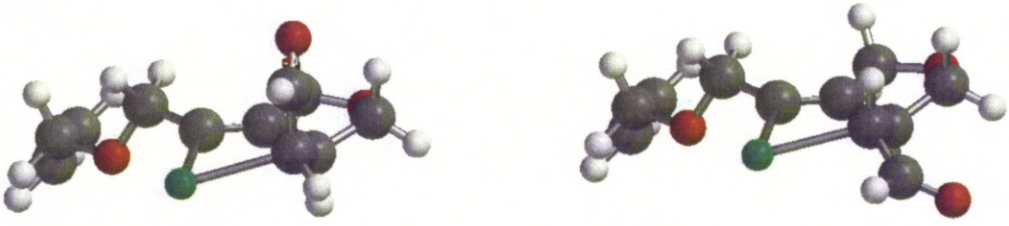


Scheme 2.11 A proposed route to 7α-hydroxybotryenalol *via* [(2+2+2)] cycloisomerisation

2.7 Diastereoselective Dienyne [(2+2+2)] Cycloisomerisation Reactions

The variation in the levels of diastereoselectivity between *cis*- to *trans*-enals is unprecedented in high-order carbocyclisation reactions and is an intriguing feature

of this transformation. It was postulated that the knowledge garnered about the operative catalytic cyclic in the preceding section would provide us with insight into this phenomenon (*cycle A,* scheme 2.7, 2.8 and 2.9) in the hope that an increase in diasteroselectivity for *trans*-dienynes could be facilitated. In section 2.4 we identified that the carbometallation step is the diastereodetermining step in the transformation. The carbometallation event occurs after coordination of the pendant alkene to the 7-membered rhodacycles **iia** and **iib**.



iia **iib**

Figure 2.13 3-Dimensional representations of transition states **iia** and **iib**

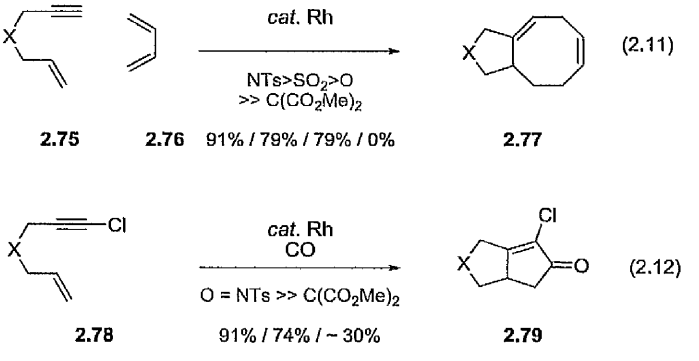
Figure 2.13 shows a 3-dimensional representation of transition-states **iia** and **iib**. From the isolated tricycle we can conclude that in the case of **iia** (*cis*-enal) the carbometallation occurs with complete selectivity (*ds* $\geq$19:1). Examination of transition state **iia** shows that the configuration is such that the aldehyde moiety is blocking one of the faces that the pendent alkene could coordinate to the rhodium centre. As such the olefin coordinates selectively to the top face installing a *trans* relationship between the ring protons.

In contrast, for *trans*-dienynes the carbometallation even occurs with 6:1 selectivity. Transition state **iib** demonstrates that the aldehyde moiety now sits in the same plane as the metal complex. The olefin now coordinates preferentially from the

bottom face installing a *cis*-relationship between the ring protons, nevertheless, whilst disfavoured; the approach of the alkene from the top face is still possible resulting in the formation of the two diastereoisomers.

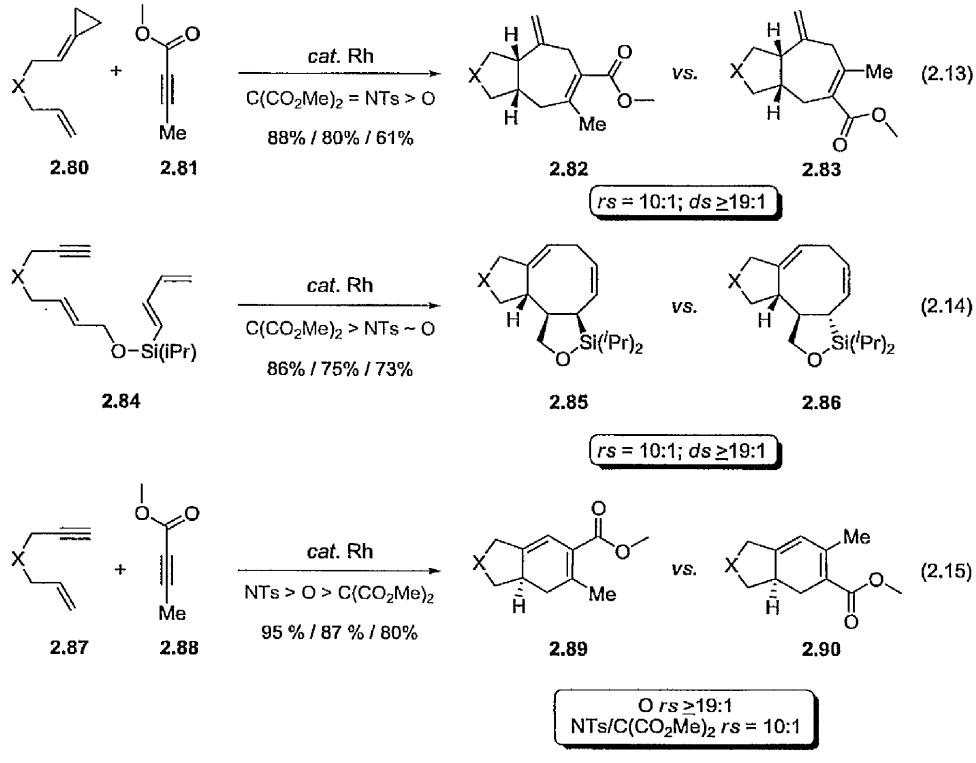
2.8 Alternative Carbon Tethers

The insufficient reactivity of the malonate tethered substrates significantly reduces the synthetic utility of this transformation for the synthesis of natural products. Significantly, the Evans group has previously observed diminished reactivity for substrates containing malonate tethers within other higher-order carbocyclisations. Specifically, in 2002 the group disclosed a semi-*inter*molecular [4+(2+2)] carbocyclisation for the construction of octanoids.[45] Whilst the transformation proceeded in high yield for oxygen, sulfonamide and sulfone tethered 1,6-enynes, the analogous malonate tethered 1,6-enynes failed to provide the desired 5,8-bicycloadducts (eqn. (2.11)). In addition, the Pauson-Khand reaction developed within our group also observed diminished reactivity for malonate containing compounds, with increased reaction times required to observe full conversion (20 hr *vs.* 42 hr) from a similar fate (eqn. (2.12)).[44]



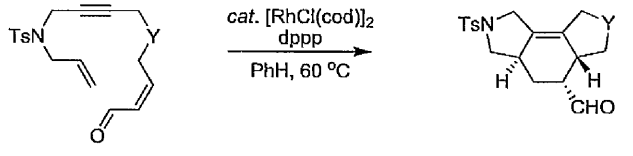
It is important to note, that the failure of substrates containing carbon tethers to undergo carbocyclisation reactions is not a universal problem. Indeed, within our research group we have reported numerous examples of carbocyclisations, in which substrates containing carbon tethers proceed with greatest or comparable efficiency (eqn. (2.12)-(2.14)).[26,41,46]

With this aspect in mind, re-examination of the reactions reveals that the 1,6-enyne unit is contained in the three reactions that demonstrate poor tolerance of malonate tethers. We hypothesised that this could be indicative of all three reactions involving this moiety in the rate determining step, whilst the remaining three carbocyclisations proceed *via* alternative pathways (eqn. (2.13)-(2.15)). We therefore hope that addressing the tolerance of carbon tethers with our [(2+2+2)] cycloisomerisation will improve the scope of other carbocyclisation reactions.



With the ultimate goal of finding a carbon tether that undergoes cycloisomerisation with greater efficiency, we investigated a series of substrates containing an alternative carbon tether. Mono-ester **2.91a** was selected to probe the reaction further,[47] and synthesised *via* a Krapcho decarboxylation.[28] Table 2.4 illustrates the results of the carbocyclisations for the substrate bearing the alternative carbon tether. Subjecting mono-ester **2.91a** to the requisite rhodium catalyst failed to provide the desired tricyclic adduct, with the starting material recovered post-reaction (entry 2). The Thorpe-Ingold effect states that cyclisations are favoured for substrates containing gem-dimethyl groups as a consequence of reducing entropy and promoting the reacting conformation.[48] It is plausible that the reduction in this effect could be accountable for the decreased reactivity in this example.

Table 2.4 Substrate scope for the [(2+2+2)] cycloisomerisation reaction of dienynes (*Z*)-α,β-unsaturated aldehydes[a]



2.59a, Y = $C(CO_2Me)_2$
2.91a, Y = $CHCO_2Me$

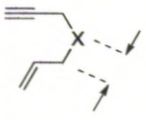
2.64a, Y = $C(CO_2Me)_2$
2.92a, Y = $CHCO_2Me$

Entry	Dienyne	Enal geometry	Dienyne	Yield (%)[b]
1	**2.59a**	*Z*	**2.64a**	61[c]
2	**2.91a**	*Z*	**2.92a**	n/r n/r

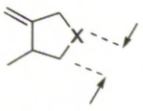
[a]All reactions were carried out on a 0.1 mmol scale. [b]Isolated yields [c]*ds* ≥19:1

Another hypothesis proposed was that the reactivity incongruity could result from differences in bond lengths. Spartan was utilised to calculate the bond length of the starting materials and cyclic products of several substrates.[49] It is important to note that *unless* the oxidative addition is the rate limiting step, this modelling is NOT representative of the rate determining transition state. Significantly, we do not believe that the initial oxidative addition is the rate determining step. Rather we hoped that this would highlight a trend and provide us with a basic tool to predict the success of a transformation before investing time in the synthesis of the substrates.

Table 2.5 Molecular modelling of bond lengths using Spartan



Linear



Cyclic

Entry	Tether	Linear	Cyclic
1	Malonate	1.54	1.56
2	Mono Ester	1.54	1.53
3	Ketal	1.54	1.52
4	NTs	1.48	1.49
5	O	1.43	1.44

Table 2.5 outlines the results of the energy minimisation lengths of the substrates and products from the [(2+2+2)] cycloisomerisation. Examination of the data reveals that the substrate with the shortest tether length is the oxygen containing compound (1.43 Å, entry 4), with the nitrogen tethered substrates marginally longer (1.48 Å, entry 5). The bond lengths of the three carbon tethers are the longest (1.54 Å, entries 1-3). Interestingly, these results map on the reactivity we previously

observed within the rhodium-catalysed [(2+2+2)] carbocyclisation reaction. Unsurprisingly, comparable bond lengths were recorded for the products of the carbocyclisation reaction.

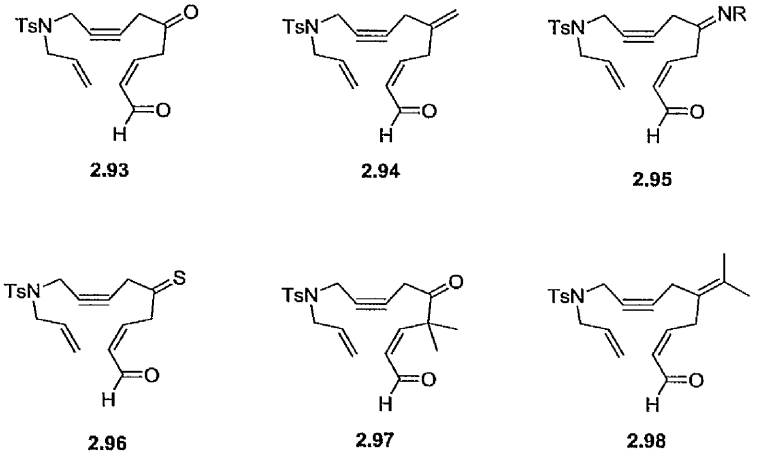
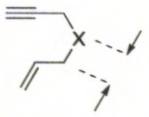


Figure 2.14 Alternative carbon tethers

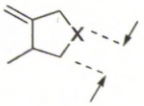
If we have correctly identified that the bond length is accountable for the detrimental reactivity of the malonate tethered substrates, then finding an alternative carbon tether with a shorter carbon-carbon bond may be challenging. Nevertheless we have identified one approach to alter the bond length between the tethering carbon atom and the adjacent carbon. It is known that a sp^2 carbon bonding to a sp^3 carbon has a reduced bond length compared to a sp^3-sp^3 carbon-carbon bond. All three carbon tethers tested (table 2.4) contained sp^3-sp^3 carbon-carbon bond and as such they all had comparable bond lengths. Installing a ketone, alkene, imine etc at the tethering position would provide a way to test this hypothesis (**2.93-2.98**, Figure 2.14). Importantly, our molecular studies show these bond lengths are still longer than those for oxygen and sulfonamide tethers. However, since the malonate tether appeared to sit in the cusp of reactivity (with some substrates cycloisomerising and others failing) we hoped that installing tethers with shorter bond lengths would

improve the reactivity. We selected ketone **2.93** to investigate, since this motif would be synthetically useful.

Table 2.6 Molecular modelling of bond lengths using Spartan



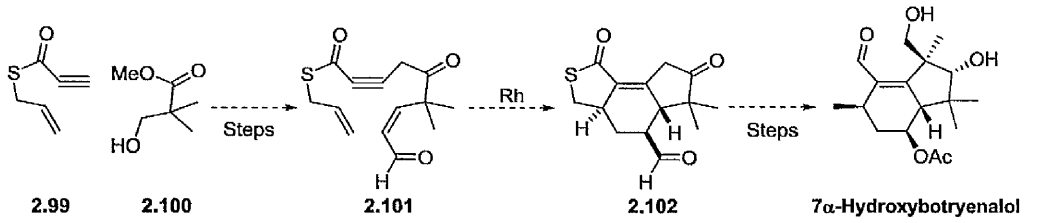
Linear



Cyclic

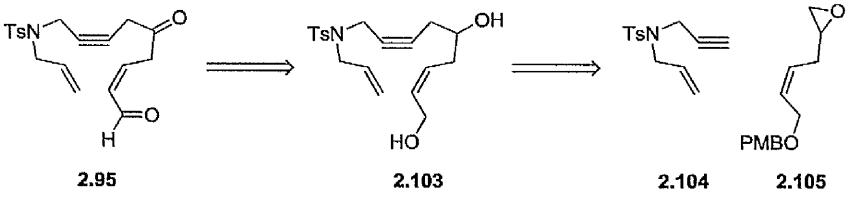
Entry	Tether	Linear	Cyclic
1	Malonate	1.54	1.56
2	Ketone	1.52	1.51
3	NTs	1.48	1.49
4	O	1.43	1.44

It is worth noting, that this ketone substrate is not without problems. It is highly possible that under the reaction condition this substrate will isomerise and the double bond fall into conjugation. This can be overcome by removing the protons on the pendant carbon, for example installing a gem-dimethyl group between the ketone and the alkene **2.97**. Gratifyingly, the gem-dimethyl ketone tether would be a useful motif towards the synthesis of 7α-hydroxybotryenalol (Scheme 2.12).[31] This approach is orthogonal to the one presented in Scheme 2.11. Nevertheless, this would make the carbon-tether cycloisomerisation very substrate specific, limiting the synthetic utility of the transformation. In addition this would add an additional variant, and could result in increased reactivity as a consequence of the Thorpe-Ingold effect rather than the alternative tether. For these reasons, dienyne **2.95** was selected for initial testing.



Scheme 2.12 An alternative route towards the synthesis of 7α-hydroxybotryenalol

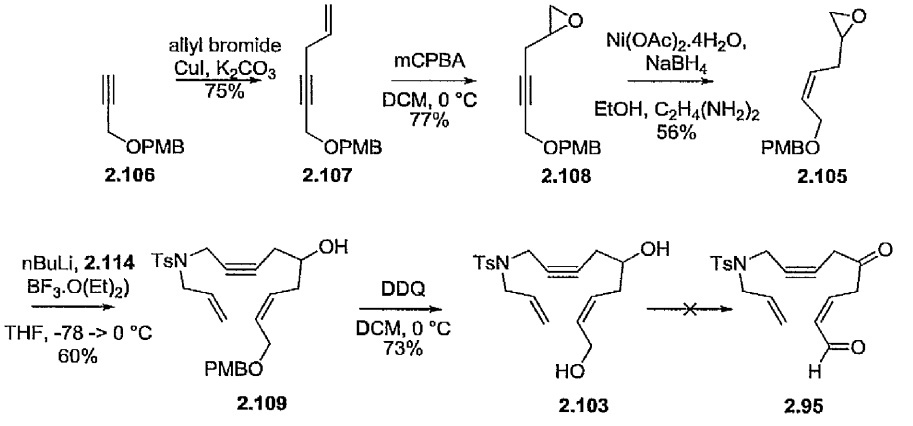
In the outset of our retrosynthetic analysis of substrate **2.95**, we were aware that a late stage oxidation may be a cause for concern. We have already mentioned our unease that subjecting **2.95** to harsh reaction conditions would result in isomerisation. In addition, *intra*molecular lactonisation will occur if the oxidation of the primary and secondary alcohols occurs sequentially. Swern oxidations have been utilised to overcome *intra*molecular lactonisation since the carbonyl products are produced simultaneously from the alkoxysulfonium ion intermediate during the addition of base.[50] Substrate **2.95** could be constructed from diol **2.103** *via* a double Swern oxidation (Scheme 2.13). Diol intermediate **2.103** could be fashioned *via* an epoxide opening of **2.105** with 1,6-enyne **2.104**.



Scheme 2.13 Retrosynthetic analysis of substrate **2.95**

The synthesis of substrate **2.95** began homologation of alkyne **2.106** followed by epoxidation with *m*CPBA. Subjecting this compound to Lindlar reduction provided a complex mixture of products as a consequence of over and under reduction. Gratifingly, $Ni(OAc)_2.4H_2O$ and sodium borohydride provided complete selectivity. Attack of the epoxide of **2.105** with alkyne **2.104** provided alcohol **2.109**

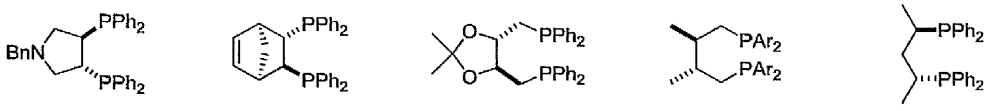
in 73% yield. Deprotection under standard DDQ conditions provided diol **2.103**. Disappointingly, attempts to oxidise this compound *via* a Swern oxidation proved unsuccessful. We believe that this substate is stable due to isomerisation and future work will focuses on the synthesis of alternative dienyne **2.97** to probe this transformation further.



Scheme 2.14 Attempted synthesis of substrate **2.95**

2.9 Enantioselectivity: Initial Studies and Optimisation

Having demonstrated the scope and limitations of the basic transformation we reasoned that an enantioselective variant should be possible utilising one of a plethora of commercially available chiral bisphosphines.[52] Given the specificity of the racemic reaction, we initiated our screen with commercially available ligands that contain a similar carbon backbone to dppp. We therefore selected the five commercially available ligands which most closely resembled dppp. (Figure 2.15)

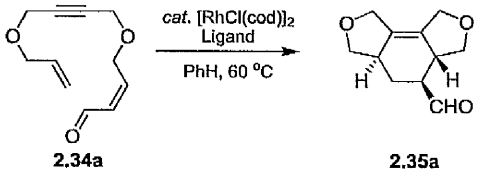


catASium D(*R*) (*S*,*S*)-NORPHOS (*S*,*S*)-DIOP (*S*,*S*)-CHIRAPHOS (*R*,*R*)-BDPP

Figure 2.15 Commercially available ligands resembling dppp

The results of screening these ligands are shown in Table 2.7. Surprisingly, no enantiocontrol was observed using the CatASium ligand (entry 1), whilst (*S*,*S*)-Chiraphos gave poor enantioselectivity and conversion (entry 4), (*S*,*S*)-Norphos and (*S*,*S*)-DIOP and showed an improved enantioselectivity (entries 2 & 3) albeit in modest yield. Gratifyingly, the greatest enantiocontrol was observed with the (*R*,*R*)-BDPP ligand which provided carbocycle **2.55a** in 85% *ee* (entry 5). Since the yield of the reaction was only moderate, the reaction required further optimisation.

Table 2.7 Initial development of the enantioselective [(2+2+2)] cycloisomerisation reaction of dienyne (*Z*)- **2.34**[a]



2.34a **2.35a**

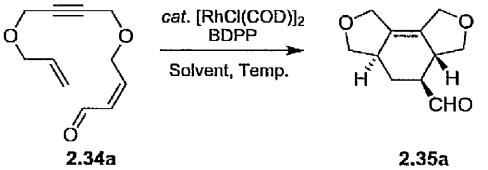
Entry	Ligand	Yield (%)[b]	%ee[c]
1	CatASium D(*R*)	4	0
2	(*S*,*S*)-NORPHOS	32	38
3	(*S*,*S*)-DIOP	15	64
4	(*S*,*S*)-CHIRAPHOS	9	9
5	(*R*,*R*)-BDPP	26	85

[a]All reactions were carried out on a 0.25 mmol scale. [b]GC yields. [c]Determined by chiral GC analysis

The influence of solvent and temperature on the reaction profile was investigated (Table 2.8). Non-polar solvents provided optimal results, with *p*-xylene, toluene and benzene being practically equivalent. In analogy to the enantioselective

*inter*molecular [(2+2)+2] carbocyclisation of enynes previously optimised in the Evans laboratory, it was hoped that using THF may prove beneficial to the development of our enantioselective reaction.[28] However, this resulted in a lowering of yield and only a modest increase enantioselectivity (+4%, entries 1 *vs.* 2). It seemed evident therefore that benzene was the most appropriate solvent. Attention then focussed on the effect of temperature on the reaction. It became apparent that there was a fine balance between minimising unreacted starting material and preventing the formation of a β-hydride elimination side product.[53] It was determined that the optimum temperature was 45 °C with a prolonged reaction time of 24 hours to provide **2.35a** in 51% yield and 88% enantiomeric excess.

Table 2.8 Solvent and temperature screening of the enantioselective [(2+2+2)] cycloisomerisation reaction of dienyne (*Z*)- **2.35a**[a]



2.34a **2.35a**

Entry	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]	%ee[c]
1	PhH	60	10	36	85
2	THF	40	"	26	89
3	PhH	50	"	37	88
4	"	40	"	19	88
5	"	50	24	51	88

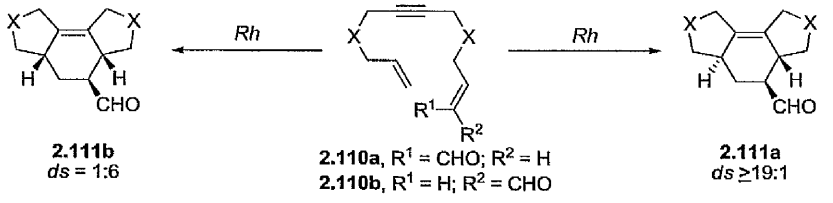
[a]All reactions were carried out on a 0.25 mmol scale. [b]GC yields. [c]% ee's determined by GC analysis.

The initial mandate for this project was to utilise ligands that are commercially available, making this methodology more functional. In the infancy of this work we realised, that while there are hundreds of commercially available phosphines, most are biaryl based and relatively few contain the requisite 3 carbon

backbone. Currently, the modest yield of this reaction would limit the application of this methodology. To this end we have investigated synthesising ligands with alternative electronics. At the present time all attempts to synthesis alternative ligands to improve the yield and enantioselectivity have been unfruitful.

2.10 Conclusion

Rhodium-Catalysed [(2+2+2)] cycloisomerisations provide an expedient route to highly functionalised tricyclic skeletons. The installation of olefin moieties facilitates the formation of tricycles with up to four new stereocentre in a single transformation.



2.111b
ds = 1:6

2.110a, R^1 = CHO; R^2 = H
2.110b, R^1 = H; R^2 = CHO

2.111a
ds ≥19:1

Scheme 2.15 Summary of Research

We have developed a diastereo- and enantioselective *intra*molecular rhodium-catalysed [(2+2+2)] carbocyclisation of carbon- and heteroatom-tethered dienynes. This study delineates some of the critical features for accessing complementary diastereoisomers through manipulating enal geometry to afford products with three new stereogenic centres. In addition, we have demonstrated that a correctly situated chiral substituent is not only able to control the stereochemistry of the transformation, but also provides valuable insight into mechanistic aspects of the catalytic cycle.

Finally, we anticipate that this transformation will provide exciting opportunities for future applications for the synthesis of natural products containing a 5-6-5 tricyclic-core. In collaboration with Professor Baik, DFT studies are ongoing to delineate the complete catalytic cycle and account for the levels of diastereoselectivity.

2.11 Experimental

2.11.1 General Experimental

All reactions were performed in oven-dried (125 °C) or flame-dried glassware under an inert atmosphere of nitrogen or argon. Syringes were oven-dried (125 °C) and then cooled in a desiccator. The following reaction solvents were dried using an alumina column solvent system: toluene (PhMe), diethyl ether (Et_2O) and dichloromethane (DCM) were dried over alumina column solvent system using the method of Grubbs.[54] The following reaction solvents were distilled from the indicated drying agents: tetrahydrofuran (THF) (sodium, benzophenone), hexanes (CaH_2), benzene (PhH) (sodium) and acetonitrile (MeCN) (CaH_2). Triethyl amine (Et_3N) was distilled from CaH_2. Brine refers to a saturated solution of NaCl. All starting material and reagents were purchased from Acros, Aldrich, Alfa Aesar, Fluka, and Strem chemical companies and were used without further purification unless noted otherwise. Analytical thin layer chromatography (TLC) was performed on Merck 60 F_{254} precoated silica-gel plates. Visualization was accomplished with a UV light and/or a $KMnO_4$, or *p*-anisaldehyde solution. Flash column chromatography (FCC) was performed by the method of Still with Merck Silica-gel 60 (230-400 mesh). Solvents for extraction and FCC were technical grade. Reported solvent mixtures for both TLC and FCC were volume/volume mixtures. Infrared spectra (IR) were obtained on a Perkin-Elmer spectrum one series FTIR spectrophotometer. Peaks are reported in cm^{-1} with the following relative intensities: s (strong), m (medium), w (weak). The Liverpool University Mass Spectroscopy Centre and EPSRC National Spectrometry Centre, Swansea, recorded Mass spectra. Highresolution electron-impact electrospray (ESI) mass spectra were obtained on a

Micromass LCT Mass spectrometer and LTQ Orbitrap XL. The specific rotation was measured with a PerkinElmer Model 343 Plus polarimeter.

^{1}H-NMR and ^{13}C-NMR were recorded on a Bruker DRX-500 MHz NMR spectrometer in the indicated deuterated solvents. For ^{1}H-NMR, $CDCl_3$ and C_6D_6 were set to 7.26 ppm ($CDCl_3$ singlet) and 7.16 (C_6D_6 singlet) respectively and for ^{13}C-NMR, CDC^{13} and C_6D_6 were set to 77.16 ppm ($CDCl_3$ center of triplet) and 128.06 ppm (C_6D_6 center of triplet) respectively. All values for ^{1}H-NMR and ^{13}C-NMR chemical shifts for deuterated solvents were obtained from Cambridge Isotope Labs. Data are reported in the following order: chemical shift in ppm (δ) (multiplicity, which are indicated by br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet)); assignment of 2nd order pattern, if applicable; coupling constants (*J*, Hz); integration. All ^{13}C-NMR spectra were reported using the descriptor (o) and (e) referring to whether the peak is odd or even, respectively, and correlate to an attached proton test (ATP) experiment.

2.11.2 General Experimental Procedures

i. General procedure for PMB deprotection

To a solution of PMB-ether (1 eq) in DCM/pH 7 buffer (10:1, 0.1 M) at 0 °C was added DDQ (2 eq) in one portion. The resultant solution was stirred at 0 °C for 1 h before being quenched by the addition of $NaHCO_3$ solution. The layers were separated and the aqueous layer further extracted with DCM (2 x). The combined

organics were dried over $MgSO_4$ and concentrated *in vacuo*. The resultant crude oil was purified by flash chromatography (25→40% EtOAc/hexanes) to afford the corresponding alcohol.

ii. General procedure for oxidation to the *cis*-enal.

To a solution of alcohol (1 eq) in DCM (0.15 M) was added $NaHCO_3$ (2 eq) and DMP (1.1 eq) in one portion. The resultant solution was stirred at rt for 15 min. The reaction mixture was then quenched by the addition of NaHCO3 and Na2S2O3 solutions (1:1) added and the resultant suspension stirred for 15 min. The layers were separated and the aqueous layer further extracted with DCM (2 x). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. The resultant crude oil was purified by flash chromatography (25-30% EtOAc/hexanes) to afford the corresponding *cis*-enal.

iii. General procedure for oxidation to the *trans*-enal.

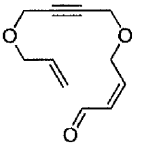
To a solution of the alcohol (1 eq) in DCM (0.1 molar) was added PCC (3 eq), $MgSO_4$ (1 eq) and sodium acetate (5 eq) in one portion. The resultant solution was stirred at rt for 1 h. The reaction mixture was then quenched by the addition of hexanes, filtered through celite, washed with DCM (3 x) and then concentrated *in vacuo*. Purification *via* FCC on silica gel (eluted with 20% EtOAc/hexanes) afforded the corresponding *trans*-aldehyde

iv. General procedure for Rhodium-catalysed [2+2+2] carbocyclisation

$[Rh(COD)Cl]_2$ (6.2 mg, 0.25 mmol) and dppp (12.4 mg, 0.03 mmol) were weighed under nitrogen funnel and added to a flame dried flask, backfilled with N2. The flask was carefully backfilled with Ar (3 x). Benzene (5 mL) was added and the resultant solution heated to 60 °C (using a preheated oil bath) and stirred for 15-20 min (the solution becomes homogeneous). Dienyne (0.25 mmol) was added to the reaction at 60 °C *via* tared microsyringe. The reaction was stirred for 10 h at 60 oC before being directly subjected to flash chromatography (30→60% EtOAc/hexane) to provide the corresponding tricycle.

2.11.3 Experimental Procedures

(*Z*)-4-(4-(Allyloxy)but-2-ynyloxy)but-2-enal[33]



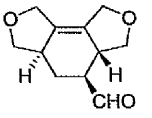
2.34a

cis-Aldehyde **2.34a** (243 mg, 1.25 mmol, 83% yield) was prepared by general procedure **ii** from **2.120** (296 mg, 1.51 mmol) and was isolated as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 10.04 (d, J = 6.0 Hz, 1H), 6.58 (dt, J = 11.5, 5.7 Hz, 1H), 6.06 (ddt, J = 11.5, 6.6, 2.0 Hz, 1H), 5.88 25 (ddt, J = 17.2, 10.5, 5.7 Hz, 1H), 5.29 (dq, J = 17.3, 1.5 Hz, 1H), 5.21 (dq, J = 10.4, 1.3 Hz, 1H), 4.57 (dd, J = 5.6, 2.0 Hz, 2H), 4.26 (t, J = 1.7 Hz, 2H), 4.18 (t, J = 1.7 Hz, 2H), 4.04 (dt, J = 5.7, 1.3 Hz, 2H).

IR (Neat): 2853 (m), 1683 (s), 1614 (w), 1352 (m), 1120 (s), 1067 (s), 927 (s) cm-1;

(3a*R*,4*R*,5a*R*)-1,3,3a,4,5,5a,6,8-octahydroisobenzofuro[5,4-c]furan-4-carbaldehyde[33]



2.35a

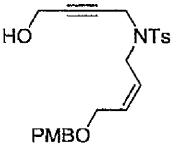
Aldehyde **2.35a** (51% yield, 88% *ee,* GC assay) was prepared by general procedure **iv** from **2.34a** (18.9 mg, 0.10 mmol) utilizing (*R,R*)-BDPP ligand and was isolated as a colourless oil.

(Astec; 140 °C to 150 °C at 2 °C/min, 150 ° to 180 °C at 10 °C/min); *t*R 42.90 min (minor), *t*R 44.49 min (major).

1H NMR (500 MHz, CDCl3) δ 10.04 (d, J = 6.0 Hz, 1H), 6.58 (dt, J = 11.5, 5.7 Hz, 1H), 6.06 (ddt, J = 11.5, 6.6, 2.0 Hz, 1H), 5.88 (ddt, J = 17.3, 10.5, 5.7 Hz, 1H), 5.29 (dq, J = 17.3, 1.5 Hz, 1H), 5.21 (dq, J = 10.4, 1.3 Hz, 1H), 4.57 (dd, J = 5.6, 2.0 Hz, 2H), 4.26 (t, J = 1.7 Hz, 2H), 4.18 (t, J = 1.7 Hz, 2H), 4.04 (dt, J = 5.7, 1.3 Hz, 2H).

IR (Neat): 2853 (m), 1683 (s), 1614 (w), 1352 (m), 1120 (s), 1067 (s), 927 (s) cm^{-1}.

(*Z*)-N-(4-Hydroxybut-2-ynyl)-N-(4-(4-methoxybenzyloxy)but-2-enyl)-4-methylbenzenesulfonamide



2.45

^{n}BuLi (4.21 mL, 10.5 mmol) was added dropwise to a stirred solution of alkene **2.112** (1.40 g, 3.51 mmol) in anhydrous THF (19 mL) at –78 °C to give a yellow solution. The resulting solution was stirred at –78 °C for 5 h before

paraformaldehyde (0.137 g, 4.56 mmol) was added in one portion. The solution was allowed to warm slowly to rt for 14 h. The reaction mixture was then quenched with NH_4Cl (50 mL). The layers were separated and the aqueous layer further extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification *via* FCC on silica gel (eluting with 30→60% EtOAc/hexanes gradient) provided alcohol **2.45** (0.86 g, 1.93 mmol, 55% yield) as a yellow oil.

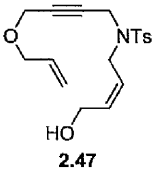
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 5.86-5.82 (m, 1H), 5.55-5.50 (m, 1H), 4.43 (s, 2H), 4.09-4.06 (m, 4H), 3.90-3.87 (m, 4H), 3.90 (s, 3H), 2.43 (s, 3H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 159.31 (e), 143.68 (e), 135.85 (e), 131.76 (o), 129.94 (e), 129.48 (o), 129.44 (o), 127.90 (o), 126.57 (o), 113.86 (o), 84.22 (e), 78.44 (e), 72.23 (e), 65.09 (e), 55.38 (o), 50.64 (e) 43.52 (e), 36.43 (e), 21.61 (o).

IR (Neat): 3433 (w), 2925 (w), 1513.18 (m), 1160 (s), 904 (s) cm^{-1}.

HRMS ($M+Na^+$): calcd for $C_{23}H_{27}NO_5S$ 452.1508 found 452.1501.

(*Z*)-N-(4-(Allyloxy)but-2-ynyl)-N-(4-hydroxybut-2-enyl)-4-methylbenzenesulfonamide



2.47

Alcohol **2.47** (460 mg, 1.32 mmol, 83 % yield) was prepared by general procedure **i** from **2.113** (745 mg, 1.59 mmol) and was isolated as a colourless oil.

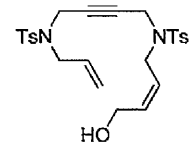
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 5.89-5.79 (m, 2H), 5.49 (dt, *J* = 11.0, 7.3 Hz, 1H), 5.26-2.50 (m, 2H), 4.20 (t, *J* = 6.1 Hz, 2H), 4.15 (s, 2H), 3.90-3.89 (m, 4H), 3.86 (d, *J* = 3.4 Hz, 2H), 2.43 (s, 3H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 143.89 (e), 135.81 (e), 134.51 (o), 133.75 (o), 129.68 (o), 127.92 (o), 125.32 (o), 118.12 (e), 81.84 (e), 79.20 (e), 70.85 (e), 58.07 (e), 57.2 (e), 43.23 (e), 36.53 (e) 21.68 (o).

IR (thin film): 3431 (w), 2923 (w), 2856 (w), 1342 (m), 1157 (s), 658 (s) cm^{-1}.

HRMS ($M+Na^+$): calcd for $C_{18}H_{23}NO_4S$ 372.1245 found 372.1240.

(*Z*)-N-Allyl-N-(4-(N-(4-hydroxybut-2-enyl)-4-methylphenylsulfonamido)but-2-ynyl)-4-methylbenzenesulfonamide



2.48

Alcohol **2.48** (318 mg, 0.63 mmol, 72 % yield) was prepared by general procedure **ii** from **2.114** (548 mg, 0.88 mmol) and was isolated as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.3 Hz, 4H), 7.31-7.29 (m, 4H), 5.84 (dt, *J* = 11.2, 6.5 Hz, 1H), 5.62-5.54 (m, 1H), 5.42-5.37 (m, 1H), 5.17 (dd, *J* = 10.1, 1.0 Hz, 1H), 5.11 (dd, *J* = 17.1, 1.3 Hz, 1H), 4.17 (t, *J* = 5.7 Hz, 2H), 3.92 (s, 2H), 3.84 (s, 2H), 3.78 (d, *J* = 3.7 Hz, 2H), 3.63 (d, *J* = 3.2 Hz, 2H), 2.43 (d, *J* = 4.2 Hz, 6H), 1.76 (t, *J* = 5.5 Hz, 1H).

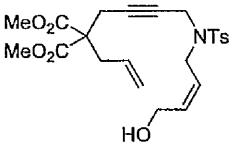
^{13}C NMR (125.8 MHz, $CDCl_3$): δ 143.98 (e), 143.91 (e), 136.13 (e), 135.99 (e), 134.35 (o), 131.88 (o), 129.73 (o), 129.79 (o), 127.74 (o), 127.71 (o), 125.30 (o),

119.89 (e), 78.97 (e), 78.31 (e), 58.10 (e), 49.23 (e), 43.15 (e), 36.20 (e), 35.87 (e), 14.31 (o).

IR (Neat): 3538 (w), 2923 (w), 1342 (m), 1153 (s), 898 (m), 661 (s) cm^{-1}.

HRMS ($M+Na^+$): calcd for $C_{25}H_{30}N_2O_5S_2$ 525.1494 found 525.1503.

(*Z*)-Dimethyl-2-allyl-2-(4-(N-(4-hydroxybut-2-enyl)-4-methylphenylsulfonamido)but-2-ynyl)malonate



2.49

Alcohol **2.49** (91 mg, 0.20 mmol, 87 % yield) was prepared by general procedure **i** from **2.115** (0.13 mg, 0.22 mmol) and was isolated as a colourless oil.

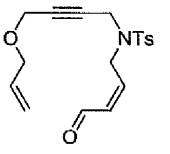
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 5.87-5.82 (m, 1H), 5.50-5.41 (m, 2H), 5.07 (d, J = 10.1 Hz, 1H), 5.01 (d, J = 17.7 Hz, 1H), 4.19 (s, 2H), 4.06 (s, 2H), 3.84 (d, J = 7.0 Hz, 2H), 3.68 (s, 6H), 2.55-2.53 (m, 4H), 2.41 (m, 3H), 2.26 (br s, 1H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 170.25 (e), 143.68 (e), 136.10 (e), 134.23 (o), 131.49 (o), 129.66 (o), 127.7 (o), 125.56 (o), 120.01 (e), 80.35 (e), 76.30 (e), 58.02 (e), 56.82 (e), 52.95 (o), 42.92 (e), 36.67 (e), 36.31 (e), 22.99 (e), 21.65 (o).

IR (Neat): 3540 (w), 2955 (w), 1733 (s), 1217 (m), 1239 (s), 904 (m), 657 (m) cm^{-1}.

HRMS ($M+Na^+$): calcd for $C_{23}H_{29}NO_7{}^{23}NaS$ 486.1562 found 486.1563.

(*Z*)-N-(4-(Allyloxy)but-2-ynyl)-4-methyl-N-(4-oxobut-2-enyl) benzenesulfonamide



2.50a

cis-Aldehyde **2.50a** (165 mg, 0.47 mmol, 75 % yield) was prepared by general procedure **ii** from **2.47** (221 mg, 0.63 mmol) and was isolated as a colourless oil.

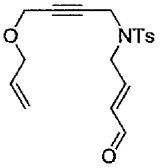
^{1}H NMR (500 MHz, $CDCl_3$): δ 10.0 (d, J = 6.5 Hz, 1H), 7.74 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.3 Hz, 2H), 6.52 (dt, J = 11.3, 7.0 Hz, 1H), 6.17-6.13 (m, 1H), 5.86-5.78 (m, 1H), 5.26-5.19 (m, 2H), 4.35 (dd, J = 7.0, 1.9 Hz, 2H), 4.17 (t, J = 1.6 Hz, 2H), 3.90 (t, J = 1.9 Hz, 2H), 3.84 (dt, J = 5.7, 1.2 Hz, 2H), 2.43 (s, 3H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 189.88 (o), 145.13 (o), 144.13 (e), 135.32 (e), 133.73 (o), 131.81 (o), 129.79 (o), 127.79 (o), 117.89 (e), 82.55 (e), 78.41 (e), 70.58 (e), 56.97 (e), 44.08 (e), 37.48 (e), 21.60 (o).

IR (Neat): 2854 (w), 1682 (m), 1346 (m), 1160 (s), 1090 (m) cm^{-1}.

HRMS ($M+Na^+$): calcd for $C_{18}H_{21}NO_4S$ 370.1089 found 370.1068.

(*E*)-N-(4-(Allyloxy)but-2-ynyl)-4-methyl-N-(4-oxobut-2-enyl) benzenesulfonamide



2.50b

trans-Aldehyde **2.50b** (166 mg, 0.48 mmol, 88% yield) was prepared by general procedure **iii** from **2.47** (0.19 mg, 0.54 mmol) and was isolated as a colourless oil.

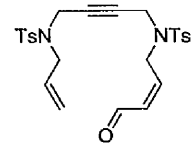
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.55 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.2 Hz, 2H), 6.73 (dt, J = 15.7, 5.6 Hz, 1H), 6.28-6.23 (m, 1H), 5.84-5.77 (m, 1H), 5.24-5.18 (m, 2H), 4.13 (t, J = 1.7 Hz, 2H), 4.07 (dd, J = 5.6, 1.3 Hz, 2H), 3.39 (t, J = 1.9 Hz, 2H), 3.83 (dt, J = 5.7, 1.3 Hz, 2H), 2.41 (s, 3H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 192.80 (o), 150.27 (o), 144.19 (e), 135.57 (e) 134.38 (o), 133.79 (o), 129.82 (o), 127.84 (o), 118.00 (e), 82.55 (e), 78.48 (e), 70.69 (e), 57.09 (e), 47.74 (e), 37.58 (e), 21.66 (o).

IR (Neat): 2923.29 (w), 1669 (s), 1346 (m), 659 (s) cm^{-1}.

HRMS ($M+Na^+$): calcd for $C_{18}H_{21}NO_4S$ 370.1089 found 370.1049.

(*Z*)-N-Allyl-4-methyl-N-(4-(4-methyl-N-(4-oxobut-2-enyl)phenylsulfonamido) but-2-ynyl)benzenesulfonamide



2.51a

cis-Aldehyde **2.51a** (154 mg, 0.31 mmol, 67% yield) was prepared by general procedure **ii** from **2.48** (230 mg, 0.458 mmol) and was isolated as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.86 (d, J = 6.3 Hz, 1H), 7.66-7.64 (m, 4H), 7.33-7.32 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 6.39 (dt, J = 13.9, 7.0 Hz, 1H), 6.13-6.09 (m, 1H), 5.59 (ddt, J = 23.3, 10.1, 6.4 Hz), 5.18-5.08 (m, 2H), 4.19 (d, J = 7.0 Hz, 2H), 3.89 (s, 2H), 3.83 (s, 2H), 3.61 (d, J = 6.4 Hz, 2H), 2.44 (s, 3H), 2.42 (s, 3H).

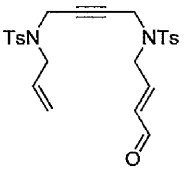
^{13}C NMR (125.8 MHz, $CDCl_3$): δ 189.94 (e), 145.18 (e), 144.45 (o), 143.75 (o), 136.16 (o), 135.45 (o), 131.93 (e), 131.57 (e), 139.99 (e), 129.73 (e), 127.79 (e),

127.76 (e), 119.96 (o), 79.60 (o), 77.83 (o), 49.31 (o), 44.26 (o), 37.34 (o), 35.83 (o), 21.74 (e), 21.69 (e).

IR (Neat): 3536 (w), 2924 (w), 1343 (m) 904 (m), 727 (s), 660 (s) cm^{-1}.

HRMS ($M+Na^+$): calcd for $C_{25}H_{28}N_2O_5S_2$ 523.1337 found 523.1361.

(*E*)-N-Allyl-4-methyl-N-(4-(4-methyl-N-(4-oxobut-2-enyl)phenylsulfonamido) but-2-ynyl)benzenesulfonamide



2.51b

trans-Aldehyde **2.51b** (550 mg, 1.10 mmol, 69 % yield) was prepared by general procedure **iii** from **2.48** (800 mg, 1.57 mmol) and was isolated as a colourless oil.

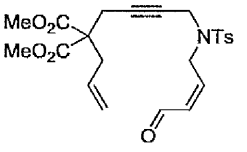
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.54 (d, J = 7.7 Hz, 1H), 7.67-7.64 (m, 4H), 7.32 (d, J = 8.1 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 6.64 (dt, J = 15.8, 5.7 Hz, 1H), 6.17-6.12 (m, 1H), 5.60 (ddt, J = 23.5, 10.1, 6.4 Hz, 1H), 5.18-5.08 (m, 2H), 3.91 (dd, J = 5.7, 1.3 Hz, 2H), 3.89 (s, 2H), 3.85 (s, 2H), 3.62 (d, J = 6.4 Hz, 2H), 2.44 (s, 3H), 2.42 (s, 3H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 192.98 (o), 144.45 (e), 143.94 (e), 136.23 (e), 131.94 (e), 129.95 (o), 129.72 (o), 127.76 (o), 127.75 (o), 119.90 (e), 79.62 (e), 77.74 (e), 49.29 (e), 47.57 (e), 37.22 (e), 35.86 (e), 21.73 (o), 21.69 (o).

IR (Neat): 2934 (w), 1690 (m), 1346 (m), 1156 (s), 1091 (m), 669 (m) cm^{-1}.

HRMS ($M+Na^+$): calcd for $C_{25}H_{28}N_2O_5S_2$ 539.1077 found 539.1066.

(*Z*)-Dimethyl 2-allyl-2-(4-(4-methyl-N-(4-oxobut-2-enyl)phenylsulfonamido)but-2-ynyl)malonate



2.52a

cis-Aldehyde **2.52a** (155 mg, 0.34 mmol, 67% yield) was prepared by general procedure **ii** from **2.49** (232 mg, 0.5 mmol) and was isolated as a colourless oil.

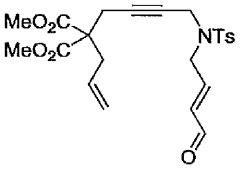
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.95 (d, J = 7.8 Hz, 1H), 7.71 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.2 Hz, 2H), 6.33 (dt, J = 11.3, 8.5 Hz, 1H), 6.06-6.02 (m, 1H), 5.69 (ddt, J = 23.5, 10.1, 6.5 Hz, 1H), 5.29-5.21 (m, 2H), 4.04 (s, 2H), 3.77 (d, J = 6.5 Hz, 2H), 3.72 (s, 6H), 3.13 (dd, J = 8.5, 1.3 Hz, 2H), 2.65 (t, J = 2.1 Hz, 2H), 2.4 (s, 3H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 190.27 (o), 169.46 (e), 144.49 (o), 143.62 (e), 136.43 (e) 136.43 (e), 133.44 (o), 132.16 (o), 129.67 (o), 127.83 (o), 120.00 (e), 79.40 (e), 53.27 (o), 36.10 (e), 30.65 (e), 23.50 (e).

IR (Neat): 2956 (w), 1736 (s), 1682 (m), 1161 (s), 664 (m) cm^{-1}.

HRMS (M+Na): calcd for $C_{23}H_{27}NO_7{}^{23}NaS$ 482.1404 found 484.1406.

(*E*)-N-Allyl-4-methyl-N-(4-(4-methyl-N-(4-oxobut-2-enyl)phenylsulfonamido) but-2-ynyl)benzenesulfonamide



2.52b

trans-Aldehyde **2.52b** (415 mg, 0.90 mmol, 72% yield) was prepared by general procedure **iii** from **2.49** (579 mg, 1.25 mmol) and was isolated as a colourless oil.

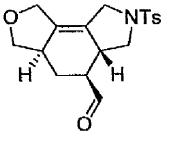
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.45 (d, J = 7.8 Hz, 1H), 7.71 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.2 Hz, 2H), 6.61 (app. quint., J = 7.7 Hz, 1H), 6.08 (dd, J = 15.6, 7.8 Hz, 1 H), 5.69 (ddt, J = 13.0, 10.0, 6.4 Hz, 1H), 5.30-5.22 (m, 2H), 4.05 (t, J = 2.1 Hz, 2H), 3.78 (d, J = 6.4 Hz, 2H), 3.78 (d, J = 6.5 Hz, 2H), 3.72 (s, 6H), 2.81 (dd, J = 7.6, 1.3, Hz, 2H), 2.63 (t, J = 2.1 Hz, 2H), 2.42 (s, 3H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 190.26 (o), 169.41 (e), 144.50 (o), 143.60 (e), 136.31 (e), 133.41 (o), 132.09 (o), 129.63 (2C, o), 127.78 (2C, o), 120.01 (e), 79.38 (e), 77.26 (e), 56.60 (e), 53.26 (2C, o), 49.05 (e), 36.04 (e), 30.57 (e), 23.43 (e), 21.65 (o).

IR (Neat): 2956 (w), 1735 (s), 1680 (s), 1598 (w), 1436 (m), 1348 (m), 1291 (m), 1207 (s), 1158 (s), 1092 (m), 898 (m), 731 (s), 662 (s) cm^{-1}.

HRMS ($M-H^-$): calcd for $C_{23}H_{27}NO_7{}^{23}NaS$ 482.1404 found 484.1406.

7-Tosyl-3,3a,4,5,5a,6,7,8-octahydro-1H-furo[3,4-e]isoindole-5-carbaldehyde



2.53a

Carbocycle **2.53a** (66.1 mg, 0.19 mmol, 75% yield) was prepared by general procedure **iv** from **2.50a** (87.1 mg, 0.25 mmol) and was isolated as a colourless oil.

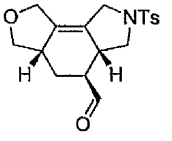
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.69 (s, 1H), 7.72 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 4.29 (d, J = 13.2 Hz, 1H), 4.16 (app. t, J = 7.5 Hz, 2 H), 4.01 (dd, J = 7.1, 5.6, 1H), 3.90 (d, A of AB, J_{AB} = 13.4 Hz, 1H), 3.67 (d, B or AB, J_{AB} = 13.4 Hz, 1H), 3.19 (dd, J = 10.9, 7.9 Hz, 1H), 2.71-2.63 (m, 3H), 2.44 (s, 3H), 2.36 (ddd, J = 12.6, 5.0, 2.5 Hz, 1H), 2.29-2.25 (ddd, J = 12.2, 9.6, 2.5 Hz, 1H), 1.57 (s, 1H), 1.17-1.10 (app q, J = 12.4 Hz, 1H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 201.69 (o), 144.02 (e), 134.10 (e), 133.02 (e), 130.14 (o), 127.79 (o), 125.67 (e), 73.24 (e), 67.41 (e), 52.85 (e), 50.78 (o), 48.49 (e), 41.65 (o), 39.94 (o), 24.70 (e), 21.85 (o).

IR (Neat): 2892 (m), 1721 (m), 1598 (w), 1341 (s), 1159 (s), 1092 (s), 1034 (s), 727 (s) cm^{-1}.

HRMS ($M+Na^+$): calcd for $C_{18}H_{21}NO_4S$ 370.1105 found 370.089.

7-Tosyl-3,3a,4,5,5a,6,7,8-octahydro-1H-furo[3,4-e]isoindole-5-carbaldehyde



2.53b

Carbocycle **2.53b** (65.2 mg, 0.19 mmol, 76%, *ds* = 4:1) was prepared by general procedure **iv 2.50b** (87.3 mg, 0.25 mmol) and was isolated as a colourless oil.

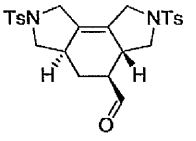
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.65 (s, 1H), 7.71 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 4.23 (dheptet, A of ABX, J_{AB} = 12.2, J_{AX} = 1.7 Hz, 1H), 4.14 (t, J = 8.2 Hz, 1H), 3.87-3.82 (m, 2H), 3.68 (d, B of AB, J_{AB} = 12.2 Hz, 1H), 3.13 (dd, J = 9.8, 8.3 Hz, 1H), 2.86-2.85 (m, 1H), 2.70-2.64 (m, 1H), 2.48-2.47 (m, 1H), 2.47 (s, 3H), 2.35 (q, J = 6.1 Hz, 1H), 2.10 (dt, J = 13.6, 6.5 Hz, 1H), 1.40-1.35 (m, 1H), 1.26 (t, J = 6.8 Hz, 1H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 201.81 (o), 143.92 (e), 134.10 (e), 132.75 (e), 129.89 (o), 127.53 (o), 127.49 (e), 72.83 (e), 68.31 (e), 52.23 (e), 48.96 (e), 48.51 (o), 36.66 (o), 35.92 (o), 22.86 (e), 21.67 (o).

IR (Neat): 2927 (w), 2853 (w), 1720 (m), 1340 (s), 1158 (s), 663 (s) cm^{-1}.

HRMS ($M+Na^+$): calcd for $C_{18}H_{21}NO_4S$ 370.1089 found 370.1105.

2,7-Bis-tosyl-1,2,3,3a,4,5,5a,6,7,8-decahydropyrrolo[3,4-e]isoindole-4-carbaldehyde



2.54a

Carbocycle **2.54a** (0.091 g, 0.18 mmol, 73%) was prepared according to the general procedure **iv 2.51a** (125 mg, 0.25 mmol) and was isolated as a colourless oil.

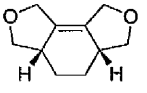
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.63 (s, 1H), 7.70-7.68 (m, 4H), 7.33 (d, J = 8.0 Hz, 4H), 3.97 (dd, J = 7.9, 6.6 Hz, 1H), 3.89 (d, A of AB, J = 13.6 Hz, 1H) , 3.81 (m, 2H), 3.56 (d, A of AB, J = 13.9 Hz, 1H), 3.54 (d, A of AB, J = 13.9 Hz, 1H), 2.56 (m, 4H), 2.44 (s, 6H), 2.30 (ddd, J = 12.8, 5.0, 2.3 Hz, 1H), 2.19 (t, J = 11.0 Hz, 1H), 1.05 (app. q, J = 12.0 Hz, 1H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 200.94 (o), 143.99 (e), 143.95 (e), 133.54 (e), 129.98 (o), 129.24 (e), 128.00 (e), 127.60 (o), 53.42 (e), 52.54 (e), 50.10 (o), 48.42 (e), 48.18 (e), 40.18 (o), 39.48 (o) 29.78 (e), 25.30 (e), 21.66 (o).

IR (Neat): 2927 (w), 2857 (w), 1719 (s), 1340 (s), 1092 (s), 672 (s).

HRMS ($M+Na^+$): calcd for $C_{25}H_{28}N_2O_5{}^{23}NaS$ 523.1337 found 523.1328.

3,3a,4,5,5a,6,7,8-Octahydro-1H-furo[3,4-*e*]isobenzofuran[23]



2.66

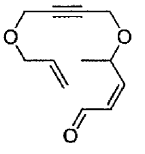
$[Rh(COD)Cl]_2$ (25.0 mg, 0. 05 mmol) and dppp (49.0 mg, 0.12 mmol) were weighed under nitrogen funnel and added to a flame dried flask, backfilled with N2. The flask was carefully backfilled with Ar (3 x). Dueterated benzene (2 mL) was

added and the resultant solution heated to 60 °C (using a preheated oil bath) and stirred for 15-20 min (the solution becomes homogeneous). Dienyne **2.34a** (19.0 mg, 0.1 mmol) was added to the reaction at 60 °C *via* tared microsyringe. The reaction was stirred for 30 min at 60 °C before being directly filtered through a cotton wool plug and washed with Dueterated benzene (1 mL) to provide the corresponding tricycle **2.66** as a crude mixture.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.16-4.28 (m, 4H), 4.17 (t, J = 8.0 Hz, 2H), 3.21 (dd, J = 10.0, 8.0 Hz, 2H), 2.57 (br s, 2H), 1.78-1.86 (m, 2H) 1.20-1.29 (m, 2H).

IR (Neat): 2926 (w), 2854 (w), 1725 (w), 10378 (s).

(*Z*)-4-(4-(allyloxy)but-2-ynyloxy)pent-2-enal



2.67a

cis-Aldehyde **2.67a** (37.4 mg, 0.18 mmol, 71 % yield) was prepared by general procedure **ii** from **2.120** (52.7 mg, 0.21 mmol) and was isolated as a colourless oil.

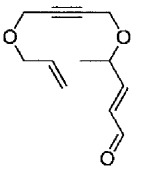
^{1}H NMR (500 MHz, $CDCl_3$): δ 10.12 (d, J = 7.5 Hz, 1H), 6.42 (dd, J = 11.4, 8.9 Hz, 1H), 6.04 (dd, J = 11.4, 7.5, 1H), 5.89 (dd, J = 16.1, 10.9, 5.7 Hz, 1H), 5.31-5.20 (m, 2H), 5.06 (dt, J = 14.6, 6.5 Hz, 1H), 4.25 (dt, J = 15.7, 1.6 Hz, 1H), 4,17 (d, J = 1.6 Hz, 2H), 4.14 (dt, J = 15.7, 1.5 Hz, 1H), 4.03 (d, J = 5.7 Hz, 2H), 1.37 (d, J = 6.5 Hz, 3H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 190.66 (o), 151.67 (o), 133.85 (o), 130.76 (o), 117.94 (e), 82.90 (e), 81.74 (e), 70.75 (e), 69.49 (o), 57.33 (e), 56.20 (e), 21.16 (o).

IR (Neat): 2980 (w), 2854 (w), 1681 (m), 1069 (vs), 1041 (vs).

HRMS ($M+NH_4^+$): calcd for $C_{12}H_{20}O_3N$ 226.1438 found 226.1441.

(*E*)-4-(4-(allyloxy)but-2-ynyloxy)pent-2-enal



2.67b

trans-Aldehyde **2.67b** (224 mg, 1.08 mmol, 69% yield) was prepared by general procedure **ii** from **2.120** (328 mg, 1.56 mmol) and was isolated as a colourless oil.

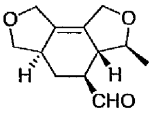
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.58 (d, J = 7.8 Hz, 1H), 6.71 (dd, J = 15.8, 5.9 Hz, 1H), 6.26 (ddd, J = 18.9, 7.8, 1.1 Hz, 1H), 5.93-5.96 (m, 1H), 5.32-5.20 (m, 2H), 4.39 (app. quint., J = 6.5 Hz, 1H), 4.26-4.14 (m, 4H), 4.04 (dt, J = 5.8, 1.3 Hz, 2H), 1.35 (d, J = 6.5 Hz, 3H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 193.44 (e), 156.94 (e), 133.96 (e), 132.04 (e), 118.04 (e), 82.81 (o), 81.93 (o), 7345 (e), 70.75 (o), 57.46 (e), 56.59 (e), 20.30 (o).

IR (Neat): 2976 (w), 2859 (w), 2239 (w), 1719 (m), 1612 (w), 1116 (o), 1064 (vs) cm^{-1}.

HRMS ($M+NH_4^+$): calcd for $C_{12}H_{20}O_3N$ 226.1438 found 226.1437.

(3*S*,3a*R*,4*S*,5a*R*)-3-methyl-1,3,3a,4,5,5a,6,8-octahydroisobenzofuro[5,4-c]furan-4-carbaldehyde



2.69a

Carbocycle **2.69a** (10.4 g, 0.13 mmol, 45%) was prepared according to the general procedure **iv** **2.67a** (23.1 mg, 0.25 mmol) and was isolated as a colourless oil.

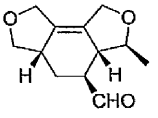
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.76 (d, *J* = 3.1 Hz, 1H), 4.44-4.41 (m, 1H), 4.22-4.16 (m, 2H), 3.51 (dq, *J* = 10.0, 6.0 Hz, 1H), 3.22 (dd, *J* = 11.1, 7.8 Hz, 1H), 2.74-2.72 (m, 1H), 2.52 (dt, *J* = 10.0, 1.4 Hz, 1H), 2.40-2.34 (m, 1H), 2.22 (ddd, *J* = 12.5, 5.3, 2.6 Hz, 1H), 1.31 (d, *J* = 6.0 Hz, 3H), 1.29-1.22 (m, 1H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 202.40 (o), 130.34 (e), 129.47 (e), 79.76 (o), 73.10 (e), 67.18 (e), 66.81 (e), 49.51 (o), 47.17 (o), 40.81 (o), 25.09 (e), 19.90 (o).

IR (Neat): 2932 (w), 2853 (m), 1719 (s), 1677 (w), 1024 (vs) cm^{-1}.

HRMS ($M+NH_4^+$): calcd for $C_{12}H_{20}O_3N$ 226.1438 found 226.1436.

(3*R*,3a*R*,4S,5a*R*)-3-methyl-1,3,3a,4,5,5a,6,8-octahydroisobenzofuro[5,4-c]furan-4-carbaldehyde



2.69b

Carbocycle **2.69b** (23.1 mg, 0.1 3mmol, 45% yield, *ds* = 6:1) was prepared according to the general procedure **iv** from **2.67b** (52.4 mg, 0.25 mmol) and was isolated as a colourless oil. major diastereoisomer:

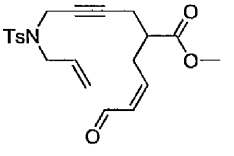
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.72 (d, J = 1.1 Hz, 1H), 4.40-4.37 (m, 1H), 4.26-4.18 (m, 4H), 3.51 (dq, J = 9.8, 6.0 Hz, 1H), 3.25 (t, J = 8.7 Hz , 1H), 2.52-2.50 (m, 2H), 2.45-2.42 (m, 1H), 2.38 (dt, J = 13.4, 5.1 Hz, 1H), 1.36 (d, J = 6.0, 3H), 1.31-1.27 (m, 1H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 202.17 (o), 131.59 (e), 129.83 (e), 79.17 (o), 73.13 (e), 67.99 (e), 67.49 (e), 47.10 (o), 43.57 (o), 36.62 (o), 24.15 (e), 19.10 (e).

IR (Neat): 2930 (w), 2848 (m), 1719 (s), 1029 (vs) cm^{-1}.

HRMS ($M+NH_4^+$): calcd for $C_{12}H_{20}O_3N$ 226.1438 found 226.1437.

(*Z*)-methyl2-(4-(N-allyl-4-methylphenylsulfonamido)but-2-ynyl)-6-oxohex-4-enoate



2.91a

cis-Aldehyde **2.91a** (56.8 mg, 0.14 mmol, 65% yield) was prepared by general procedure **ii** from **2.122** (37.2 mg, 0.092 mmol) and was isolated as a colourless oil.

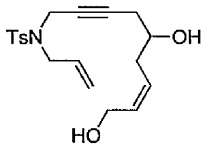
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.99 (d, J = 7.7 Hz, 1H), 7.72 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.3 Hz, 2H), 6.44 (dt, J = 11.2, 8.2 Hz, 1H), 6.03 (ddt, J = 11.2, 9.5, 1.8 Hz, 1H), 5.75-5.67 (m, 1H), 5.30-5.21 (m, 2H), 3.79 (d, J = 6.4 Hz, 2H), 3.67 (s, 3H), 2.91-2.85 (m, 1H), 2.79-2.73 (m, 1H), 2.56-2.51 (m, 1H), 2.42 (s, 3H), 2.38-2.33 (m, 2H), 2.29-2.22 (m, 2H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 190.42 (o), 172.95 (e), 147.35 (o), 143.46 (e), 136.29 (e), 134.82 (o), 131.97 (o), 129.48 (o), 127.71 (o), 119.81 (e), 81.71 (e), 75.56 (e), 52.20 (o), 49.07 (e), 43.44 (o), 36.13 (o), 28.85 (e), 21.56 (o), 20.80 (e).

IR (Neat): 2953 (w), 1733 (s), 1679 (m), 1346 (s), 1158 (vs) cm^{-1}.

HRMS ($M+Na^+$) calcd for $C_{21}H_{25}NO_5{}^{23}NaS$ 426.1351 found 426.1353.

(*Z*)-N-allyl-N-(5,9-dihydroxynon-7-en-2-ynyl)-4-methylbenzenesulfonamide



2.103

Diol **2.103** (138 mg, 0.4 mmol, 73 % yield) was prepared by general procedure **i** from **2.109** (252 mg, 0.5 mmol) and was isolated as a colourless oil.

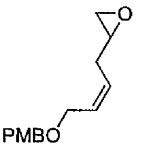
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 5.88 (dt, *J* = 13.9, 7.0 Hz, 1H), 5.57 (ddt, *J* = 16.8, 10.1, 6.4 Hz, 1H), 5.60-5.54 (m, 1H), 5.30-5.23 (m, 2H), 4.18 (dd, *J* = 12.3, 7.2 Hz, 1H), 4.11 (dd, *J* = 12.3, 6.8 Hz, 1H), 4.07 (s, 2H), 3.83 (d, *J* = 6.4 Hz, 2H), 3.61-3.56 (m, 1H), 2.56 (br s, 1H), 2.44 (s, 3H), 2.40 (br s, 1H), 2.31-2.22 (m, 2H), 2.20 (dd, *J* = 5.8, 2.3 Hz, 2H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 143.67 (e), 136.07 (e), 132.06 (o), 131.79 (o), 129.51 (o), 128.47 (o), 127.77 (o), 119.74 (e), 82.12 (e), 75.60 (e), 68.80 (o), 57.67 (e), 49.15 (e), 36.21 (e), 33.85 (e), 27.08 (e), 21.55 (o).

IR (Neat): 3361 (br, w), 2916 (w), 1597 (w), 1344 (s), 1157 (vs), 1092 (s).

HRMS ($M+Na^+$) calcd for $C_{19}H_{25}NO_4{}^{23}NaS$ 386.1402 found 386.1387.

(*Z*)-2-(4-(4-methoxybenzyloxy)but-2-enyl)oxirane



2.105

To a solution of $Ni(OAc)_2 \cdot 4H_2O$ (45.0 mg, 0.18 mmol) in ethanol (3 mL) at 0 °C was added sodium borohydride (6.55 mg, 0.17 mmol).[53] The reaction flask was stirred at room temperature for five min and ethylenediamine (0.02 mL, 0.34 mmol) was added and stirring was continued for five min more. A solution of **2.108** (0.20 g, 0.86 mmol) in ethanol (2 mL) was added and the atmosphere was exchanged from argon to hydrogen. After 1 h the reaction mixture was quenched by the addition of water and the layers separation. The aqueous layer was extracted with DCM (3 x 20 mL) and the combined extracts were dried and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (40% EtOAc in hexanes) on silica gel to afford **2.105** (113 mg, 0.48 mmol, 56 % yield) as a colorless oil.

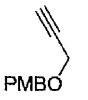
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (d, J = 8.3 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 5,78-5.73 (m, 1H), 5.65-5.60 (m, 1H), 4.45 (s, 2H), 4.04 (dd, J = 6.5, 0.6 Hz, 2H), 3.81 (s, 3H), 2.97-2.94 (m, 1H), 2.74 (t, J = 4.7 Hz, 1H), 2.49 (d, J = 4.7, 2.7 Hz, 1H), 2.41-2.29 (m, 2H),

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 145.87 (e), 130.30 (e), 129.42 (o), 129.23 (o), 126.97 (o), 113.81 (o), 71.94 (e), 65.31 (e), 55.29 (o), 51.33 (o), 46.52 (e), 30.46 (e).

IR (Neat): 2996 (w), 2838 (w), 1612 (m), 1512 (s), 1245 (vs), 1032 (s).

HRMS ($M+Na^+$) calcd for $C_{14}H_{18}O3N$ 252.1594 found 252.1590.

1-methoxy-4-((prop-2-ynyloxy)methyl)benzene[57]



2.106

A solution of (4-methoxyphenyl)methanol (9.00 mL, 71.7 mmol) in THF (350 mL) was added via cannula to a dry flask containing NaH (2.87 g, 71.7 mmol) at 0 °C. The resultant suspension was stirred for 30 min whilst warming to rt. The reaction mixture was recooled to 0 °C and a solution of 3-bromoprop-1-yne (7.95 mL, 71.7 mmol) in DMF (350 mL) was added via cannula. The resultant solution was stirred for 30 min, the heated to reflux. The reaction was allowed to reflux for a further 16 h. The reaction mixture was the quenched by the addition of NH_4Cl (350 mL). The layers were separated and the aqueous layer futher extracted with Et_2O (3 x 350 mL) and dried over $MgSO_4$. The crude oil was purified via flash chromatography (20 % EtOAc/hexanes) to afford the title compound **2.106** (10.7 g, 60.5 mmol, 84 % yield) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 8.5 Hz, 2H), 4.55 (d, J = 2.4 Hz, 2H), 4.14 (d, J = 2.4 Hz, 2H), 3.81 (s, 3H), 2.46 (t, J = 2.4 Hz, 1H).

IR (Neat): 2908 (w), 2838 (w), 2116 (w), 1612 (m), 1511 (s), 1073 (s), 1031 (s).

1-((hex-5-en-2-ynyloxy)methyl)-4-methoxybenzene[57]

2.107

To a solution of **2.106** (3.00 g, 17.0 mmol) in DMF (68 mL) was added 3-bromoprop-1-ene (1.47 mL, 17.0 mmol), K_2CO_3 (3.53 g, 25.5 mmol), tetrabutylammonium iodide (6.29 g, 17.0 mmol) and Copper(I) Iodide (3.24 g, 17.0 mmol) at rt. After stirring for 5 h, the reaction mixture was quenched with water. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude oil was purified via flash chromatography (20 % EtOAc/hexanes) to afford the title compound **2.107** (2.75 g, 12.7 mmol, 75 % yield) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 5.86 (m, 1H), 5.36 (dq, J = 17.0, 1.7 Hz, 1H), 5.16 (dq, J = 10.0, 1.7 Hz, 1H), 4.56 (s, 2H), 4.19 (t, J = 2.0 Hz, 2H), 3.83 (s, 3H), 3.11 (dt, J = 7.2, 2.0 Hz, 2H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 159.41 (e), 132.41 (o), 129.41 (e), 129.74 (o), 116.30 (e), 113.88 (o), 83.55 (e), 78.45 (e), 71.13 (e), 57.36 (e), 55.35 (o), 23.21 (e).

IR (Neat): 3003 (w), 2837 (w), 2280 (w), 1612 (w), 1512 (s), 1248 (vs), 1069 (s), 1034 (s).

HRMS ($M+NH_4^+$) calcd for $C_{14}H_{20}NO_2$ 234.1489 found 234.1489.

2-(4-(4-methoxybenzyloxy)but-2-ynyl)oxirane

2.108

Compound **2.107** (2.00 g, 9.25 mmol) was dissolved in DCM (90 mL) and cooled to 0 °C. To this stirred solution was added mCPBA (3.19 g, 9.25 mmol). After 10 min at the same temperature, the reaction was allowed to warm to 23 °C. After 14 h the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous Na_2SO_3 (10 mL). The reaction mixture was then vigorously stirred for an additional 15 min, and then diluted with hexanes (25 mL), and the layers were separated. The organic layer was then washed with saturated aqueous $NaHCO_3$ (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (1-5% EtOAc in hexanes) on silica gel to afford **2.108** (1.65 g, 7.1 mmol, 77%) as a colorless oil.

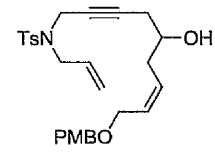
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 (d, J = 8.6 Hz, 2H), 6.91 (d, J = 8.6 Hz, 2H), 4.54 (s, 2H), 4.15 (t, J = 2.3 Hz, 2H), 3.83 (s, 3H), 3.17-3.14 (m, 1H), 2.83 (t, J = 4.7, 1H), 2.71 (dd, J = 4.7, 2.6 Hz, 1H), 2.70 (ddt, J = 17.4, 4.3, 2.3, 1H), 2.57 (ddt, J = 17.4, 4.7, 2.3 Hz, 1H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 159.46 (e), 129.90 (o), 129.59 (e), 113.92 (o), 81.12 (e), 78.52 (e), 71.32 (e), 57.31 (e), 55.41 (o), 49.99 (o), 46.58 (e), 22.70 (e).

IR (Neat): 2998 (w), 2838 (w), 1612 (m), 1512 (s), 1246 (vs), 1067 (s) cm^{-1}.

HRMS ($M+NH_4^+$) calcd for $C_{14}H_{20}NO_3$ 250.1438 found 250.1438.

(*Z*)-N-allyl-N-(5-hydroxy-9-(4-methoxybenzyloxy)non-7-en-2-ynyl)-4-methylbenzenesulfonamide



2.109

n-Butyllithium (1.6M, hexanes, 1.74 mL, 2.79 mmol) was added to the solution of N-allyl-4-methyl-N-(prop-2-ynyl)benzenesulfonamide (0.58 g, 2.33 mmol) in THF (6 mL) at -78°C.[55] The reaction was stirred for 15 min, then allowed to warm to rt and stirred for a further 70 min. The solution was re-cooled to -78°C and boron trifluoride diethyl etherate (0.324 mL, 2.56 mmol) was added. After 30 min of stirring a solution of epoxide **2.105** (0.44 g, 1.86 mmol) in THF (3 mL) was added via cannula. The solution mixture was stirred at rt overnight before quenching with saturated aqueous NaCl (10 mL) and extracted with ether (15 mL). The organic extracts were dried with $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (40% EtOAc in hexanes) on silica gel to afford **2.109** (0.67 g, 1.38 mmol, 73%) as a colorless oil.

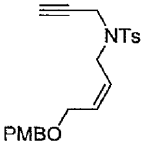
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.2 Hz, 2H), 6.88 (d, J = 8.2 Hz, 2H), 5.82-5.78 (m, 1H), 5.76-5.68 (m, 1H), 5.58 (dd, J = 18.0, 8.4 Hz, 1 H), 5.28-5.21 (m ,2H), 4.44 (s, 2H), 4.43 (br s, 1H), 4.06 (s, 2H), 3.98 (t, J = 5.6 Hz, 2H), 3.80 (s, 5H), 3.54-3.49 (m, 1H), 2.41 (s, 3H), 2.26 (d, J = 4.6 Hz, 1H), 2.18 (t, J = 6.9 Hz, 2H), 2.13 (d, J = 5.8 Hz, 2H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 159.29 (e), 143.54 (e), 136.14 (e), 132.15 (o), 130.01 (e), 129.53 (o), 129.46 (o), 129.39 (o), 129.14 (o), 127.80 (o), 119.71 (e), 113.84 (o), 82.32 (e), 75.22 (e), 72.34 (e), 69.12 (o), 65.13 (e), ,55.25 (o), 49.15 (o), 36.17 (e), 34.39 (e), 26.96 (e), 21.52 (o).

IR (Neat): 3436 (br, w), 2859 (w), 1612 (w), 1513 (m), 12146 (s), 1158 (vs), 1090 (s).

HRMS ($M+Na^+$) calcd for $C_{27}H_{33}NO_5{}^{23}NaS$ 506.1977 found 506.1975.

(*Z*)-N-(4-(4-Methoxybenzyloxy)but-2-enyl)-4-methyl-N-(prop-2ynyl) benzenesulfonamide



2.112

A solution of sulphonamide **2.44** (2.49 g, 9.18 mmol) in DMF (20 mL) was added *via* cannula to a dry flask containing NaH (0.37 g, 9.18 mmol) at 0 °C. The resultant suspension was stirred for 30 min whilst warming to rt. The reaction mixture was then recooled to 0 °C and a solution of bromide **2.43** (1.92 g, 9.18 mmol) in DMF (20 mL) was added *via* cannula and the resultant solution stirred at rt for 16 h. The reaction mixture was then quenched by the addition of H_2O (100 mL) and Et_2O (100 mL). The layers were separated and the aqueous layer further extracted with Et_2O (3 x 40 mL). The combined organic layers were washed with H_2O (3 x 100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification *via* FCC on silica gel (eluting with 30-40% EtOAc/hexanes gradient) provided the title compound **2.112** (3.59 g, 9.00 mmol, 98% yield) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.3 Hz, 2H), 7.23 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 5.84 (dt, J = 11.2, 6.2 Hz, 1H),

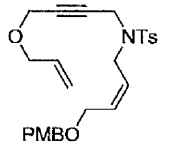
5.54-5.49 (m, 1H), 4.41 (s, 2H), 4.08-4.07 (m, 4H), 3.87 (d, J = 7.2 Hz, 2H), 3.79 (s, 3H), 2.43 (s, 3H), 2.38 (t, J = 2.4, 1H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 159.35 (e), 143.72 (e), 135.99 (e), 132.34 (o), 130.20 (e), 129.62 (o), 129.53 (o) 127.87 (o), 126.43 (o), 113.91 (o), 76.82 (e), 73.86 (e), 72.28 (e), 65.22 (e), 55.37 (o) 43.34 (e), 35.97 (e), 21.66 (o).

IR (Neat): 3703 (m), 2973 (s), 2923 (s), 1346 (m), 1164 (s), 1059 (s) cm^{-1}.

HRMS ($M+Na^+$): calcd for $C_{22}H_{25}NO_4S$ 422.1402 found 422.1421.

(*Z*)-N-(4-(Allyloxy)but-2-ynyl)-N-(4-(4-methoxybenzyloxy)but-2-enyl)-4-methylbenzenesulfonamide



2.113

A stirred solution of alcohol **2.45** (0.83 g, 1.92 mmol) in THF (6 mL) was added *via* cannula to a flask containing NaH (77.0 mg, 1.92 mmol) at 0 °C. The resulting suspension was stirred at 0 °C for 15 min before the sequential addition of DMF (6 mL), allyl bromide (0.17 mL, 1.92 mmol) and TBAI (0.071 g, 0.192 mmol). The reaction was then stirred for a further 15 min at 0 °C and rt for 16 h before being quenched by the addition of H_2O (20 mL). The layers were separated and the aqueous layer further extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification *via* FCC on silica gel (eluting with 30% EtOAc/hexanes) to afford the title compound **2.113** (0.63 g, 1.67 mmol, 87% yield) as a yellow oil

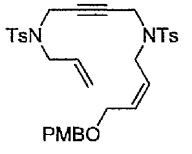
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.5 Hz, 2H), 7.24 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 5.86-5.77 (m, 2H), 5.55-5.50 (m, 1H), 5.45-5.18 (m, 2H), 4.41 (s, 2H), 4.12 (s, 2H), 4.07 (d, J = 6.4 Hz, 2H), 3.87-3.85 (m, 4H), 3.82 (d, J = 5.0 Hz, 2H), 3.80 (s, 3H), 2.42 (s, 3H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 159.38 (e), 143.63 (e), 136.11 (e), 133.94 (o), 132.29 (o), 130.25 (o), 129.85 (e), 129.61 (o), 129.48 (o), 127.93 (e), 126.48 (o), 117.84 (e), 113.94 (o), 81.71 (e), 79.22 (e), 72.28 (e), 70.56 (e), 57.16 (e), 55.34 (o), 43.53 (e), 36.38 (e), 21.67 (o).

IR (Neat): 2923 (m), 2845 (m), 1513 (m), 1346 (s), 1247 (m), 1161 (s) cm^{-1}.

HRMS ($M+Na^+$): calcd for $C_{26}H_{31}NO_5S$ 492.1821 found 492.1835.

(*Z*)-N-Allyl-N-(4-(N-(4-(4-methoxybenzyloxy)but-2-enyl)-4-methylphenylsulfonamido)but-2-ynyl)-4-methylbenzenesulfonamide



2.114

To a solution of alcohol **2.45** (0.92 g, 2.15 mmol), sulphonamide **2.46** (0.38 g, 1.79 mmol) and triphenylphosphine (0.56 g, 2.15 mmol) in THF (3.6 mL) at 0 °C, was added diisopropyl azodicarboxylate (0.43 mL, 2.15 mmol) dropwise. The resultant solution was stirred at rt for 7 h before being concentrated *in vacuo*. The resultant crude oil was purified by flash chromatography (30→50% EtOAc/hexanes gradient) to afford the title compound **2.114** (1.01 g, 2.00 mmol, 91% yield) as a colourless oil; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.64-7.60 (m, 4H), 7.29-7.26 (m, 4H), 7.23 (d, J = 8.5, 2H), 6.86 (d, J = 8.5 Hz, 2H), 5.79 (dt, J = 11.0, 5.9 Hz, 1H), 5.63-5.55 (m, 1H),

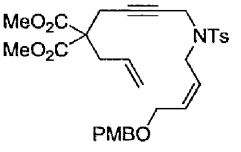
5.39 (dt, J = 11.9, 7.2 Hz, 1H), 5.15 (d, J = 10.1 Hz, 1H), 5.08 (d, J = 17.1, 1H), 4.40 (s, 2H), 3.99 (d, J = 6.3 Hz, 2H), 3.84 (s, 2H), 3.81 (s, 2H), 3.78 (s, 3H), 3.72 (d, J = 7.0 Hz, 2H), 3.60 (d, J = 6.3 Hz, 2H), 2.40 (s, 6H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 159.16 (e), 143.68 (e), 143.63 (e), 135.84 (e), 135.83 (e), 131.89 (o), 131.71 (o), 129.90 (e), 129.50 (o), 129.46 (o), 129.21 (o), 127.49 (o), 127.47 (o), 125.97 (o), 119.59 (e), 113.71 (o), 78.34 (e), 78.24 (e), 72.06 (e), 65.00 (e), 55.14 (o), 48.92 (e), 43.27 (e), 35.88 (e), 35.67 (e), 21.41 (o).

IR (Neat): 2923 (w), 2256 (w), 1513 (m), 1345 (m), 727 (s) cm^{-1}.

HRMS (M+Na$^+$): calcd for $C_{33}H_{38}N_2O_6S_2$ 645.2069 found 645.2076.

(*Z*)-Dimethyl-2-allyl-2-(4-(N-(4-(4-methoxybenzyloxy)but-2-enyl)-4-methylphenylsulfonamido)but-2-ynyl)malonate



2.115

To a solution of triphenylphosphine (0.50 g, 1.83 mmol) in DCM (8 mL) at –78 °C was added N-bromosuccinimide (0.33 g, 1.83 mmol) in one portion. The resultant solution was stirred at -78 °C for 15 min before the addition of alcohol **2.45** (0.60 g, 1.41 mmol) in DCM (2 mL) *via* cannula. The resultant solution was then stirred at –78 °C for a further 2.5 h. The reaction mixture was then quenched by the addition of $NaHCO_3$ solution (10 mL). The layers were separated and the aqueous layer further extracted with DCM (3 x 10 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. Purification *via* FCC on silica gel (eluting with 30% EtOAc/hexanes) provided the bromide which was used directly in the next reaction.

To a dry flask containing sodium hydride (34.0 mg, 0.86 mmol, 60% dispersion in mineral oil), was added dimethyl allylmalonate (14 μL, 0.86 mmol) in DMF (2 mL) at 0 °C. The resultant suspension was stirred at 0 °C for 15 min and rt for 30 min. The reaction mixture was then cooled to 0 °C and the bromide (352 mg, 0.71 mmol) then added in DMF (2 mL) *via* cannula and the resultant solution stirred at rt for 16 h. The reaction mixture was then quenched by the addition of H_2O (5 mL) and Et_2O (5 mL). The layers were separated and the aqueous layer further extracted with Et_2O (3 x 5 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. Purification *via* FCC on silica gel (eluting with 30% EtOAc/hexanes) provided the title compound **2.115** (0.81g, 1.07 mmol, 76%) as a yellow oil.

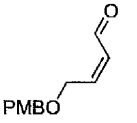
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, J = 8.3 Hz, 2H), 7.28 (d, J = 8.3 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 6.88-6.86 (m, 2H), 5.82 (dt, J = 11.2, 6.3 Hz, 1H), 5.53-5.43 (m, 2H), 5.07 (dd, J = 10.1, 1.7 Hz, 1H), 5.02 (dd, J = 16.9, 1.6 Hz, 1H), 4.43 (s, 2H), 4.09 (dd, J = 6.4, 1.1 Hz, 2H), 4.05 (t, J = 1.9 Hz, 2H), 3.82 (d, J = 7.2 Hz, 2H), 3.80 (s, 3H), 3.68 (s, 6H), 2.56-2.55 (m, 4H), 2.42 (s, 3H).

^{13}C NMR (125.8 MHz, $CDCl_3$): 169.94 (e), 159.21 (e), 143.50 (e), 136.15 (e), 132.03 (o), 131.58 (o), 130.13 (e), 129.57 (o), 129.38 (o), 119.79 (e), 113.77 (o), 80.20 (e), 76.22 (e), 65.17 (e), 65.11 (e), 56.66 (e), 55.23 (o) 52.74 (o), 43.15 (e), 36.53 (e), 36.24 (e), 29.67 9e), 22.83 9e), 21.52 (o).

IR (Neat): 2956 (w), 1735 (s), 1239 (s), 1043 (s), 731 (m) cm^{-1}.

HRMS ($M+Na^+$): calcd for $C_{31}H_{37}NO_8{}^{23}NaS$ 606.2138 found 606.2145.

(*Z*)-4-(4-methoxybenzyloxy)but-2-enal



2.116

To a solution of DMSO (3.99 mL, 56.2 mmol) in DCM (125 mL) at -78 °C was added oxalyl chloride (2.46 mL, 28.1 mmol) dropwise and the mixture was stirred for 15 minutes. At the same temperature, a solution of (*Z*)-4-(4-methoxybenzyloxy)but-2-en-1-ol (3.90 g, 18.7 mmol) in DCM (63 mL) was added and the resultant solution was stirred for 1 hat which point triethylamine (10.4 mL, 74.9 mmol) was added. The reaction was stirred for 2 hours whilst warming to -50 °C. The reaction was quenched with saturated ammonium chloride solution (50 mL) and the layers were separated. The aqueous phase was extracted with DCM (2x, 100 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. Purification *via* FCC on silica gel (eluting with 10% EtOAc/hexanes) provided the title compound **2.116** (2.28 g, 11.0 mmol, 59%) as a colourless oil.

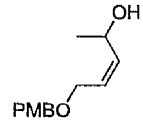
^{1}H NMR (500 MHz, $CDCl_3$): δ 10.05 (d, J = 6.8 Hz, 1H), 7.27 (d, J = 8.2 Hz, 2H), 6.89 (d, J = 8.2 Hz, 2H), 6.63 (app hex, J = 5.7 Hz, 1H), 6.07-6.03 (m, 1H), 4.52 (s, 2H), 4.49 (dd, J = 5.6, 1.9 Hz, 2H), 3.81 (s, 3H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 191.59 (e), 159.61 (o), 147.81 (e), 129.94 (e), 129.86 (e), 129.51 (o), 114.09 (e), 72.86 (o), 66.70 (o), 55.41 (o).

IR (Neat): 2955 (w), 1686 (m), 1472 (w), 1255 (m), 1093 (s), 776 (vs).

HRMS ($M+NH_4^+$): calcd for $C_{12}H_{14}O_3$ 224.1285 found 224.1281.

(*Z*)-5-(4-methoxybenzyloxy)pent-3-en-2-ol



2.117

Methylmagnesium bromide (10.2 mL, 30.5 mmol) was added dropwise to a solution of **2.116** (4.20 g, 20.4 mmol) in Et_2O (30 mL) at -78 °C. Reaction was stirred for 1h at -78 and warmed to -40 °C. The reaction was quenched with NH_4Cl solution (30 mL) and the aqueous layer extract with Et_2O (30 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. Purification *via* FCC on silica gel (eluting with 50% EtOAc/hexanes) provided alcohol **2.117** (2.43 g, 10.9 mmol, 54%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.5Hz, 2H), 5.65-5.64 (m, 2H), 4.61-4.55 (m, 1H), 4.46 (s, 2H), 4.14-4.11 (m, 1H), 4.05-4.03 (m, 1H), 3.81 (s, 3H), 1.90 (d, J = 3.4 Hz, 1H), 1.25 (d, J = 6.4 Hz, 3H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 146.80 (e), 137.62 (o), 129.48 (o), 127.09 (o), 125.08 (e), 113.87 (o), 72.19 (e), 65.45 (e), 63.99 (o), 55.29 (o), 23.32 (o).

IR (Neat): 3362 (br, w), 2956 (w), 1463 (w), 1254 (m), 1081 (s), 774 (vs).

HRMS ($M+NH_4^+$): calcd for $C_{13}H_{22}O_3N$ 240.1600 found 240.1594.

4-(allyloxy)but-2-yn-1-ol[55]

2.118

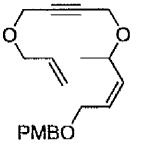
A solution of butyne-1,4-diol (9.50 g, 110 mmol) in THF (150 mL) was added *via* cannula to a dry flask containing NaH (4.41 g, 110 mmol, 60% suspension in mineral

oil) at 0 °C. The resultant suspension was stirred for 30 min whilst warming to rt. The reaction mixture was recooled to 0 °C and a solution of allyl bromide (7.20 mL, 83.0 mmol) in THF (50 mL) was added *via* cannula, followed by TBAI (4.08 g, 11.0 mmol) in one portion. The resultant solution was stirred for 30 min and then heated to reflux for 10 h. The reaction mixture was cooled to rt before quenching by the addition of NH_4Cl (100 mL) and Et_2O (100 mL). The layers were separated and the aqueous layer further extracted with Et_2O (3 x 100 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. Purification *via* FCC on silica gel (eluting with 20→50 % EtOAc/hexanes) provided alcohol **2.118** (6.63 g, 52.6 mmol, 63%) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.93-5.85 (m, 1H), 5.30 (d, J = 17.3 Hz, 1H), 5.21 (d, J = 10.4 Hz, 1H), 4.31 (d, J = 5.7 Hz, 2H), 4.18 (s, 2H), 4.05 (d, J = 5.7 Hz, 2H).

IR (Neat): 3384 (w), 2858 (w), 1647 (w), 1350 (w), 1121 (vs), 1065 (vs).

(*Z*)-1-((4-(4-(allyloxy)but-2-ynyloxy)pent-2-enyloxy)methyl)-4-methoxybenzene



2.119

To a solution of triphenylphoshine (3.94 g, 15.0 mmol) in DCM (75 mL) at -78 °C was added NBS (2.67 g, 15.0 mmol) in one portion and for 15 min. A solution of alcohol **2.117** in DCM (75 mL) was then added *via* cannula and stirred at -78 °C for 1 h, then warmed to -40 °C for 1 h. The reaction mixture was quenched by the addition of $NaHCO_3$ solution (250 mL). The layers were separated and the aqueous layer further extracted with DCM (100 mL x 2). The combined organics were dried

($MgSO_4$) and concentrated *in vacuo*. The resultant crude oil was purified by flash chromatography (25% EtOAc/hexanes) and disolved in THF (20 mL) (Solution A).

A solution of **2.118** (2.27 g, 26.4 mmol) in THF (70 ml) was added *via* cannula to a dry flask containing NaH (1.06 g, 26.4 mmol, 60% suspension in mineral oil) at 0 °C. The resultant suspension was stirred for 30 min whilst warming to rt. The reaction mixture was recooled to 0 °C and Solution A was then added *via* cannula, followed by TBAI (488 mg, 1.32 mmol) in one portion. The resultant solution was stirred for 30 min and then heated to reflux. The reaction was allowed to reflux for a further 16 h. The reaction mixture was then quenched by the addition of NH_4Cl (100 mL) and Et_2O (100 mL). The layers were separated and the aqueous layer further extracted with Et_2O (2 x 75 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. The crude oil was purified *via* flash chromatography (20→50 % EtOAc/hexanes) to afford alcohol **2.119** (2.43 g, 8.79 mmol, 67%) as a yellow oil.

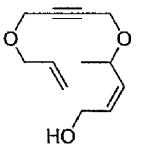
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 (d, J = 8.5 Hz, 2H), 6.91 (d, J = 8.5 Hz, 2H), 5.92 (ddt, J = 16.2, 11.0, 5.7 Hz, 1H), 5.80 (dt, J = 11.4, 6.1 Hz, 1H), 5.47 (dd, J = 11.4, 9.5 Hz, 1H), 5.34-5.22 (m, 2H), 4.48-4.47 (m, 2H), 4.23-4.16 (m, 2H), 4.20 (s, 2H), 4.13 (ddd, J = 14.7, 6.5, 1.3 Hz, 2H), 4.10-4.05 (m, 2H), 4.03 (d, J = 5.6 Hz, 1H), 3.83 (s, 3H), 1.26 (d, J = 6.3 Hz, 3H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 140.24 (e), 133.97 (o), 130.23 (e), 129.68 (o), 129.33 (o), 117.73 (e), 113.85 (o), 82.78 (e), 81.80 (e), 72.12 (e), 70.62 (e), 69.80 (o), 69.69 (o), 65.51 (e), 57.45 (e), 55.45 (e), 55.28 (o), 21.25 (o).

IR (Neat): 2853 (w), 1613 (w), 1513 (w), 1513 (s), 1246 (vs), 1067 (vs).

HRMS ($M+NH_4^+$): calcd for $C_{20}H_{26}O_4{}^{23}Na$ 353.1729 found 353.1743.

(*Z*)-4-(4-(allyloxy)but-2-ynyloxy)pent-2-en-1-ol



2.120

Alcohol **2.120** (248 mg, 0.75 mmol, 74 % yield) was prepared by general procedure **ii** from **2.119**(117 mg, 0.56 mmol) and was isolated as a colourless oil.

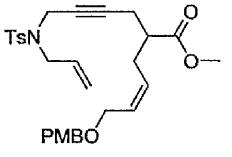
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.90 (ddt, J = 17.2, 10.5, 5.7 Hz, 1H), 5.82-5.77 (m, 1H), 5.40 (ddt, J = 10.6, 9.2, 1.6 Hz, 1H), 5.33-5.22 (m, 2H), 4.52 (ddt, J = 9.1, 6.4, 0.9 Hz, 1H), 4.36 (ddd, J = 11.9, 7.3, 4.0 Hz, 1H), 4.28 (t, J = 1.7 Hz, 1H), 4.20-4.14 (m, 3H), 4.12 (dt, J = 15.3, 1.2 Hz, 1H), 4.06 (dt, J = 5.7, 1.2 Hz, 2H), 1.25 (d, J = 6.3 Hz, 3H), 1.81 (t, J = 5.5 Hz, 1H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 133.85 (o), 133.06 (o), 131.94 (o), 118.02 (e), 82.63 (e), 82.13 (e), 70.82 (e), 69.30 (o), 58.50 (e), 57.48 (e), 55.35 (e), 21.28 (o).

IR (Neat): 3407 (br, w), 2855 (w), 1713 (w), 1351 (m), 1067 (vs), 1031 (s).

HRMS ($M+NH_4^+$): calcd for $C_{12}H_{22}O_3N$ 228.1594 found 228.1592.

(*Z*)-methyl 2-(4-(N-allyl-4-methylphenylsulfonamido)but-2-ynyl)-6-(4-methoxybenzyloxy)hex-4-enoate



2.121

A solution of (Z)-dimethyl 2-(4-(N-allyl-4-methylphenylsulfonamido)but-2-ynyl)-2-(4-(4-methoxybenzyloxy)but-2-enyl)malonate[33] (0.187 g, 0.320 mmol), NaCl (0.056 g, 0.961 mmol), Water (0.023 mL) in DMSO (0.462 mL) was heated to 160 °C

overnight. The reaction mixture was allowed to cool to rt and then worked up by adding water (2 mL) and extracting with EtOAc (4 x 2 mL). The combined organic extracts were washed with wate, brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification *via* FCC on silica gel (eluting with 30→50 % EtOAc/hexanes) provided the title compound **2.121** (0.120 g, 0.228 mmol, 71.3 % yield) as a colorless oil.

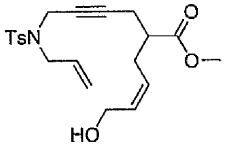
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.7 Hz, 2H), 6.91 (d, J = 8.7 Hz, 2H), 5.78-5.69 (m, 2H), 5.42 (dtt, J = 9.5, 7.6, 1.7 Hz, 1H), 5.31-5.23 (m, 2H), 4.45 (s, 2H), 4.06 (t, J = 2.0 Hz, 2H), 4.02 (ddd, J = 6.3, 3.7, 1.5 Hz, 2H), 3.83 (s, 3H), 3.80 (d, J = 5.9 Hz, 2H), 3.66 (s, 3H), 2.44 (s, 3H), 2.38 (m, 2H), 2.32 (app q, J = 7.1 Hz, 1H), 2.25 (q, J = 6.8 Hz, 2H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 82.81 (e), 74.36 (e), 72.05 (e), 65.34 (e), 55.28 (o), 51.86 (o), 48. 92 (e), 44.03 (o), 36.17 (e), 21.53 (o), 20.54 (e)

IR (Neat): 2952 (w), 2255 (w), 1736 (m), 1182 (vs).

HRMS ($M+Na^+$) calcd for $C_{29}H_{35}NO_6{}^{23}NaS$ 548.2083 found 548.2057.

(*Z*)-methyl 2-(4-(N-allyl-4-methylphenylsulfonamido)but-2-ynyl)-6-hydroxyhex-4-enoate



2.122

Alcohol **2.122** (69.2 mg, 0.17 mmol, 81%) was prepared by general procedure **ii** from **2.121** (111 mg, 0.21 mmol) and was isolated as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, J = 8.1 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 5.76-5.69 (m, 2H), 5.40-5.35 (m, 1H), 5.29-5.21 (m, 2H), 4.19 (dd, J = 12.6, 7.2 Hz,

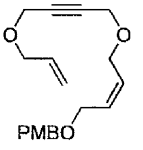
1H), 4.14-4.408 (m, 1H), 4.05 (s, 2H), 3.79 (d, J = 6.5 Hz, 2H), 3.66 (s, 3H), 2.43 (s, 3H), 2.41-2.36 (m, 2H), 2.31-2.17 (m, 3H), 2.04 (s, 1H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 173.29 (e), 147.38 (o), 143.49 (e), 136.31 (e), 132.09 (o), 132.00 (o), 129.50 (o), 127.82 (o), 229.83 (e), 81.73 (e), 72.78 (e), 52.22 (e), 49.09 (o), 43.47 (e), 36.15 (o), 33.66 (o), 28.87 (e), 21.59 (o), 20.83 (e).

IR (Neat): 3545 (br, w), 2955 (w), 1735 (s), 158 (w), 1206 (m), 1161 (vs).

HRMS ($M+Na^+$) calcd for $C_{21}H_{27}NO_5{}^{23}NaS$ 428.1508 found 428.1522.

(*Z*)-1-((4-(4-(allyloxy)but-2-ynyloxy)but-2-enyloxy)methyl)-4-methoxybenzene



2.123

To a solution of triphenylphoshine (2.52 g, 9.60 mmol) in DCM (48 mL) at -78 °C was added NBS (1.71 g, 9.60 mmol) in one portion and for 15 min. A solution of alcohol (*Z*)-4-(4-methoxybenzyloxy)but-2-en-1-ol (2.00 g, 9.20 mmol) in DCM (48 mL) was then added *via* cannula and stirred at -78 °C for 1 h, then warmed to -40 °C for 1 h. The reaction mixture was quenched by the addition of $NaHCO_3$ solution (100 mL). The layers were separated and the aqueous layer further extracted with DCM (100 mL x 2). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. The resultant crude oil was purified by flash chromatography (25% EtOAc/hexanes) and disolved in THF (20 mL) (Solution A).

A solution of **2.118** (0.877 g, 7.11 mmol) in THF (35 mL) was added *via* cannula to a dry flask containing NaH (0.28 g, 7.11 mmol, 60% suspension in mineral oil) at 0 °C. The resultant suspension was stirred for 30 min whilst warming

to rt. The reaction mixture was recooled to 0 °C and Solution A was then added *via* cannula, followed by TBAI (0.26 mg, 7.11 mmol) in one portion. The resultant solution was stirred for 30 min and then heated to reflux. The reaction was allowed to reflux for a further 16 h. The reaction mixture was then quenched by the addition of NH_4Cl (100 mL) and Et_2O (100 mL). The layers were separated and the aqueous layer further extracted with Et_2O (2 x 75 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. The crude oil was purified *via* flash chromatography (20→50 % EtOAc/hexanes) to afford alcohol **2.123** (1.44 g, 4.55 mmol, 64%) as a yellow oil.

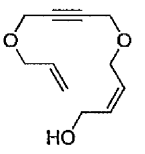
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 5.90 (ddt, J = 16.3, 10.4, 5.7 Hz, 1H), 5.82-5.78 (m, 1H), 5.74-5.69 (m, 1H), 5.31 (dq, J = 16.3, 1.2 Hz, 1H), 5.22 (dd, J = 10.4, 1.2 Hz, 1H), 4.44 (s, 2H), 4.19-4.18 (m, 4H), 4.12-4.10 (m, 2), 4.08 (d, J = 6.3 Hz, 2H), 4.05 (dt, J = 5.9, 1.3 Hz, 2H), 3.80 (s, 3H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 159.38 (e), 134.06 (o), 130.53 (o), 130.31 (e), 129.57 (o), 128.67 (o), 118.04 (e), 113.94 (o), 82.56 (e), 82.36 (e), 72.11 (e), 70.81 (e), 65.57 (e), 65.41 (e), 57.65 (e), 57.53 (e), 55.42 (o).

IR (Neat): 2853 (w), 1612 (m), 1513 (ws), 1246 (s), 1067 (vs), 928 (s).

HRMS ($M+NH_4^+$): calcd for $C_{19}H_{28}NO_4$ 334.2018 found 334.2022.

(*Z*)-4-(4-(allyloxy)but-2-ynyloxy)but-2-en-1-ol



2.124

Alcohol **2.124** (0.89 mg, 0.46 mmol, 60 % yield) was prepared by general procedure **ii** from **2.123** (150 mg, 0.76 mmol) and was isolated as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.88 (dtt, J = 17.2, 10.4, 5.8 Hz, 1H), 5.81 (ddt, J = 11.3, 6.6, 1.4 Hz, 1H), 5.65 (dtt, J = 11.4, 6.5, 1.4 Hz, 1H), 5.29 (dq, J = 17.2, 1.6 Hz, 1H), 5.20 (dq, J = 10.4, 1.4 Hz, 1H), 4.20-4.18 (m, 6H), 4.13 (d, J = 6.6 Hz, 2H), 4.04 (dt, J = 5.8, 1.3 Hz, 2H), 2.18 (br s, 1H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 133.94 (o), 133.19 (o), 127.45 (o), 118.06 (e), 82.72 (e), 82.16 (e), 70.81 (e), 65.07 (e), 58.65 (e), 57.59 (e), 57.47 (e).

IR (Neat): 3417 (br, w), 2854 (w), 1648 (w), 1350 (m), 1062 (vs), 929 (s).

HRMS ($M+H^+$): calcd for $C_{11}H_{17}O_3$ 197.1178 found 197.1179.

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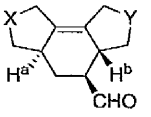
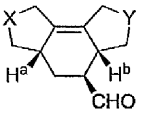
2.11 Appendix 1



2.35/2.53-2.55/2.61a



2.35/2.53-2.55/2.61b

Entry	X	Y		$H^a + H^b$
1	O	NTs	**2.53a**	2.71
2	"	"	**2.53b**	2.86 + 2.70
3	NTs	"	**2.54a**	2.56
4	"	"	**2.54b**	-
5	$C(CO_2Me)_2$	"	**2.55a**	-
6	"	"	**2.55b**	-
7	O	O	**2.35a**	2.81
8	"	"	**2.35b**	2.93 + 2.69
9	NTs	"	**2.61a**	2.67
10	"	"	**2.61b**	2.77 + 2.61

Chapter 3

Rhodium-Catalysed Silicon-Tethered [(4+2+2)] Cycloisomerisation Reaction and its Utilisation in the Synthesis of (+)-Epoxydictymene

3.1. Introduction

Over the last decade there has been increasing interest within our research group in working towards the application of new methodologies for target directed synthesis.[1-2] In order for the aforementioned methodology to be a viable synthetic route for the total synthesis of natural products the transformation must be tolerant of a vast number of moieties which occur in nature. One of the defining features of rhodium-catalysed [m+n+o] carbocyclisations is that they proceed under relatively mild reaction conditions. The ability of higher-order carbocyclisation reactions to construct structurally complex advanced intermediates in a single transformation makes this an expedient and efficient stratagem for the realisation of natural products. Finally, the application of methodology to natural product synthesis is also beneficial as it serves to highlight the areas of a transformation which require further development and investigation. In this way, Nature can inspire and direct the field of research, increasing the synthetic utility of the transformation.

The following chapter will describe our efforts toward the synthesis of (+)-epoxydictymene, a highly functionalised medium sized sesquiterpene (Figure 3.1).[3] Initial attention will focus on highlighting the previous syntheses of this intriguing natural product and delineating the historic development of the key transformation

identified within our retrosynthetic analysis. We will conclude by describing our progress towards the realisation of the natural product.

3.1.1. Natural Products Containing 5,8-Bicyclic Skeletons

To date, more than one hundred terpenoid natural products have been isolated containing a distinctive eight-membered ring fused to a smaller five- or six-membered ring.[4] This characteristic skeleton has long captivated synthetic chemists in part due to the intriguing conformation of this system,[5] and partly as a result of the challenges associated in successfully assembling these motifs.[4a] Figure 3.1 displays a selection of influential natural products containing 5,8- and 6,8- ring systems.[6]

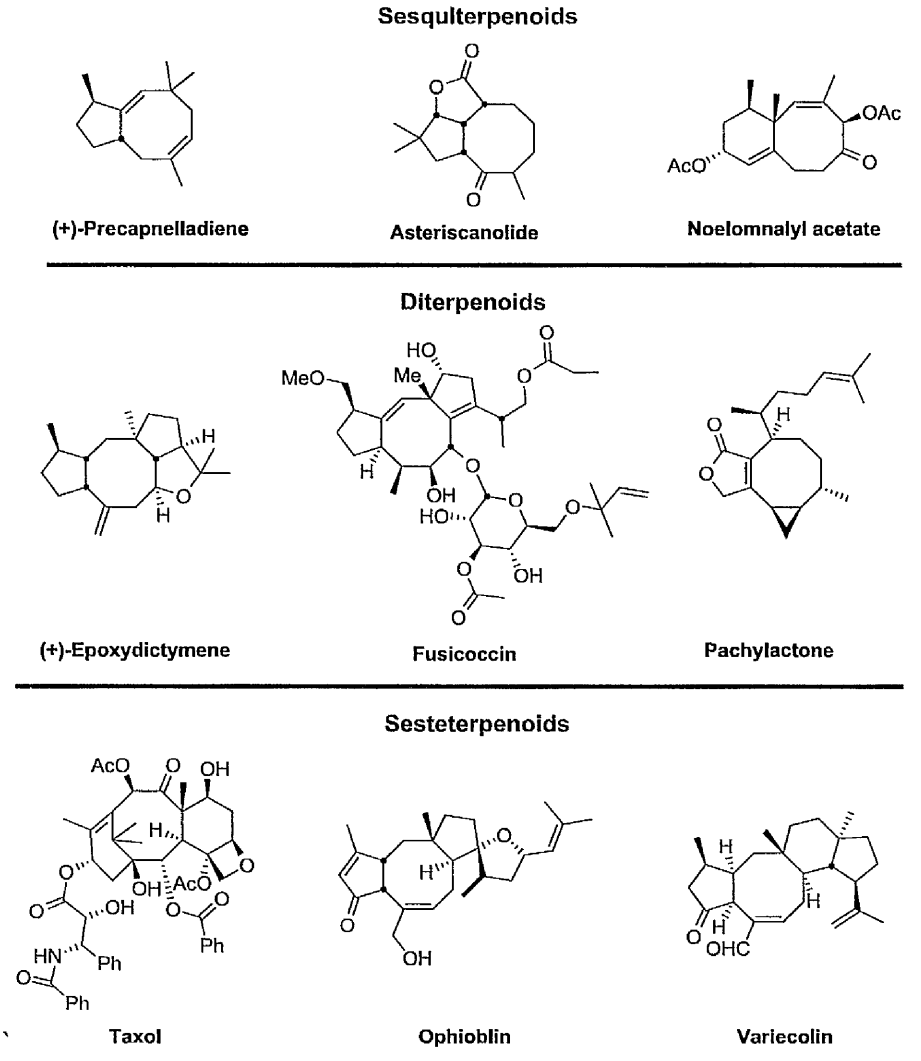


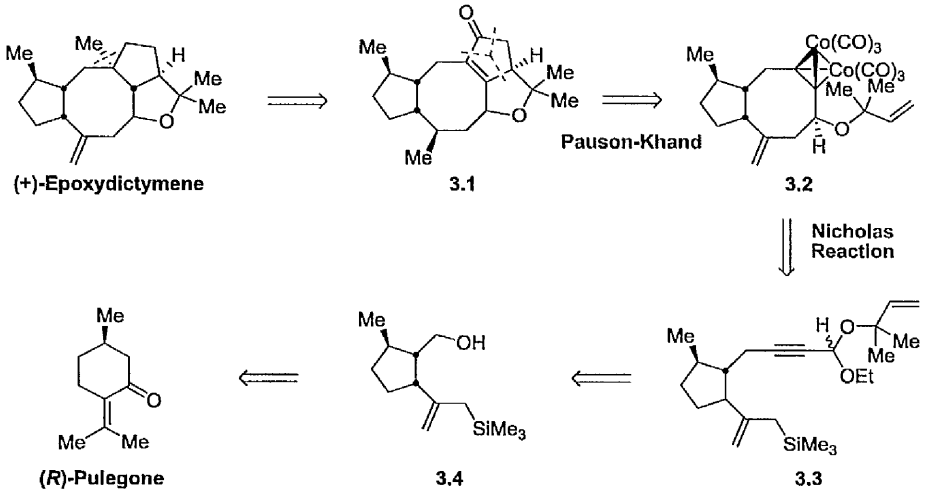
Figure 3.1 A selection of sesqulterpenoids, diterpenoids and sesteterpenoids natural products containing 5,8- and 6,8-bicyclic skeletons

(+)-Epoxydictymene represents the most structurally complex member of the fusicoccane family (figure 3.1).[3] It was isolated from the brown algae *Dictyota dichotoma* in 1983 by the Matsumoto research group. X-ray crystallography of a p-bromophenylurethane derivative of the natural product provided conclusive confirmation of the absolute configuration. Interesting features of the natural product include a tetracyclic framework containing a highly strained *trans*-5,5 ring system and a total of seven stereocenters, five of which are located on the central octane

ring, and one which is a quaternary centre. Two synthetic routes to (+)-epoxydictymene have been disclosed and the ensuing sections will describe the defining features in each of these syntheses.

3.1.2 Schreiber's Synthesis of (+)-Epoxydictymene

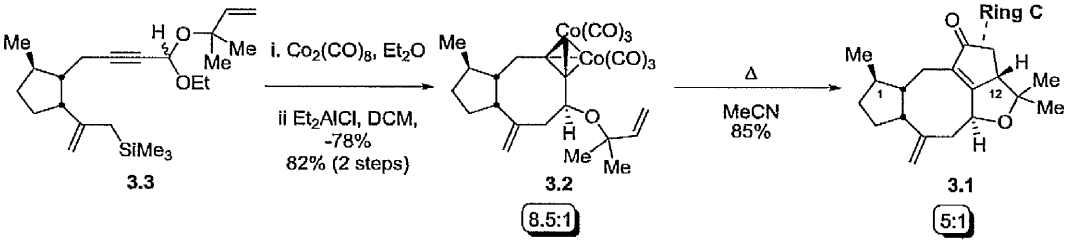
In 1994, the Schreiber group disclosed the first total synthesis of (+)-epoxydictymene, employing two sequential cobalt-catalysed transformations for the construction of the 5,8,5,5-tetracyclic core.[7] Schreiber's retrosynthetic analysis of (+)-epoxydictymene is outlined below (Scheme 3.1).



Scheme 3.1 Schreiber's retrosynthetic analysis of (+)-epoxydictymene

The principal transformations in the synthesis are a Lewis acid catalysed Nicholas reaction,[8] and a subsequent cobalt catalysed Pauson-Khand reaction.[9] Key intermediate **3.3** was prepared in 8 steps from commercially available (*R*)-pulegone. Treatment of dienyne **3.3** with the requisite dicobalt hexacarbonyl complex afforded organometallic **3.2** in 82% yield, as an 8.5:1 mixture of diastereoisomers. Subjecting

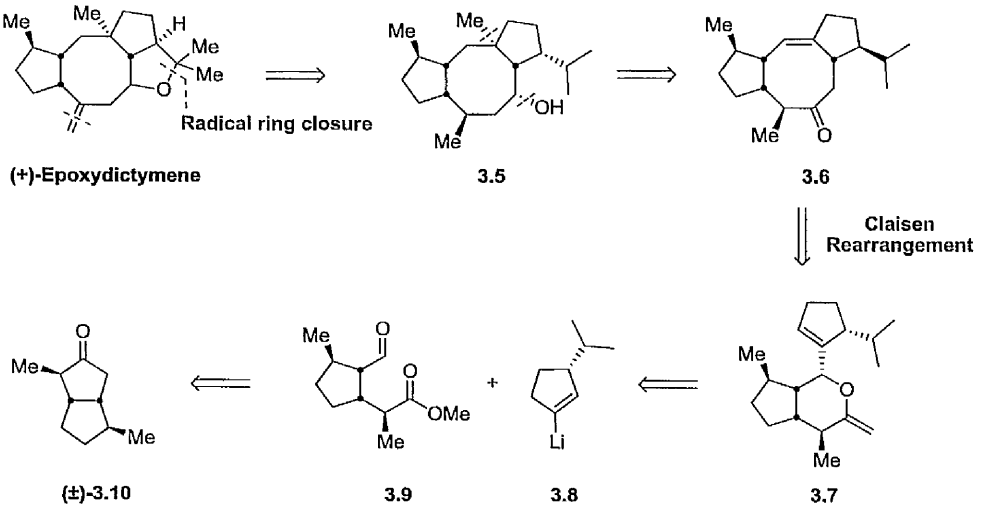
the organo-cobalt adduct to elevated temperatures in acetonitrile facilitated a subsequent Pauson-Khand reaction, providing intermediate **3.1** in 85% yield as a 5:1 mixture of diastereoisomers. Unfortunately, X-ray crystallography revealed that the major diastereoisomer contained the incorrect stereochemistry at the ring junction between the two five–membered rings (C^{12}). Consequently, the completion of the target molecule involved correction of the stereochemistry and installation of the methyl group at C^{1}. Disappointingly, achieving this goal required cleavage and reconstruction of the C ring in a stepwise and convoluted manor, adding several steps to the synthesis. The synthesis of (+)-epoxydictymene was complete in 23 longest linear steps and 4.4% overall yield.



Scheme 3.2 The key transformations of Schreibers' synthesis of (+)-epoxydictymene

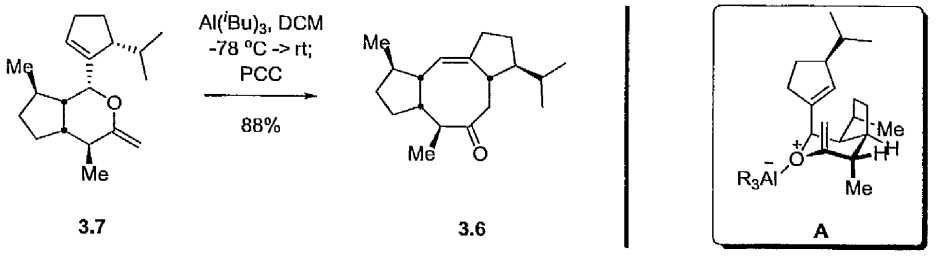
3.1.3 Paquette's Synthesis of (+)-Epoxydictymene

Paquette *et al.* reported the synthesis of (+)-epoxydictymene in 1997, followed by a full paper later the same year.[10] The two key features of this synthesis are a late stage radical cyclisation to construct the highly strained tetrahydrofuran ring and a Claisen rearrangement for the construction of the central octane ring.[11] Scheme 3.4 describes Paquette's retrosynthetic analysis of the molecule.



Scheme 3.3 Paquette's retrosynthetic analysis of (+)-epoxydictymene

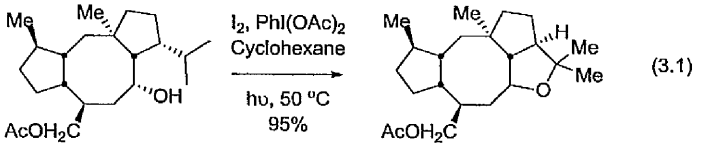
Lactone **3.7** was prepared in 5 steps from intermediate (±)-**3.10**, involving a resolution utilising Johnson's sulfoximine protocol. The immediate exposure of compound **3.7** to triisobutylaluminium resulted in a Claisen rearrangement. The resulting mixture of cyclooctenols was directly oxidized with PCC to provide the homogeneous ketone **3.6**. The authors postulated that the rearrangement proceeds through the chair-like transition-state **A** depicted in scheme 3.4.



Scheme 3.4 The Claisen rearrangement in Paquette's synthesis of (+)-epoxydictymene

The remaining critical feature of the synthesis is the late stage radical construction of the THF ring. A series of classical manipulations provided

intermediate **3.11** from tricycle **3.6**. The irradiation of a solution of **3.11**, iodobenzene diacetate and iodine facilitates an *intra*molecular abstraction of the tertiary isopropyl hydrogen and subsequent cyclisation to generate tetracyclic **3.12** in 95% yield (eqn. (3.1)). In order to prevent the formation of undesired delocalised allylic radical, the exo cyclic methylene unit had to be masked during this transformation, adding an extra five steps to the synthesis. The natural product was constructed in 32 longest linear steps and 1.5% yield from known intermediate (±)-**3.10**. Whilst the late stage construction of the THF ring in Paquette's synthesis proved to be an eloquent solution to the formation of the highly strained ring system, the overall synthesis was considerably longer than the original reported by Schreiber and lower yielding.



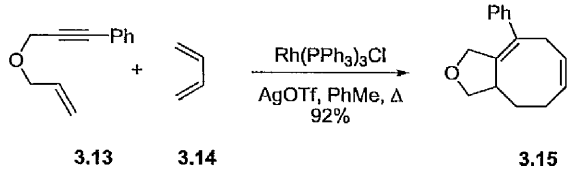
3.11 **3.12** (3.1)

3.2 Rhodium-Catalysed [(4+2+2)] Cycloisomerisation Reaction

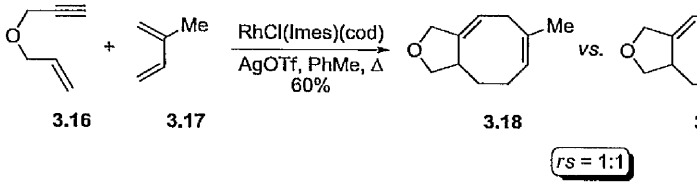
3.2.1 Rhodium-Catalysed Semi-*Inter*molecular [4+(2+2)] Cycloisomerisation Reaction

An ongoing area of research within the Evans group is the practical construction of small and medium fused rings *via* carbocyclisation reactions. The difficulty associated in accessing 5,8-bicyclic systems along with the abundance of

natural products containing this motif, piqued the interest of our group and drove the development of a rhodium-catalysed [4+(2+2)] carbocyclisation. To this end a series of 5,8-bicyclic systems were constructed in good yields by the semi-*inter*molecular carbocyclisation of a series of 1,6-enynes with 1,3-butadiene.[12] For instance, treatment of 1,6-enyne **3.13** and 1,3-butadiene **3.14**, with Wilkinson's catalyst modified *in situ* with silver triflate, provided 5,8-octadiene **3.15** in excellent yield (92%, eqn. (3.2)).



3.13 **3.14** **3.15** (3.2)

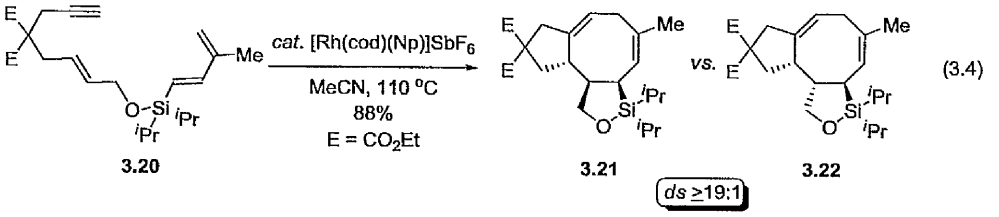


3.16 **3.17** **3.18** **3.19** (3.3)

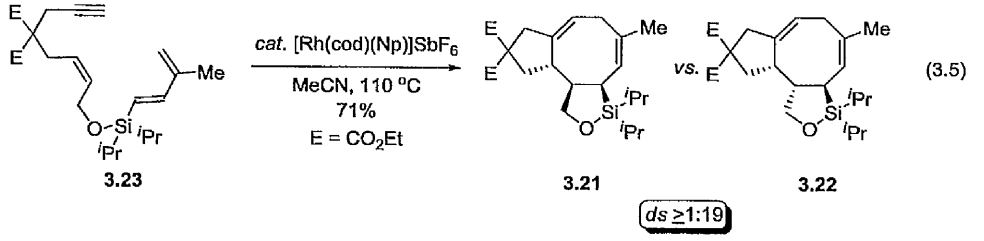
rs = 1:1

Whilst the reaction proceeds in excellent yields for nitrogen-, oxygen- and sulphur-tethered 1,6-enynes, the malonate-tethered analogues failed to provide any of the desired bicyclic adduct. Arguably, this appreciably reduces the synthetic utility of this transformation for the synthesis of natural products. In a later report the group disclosed that unsymmetrical dienes undergo carbocyclisation without regiocontrol. Treatment of 1,6-enyne **3.16** and isoprene **3.17** with the requisite rhodium-catalyst furnished cycloadducts **3.18/3.19** in 60% yield, as a 1:1 mixture of regioisomers (eqn. (3.3)). The lack of regiocontrol further limits the potential of this methodology to be implemented in target directed synthesis.

3.2.2 Rhodium-Catalysed Silicon-Tethered [(4+2+2)] Cycloisomerisation Reaction



(3.4)



(3.5)

The Evans group postulated that temporarily tethering the three π-components together, rendering the reaction fully *intra*molecular, would circumvent the issues associated with controlling regioselectivity.[13] Temporary-silicon tethers (TST) had previously been exploited in several types of transformations, including cycloadditions, radical reactions and olefin metathesis.[14-17,1c] Nevertheless, TST had not been implemented in rhodium-catalysed higher-order carbocyclisations reactions. To this end, the group reported the first example of an *intra*molecular rhodium-catalysed silicon-tethered [(4+2+2)] cycloisomerisation reaction of diene-enynes. Interestingly, manipulation of the geometry of the internal olefin facilitated access to complementary 5,8,5-tricyclic diastereoisomers in good yields. Heating silicon-tethered **3.20** with the [Rh(cod)(Np)]SbF_6 catalyst in a sealed tube, furnished tricyclic adduct **3.21** in good yield and excellent diastereocontrol (88%, *ds* ≥19:1, eqn. (3.4)). Subjecting the geometric isomer **3.23**, to the same reaction conditions

provides complementary cyclooctadiene **3.22**, in 71% yield and excellent diastereoselectivity (*ds* ≥1:19, eqn. (3.5)).

The success of the malonate tethered substrates in this transformation is in direct comparison with the semi-*inter*molecular reaction previously reported (*vide supra*). This is indicative that an alternative catalytic cycle is in operation in these transformations. The authors proposed that during the TST [(4+2+2)] carbocyclisation, the initial oxidative addition occurs between the alkene and alkyne to provide a rhodium-pentene metallacycle intermediate. The ensuing carbometallation is the diastereo-determining step, dictated by the conformation during coordination of the diene to the rhodium-centre. The high levels of diastereoselectivity observed result from the preferential formation of transition states **B** and **D** as a result of minimisation of steric congestion between one of the isopropyl groups and the internal proton on the 1,3-butadiene (figure 3.2).

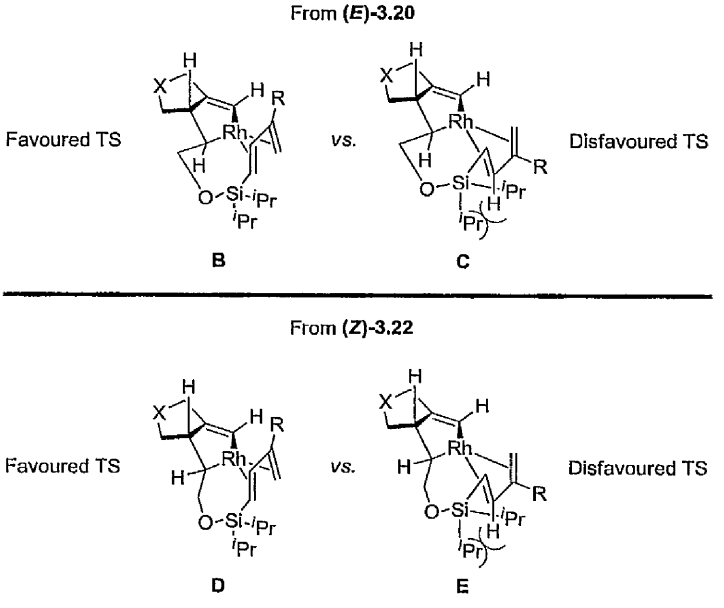
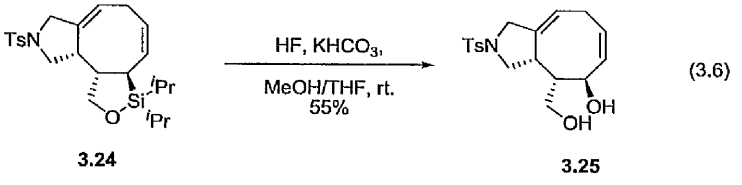


Figure 3.2 Proposed transition structures for the observed diastereoselectivity in the [(4+2+2)] cycloisomerisation of 1,6-enynes **(*E*)- 3.20** and **(*Z*)- 3.23**

The high levels of selectivity and impressive yield make this methodology an excellent choice for the construction of natural products, facilitating bond disconnections which otherwise would have been inconceivable. Nevertheless, for this methodology to be a plausible synthetic instrument it was crucial to demonstrate that the *temporary*-tether can be removed efficiently without degradation of the 5,8-bicyclic architecture. Importantly, the group demonstrated the successful cleavage of silicon tether *via* Tamao oxidation conditions providing diol **3.25** in an encouraging 55% yield (eqn. (3.6)).[18]



3.24 **3.25** (3.6)

3.3 Retrosynthetic Analysis of (+)-Epoxydictymene

Despite present intriguing chemistry, the (+)-epoxydictymene syntheses of Schreiber and Paquette are relatively long for the construction of a medium sized natural compound, even one which is structurally complex. As such, an efficient synthesis of (+)-epoxydictymene currently remains elusive. We postulated that utilising the methodology developed in our group we could develop a more efficient route to (+)-epoxydictymene. Scheme 3.5 describes the general features of our retrosynthetic analysis of (+)-epoxydictymene.

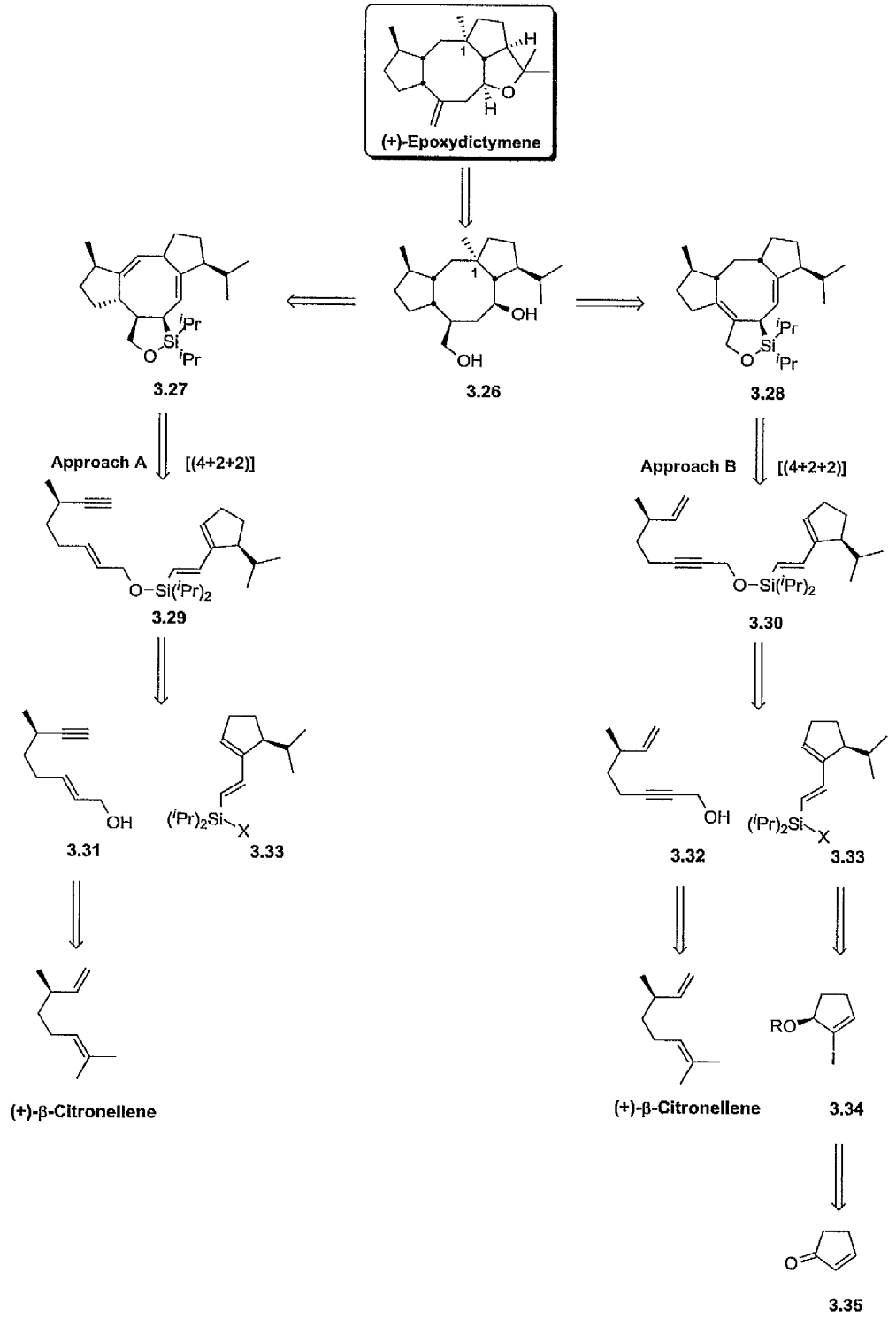
During the infancy of our analysis we were heedful of the difficulty faced by Schreiber in the installation the correct *trans*-geometry across the highly strained 5,5-

ring system. Therefore, the most logical approach to circumvent this issue involved taking the lead from Paquette's synthesis and designating the THF moiety as the final ring to be constructed. Tricycle **3.26** is a key intermediate from Paquette's synthesis; we identified this as a potential intermediate for a formal synthesis of (+)-epoxydictymene. In the forward direction, Paquette converted compound **3.11** into the natural product *via* a radical cyclisation (*c.f.* section 3.1.3, eqn. (3.1)).

Intermediate **3.26** remains a highly functionalised medium size molecule, containing all of the atoms of the natural product, and with all seven of the stereogenic centres already installed. It was observed that this tricyclic adduct bears similarities to the compounds obtained in the silicon-tethered [(4+2+2)] methodology developed within our group. Intermediate **3.26** could be obtained from intermediate **3.27** and **3.28** through cleavage of the silicon-tether, installation of the quaternary centre at C^1 and a short sequence of additional functional group manipulations.

Key intermediates **3.27** and **3.28** could be fashioned *via* a rhodium-catalysed silicon-tethered [(4+2+2)] cycloisomerisation reaction of diene-enynes **3.29** and **3.30**, respectively. In the synthetic direction, the two carbocyclisation reactions differ in the manner in which we plan to obtain an asymmetric sample of (+)-epoxydictymene. **Approach A** is based on the assumption that the enantioselective variant of the previously disclosed [(4+2+2)] can be developed. Nevertheless, all previous attempts to develop the asymmetric version have been unfruitful. Whilst **approach B** hinges of the assumption that the C^1 stereocenter adjacent to an olefin can induce the correct stereochemistry at the bridging centres of the tetracycle

through stereoinduction. Significantly, the cycloisomerisation of a diene-enyne of the type **3.30** has not previously been described.



Scheme 3.5 Retrosynthetic analysis of (+)-epoxydictymene

As such, this approach will require the development of a new carbocyclisation transformation. The successful cycloisomerisation of **3.29** and **3.30** will install the core of (+)-epoxydictymene and complete three of the four rings of the natural product.

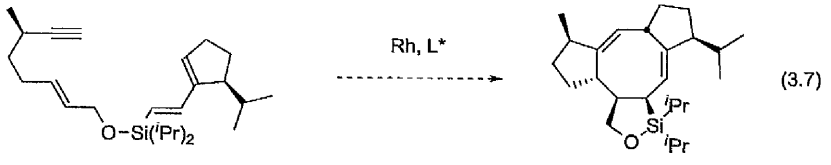
Retrosynthetic analysis of substrates **3.29** and **3.30** reveals that both intermediates could be procured by the coupling of silane **3.33** and either alcohol **3.31** or **3.32**, respectively. The feasibility of this transformation was demonstrated during the substrate preparation for the [(4+2+2)] methodology described above (eqn. (3.4) & (3.5)). The one-step protocol was achieved *via* the bromination of the silyl group with N-bromosuccinimide (NBS), followed by the addition of the alcohol.[13] The retrosynthetic analysis of optical active alcohols **3.31** and **3.32** reveals that they can be prepared from (+)-β-citronellene *via* the oxidative cleavage of the isobutene moiety followed by the subsequent alkene/alkyne formation. The methyl group of naturally occurring (+)-β-citronellene provides the C^1 stereocenter of the natural product.

The next synthetic obstacle is now the asymmetric installation of the asymmetric isopropyl moiety (fragment **3.33**); this feat remains a challenging task for organic chemists. To this end, the Roshell group have developed an eloquent S_N2' reaction and demonstrated the utility of this transformation in total synthesis of (+)-estrogen.[19-20] Iodide **3.34** emerged as a potential synthetic precursor, which in turn could be accessed from commercially available **3.35** *via* α-halogenation followed by CBS reduction of the requisite cyclic enone.[21]

The following sections will describe the rationale behind **approaches A** and **B** in greater detail. In addition, a series of preliminary experiments are described, designed to probe the practicality of each approach.

3.4 Approach A: Enantioselectivity within the Rhodium-Catalysed Silicon-Tethered [(4+2+2)] Cycloisomerisation Reaction

The principle transformation in the synthesis of (+)-epoxydictymene *via* **approach A** is an asymmetric rhodium-catalysed TST [(4+2+2)] cycloisomerisation (eqn (3.7)). The main obstacle associated with achieving this feat is that replacing the optimal ligand of a racemic transformation with an analogous asymmetric variant can have detrimental effect on efficiency of the reaction.

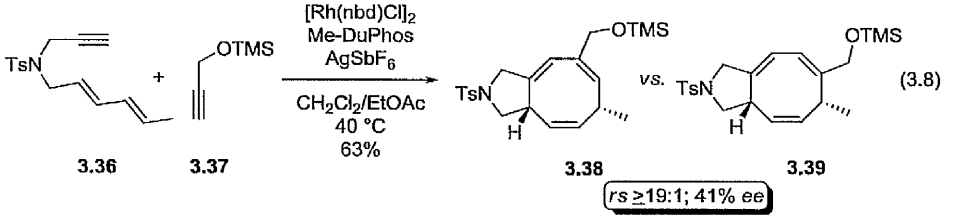


3.29 **3.27** (3.7)

3.4.1 Historical Bearing

Examination of the literature revealed that there is a disparity between the developments within asymmetric transition metal-catalysed [4+2+2] and those of other [m+n+o] carbocyclisations. Surprisingly, there have only been two examples of asymmetric rhodium-catalysed [4+2+2] carbocyclisations. In an isolated example, the Gilbertson group reported that treatment of diene-yne **3.36** and alkyne **3.37** with a asymmetric Me-DuPhos-rhodium complex provided diene **3.38** in 63% yield and in

moderate enantiomeric excess (41% *ee*, eqn. (3.8)).[22] This was the only asymmetric example in the report, with the author disclosing that all other substrates proceed with lower levels of enantioselectivity.



Rovis *et al.* reported a carbocyclisation for the construction of optically active bicyclic ε-lactams.[23] Upon exposure to the requisite asymmetric phosphoramidite **L1** rhodium-complex isocyanate **3.40** and alkyne **3.41** underwent carbocyclisation to provide lactam **42** in 82% yield and excellent regio- and enantioselectivity (*rs* ≥19:1, 99% *ee*, eqn. (3.9)). This methodology was shown to be general, tolerating various tethers and incorporating electron rich and poor alkynes.

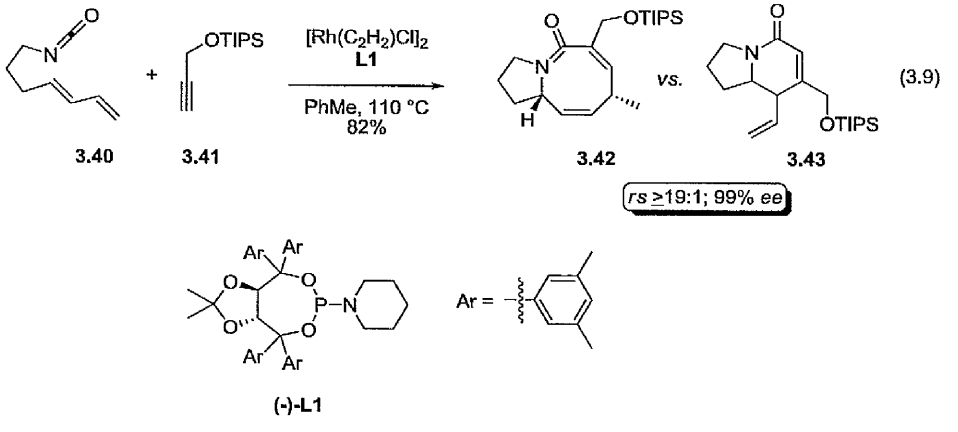
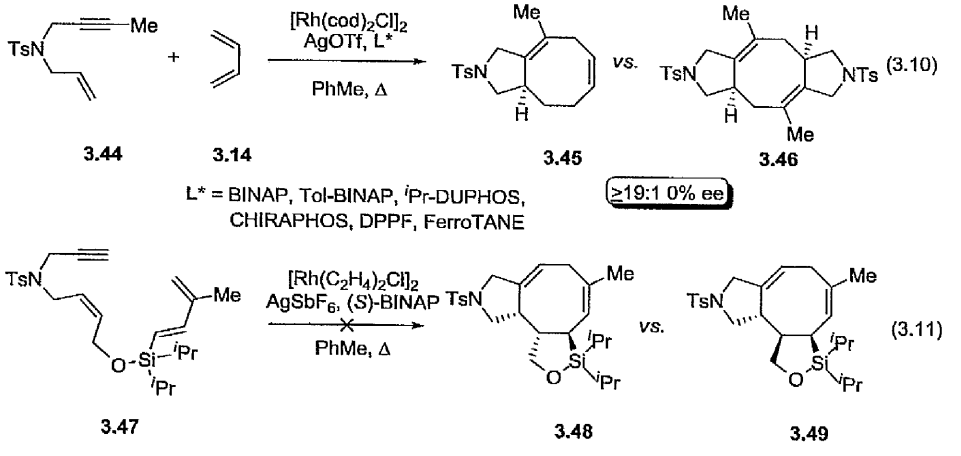


Figure 3.3 Phosphoramidite Ligand **L1**

Previous efforts within our research group to develop an asymmetric variant of the rhodium-catalysed [4+2+2] cycloisomerisation proved to be unsuccessful (eqn.

(3.10) + (3.11)).[24] In the case of the semi-*inter*molecular [4+(2+2)] carbocyclisation, modification of the catalyst by the addition of chiral phosphines failed to have any impact on the enantiomeric excess of the transformation (eqn. (3.10)). In addition, $[Rh((S)\text{-Tol-BINAP})Cl]_2$ and a asymmetric rhodium-carbene complex were isolated and subsequently utilised in the reaction, however no level of enantioselectivity was observed. The investigators hypothesised that the excess butadiene substrate was ligating to the rhodium-centre preventing the formation of the asymmetric catalyst *via* competitive inhibition. Subsequent research briefly examined the viability of developing an asymmetric rhodium-catalysed TST [(4+2+2)] carbocyclisation. The addition of (*S*)-BINAP ligand to the reaction hindered the catalyst turnover, preventing the formation of the desired 5,8-bicyclic adduct (eqn. (3.11)).



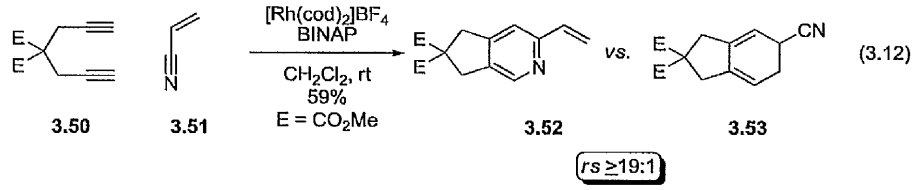
Arguably, a satisfactory asymmetric [4+2+2] carbocyclisation for the construction of bicyclooctanes has yet to be disclosed. This methodology would unquestionably be a beneficial addition to the arsenal of an organic synthetic chemist since the majority of cyclic adducts isolated from natural sources exist as a single enantiomer.[25]

3.4.2 Active Catalyst Postulation

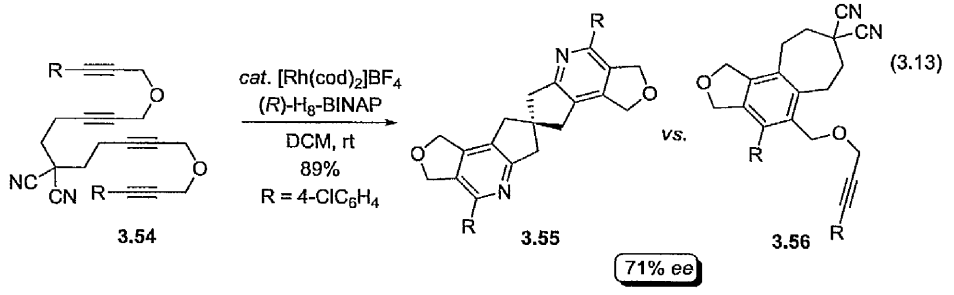
Our exploration of an asymmetric rhodium-catalysed TST [(4+2+2)] cycloisomerisation began with the examination of the racemic variant.[13,24] The original investigation probed the effect of various rhodium-catalysts, silver salts and solvents. The optimal conditions for the transformation were found to be [(cod)Rh(Np)]SbF_6 catalyst refluxing in acetonitrile. Interestingly, the influence of solvent on the efficiency of the reaction was far more significant than varying any other parameters, with acetonitrile demonstrating superior activity for the transformation. We hypothesized that the acetonitrile could in fact be acting in a different capacity in this transformation with the active catalyst being a rhodium-acetonitrile complex.

Rhodium-acetonitrile complexes have been utilised as catalysts and are available from commercial sources.[26] The ability of nitrile moieties to coordinate to a rhodium-centre is apparent in their application as substrates within carbocyclisation reactions. In 2006, Tanaka *et al.* described a rhodium-catalysed semi-*inter*molecular [(2+2)+2] carbocyclisation for the construction of bicyclic pyridines in good yields.[27] Treatment of diyne **3.50** and nitrile **3.51** with a rhodium-BINAP complex provided pyridine **3.52** in good yield and excellent selectivity (59%, *rs* ≥19:1, eqn. (3.12)). This example is of particular interest since the nitrile group is incorporated into the metallacycle in preference to the neighbouring olefin, demonstrating the high affinity of rhodium to this moety.[28] Subsequent research within the Tanaka group disclosed a double [(2+2+2)] cycloisomerisation for the construction of spirobipyridine adducts.[29] Interestingly in this example, the nitrile motif is incorporated into the

metallacycle in preference to the cycloisomerisation of the 1,6,12-triyne unit (89%, 71% *ee*, eqn. (3.13)).



(3.12)



(3.13)

Assuming that the acetonitrile ligands are optimal to promote the catalytic turn-over of this transformation, displacing these ligands with chiral biaryl ligands *might* be detrimental to the reaction activity. For example, frequently used biaryl phoshine ligands (such as (*S*)-BINAP) differ considerably from a ligating acetonitrile molecule in electronics, coordination number and cone angle. Indeed, reduced catalytic turnover was observed upon the addition of (*S*)-BINAP (eqn. (3.11)). During our investigation we can examine these factors systematically, specifically, investigating the effect of mono *vs.* bidentate ligands and varying the electronic properties of the ligand on the reaction course.

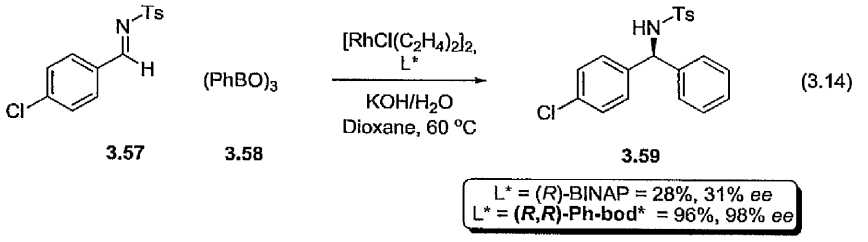
Further, *assuming* that our hypothesis is correct, and the acetonitrile is ligating to the rhodium-centre then this *may* prevent the coordination of the chiral ligand to the metal centre. In a reaction performed at 0.5 molar concentration utilising 12 mol% chiral ligand, the ratio of chiral ligand to acetonitrile solvent is

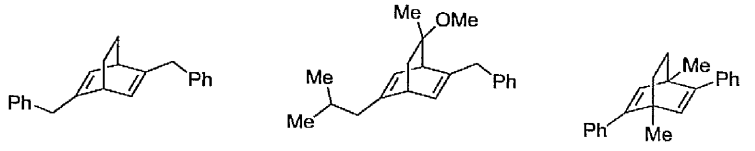
1:3830. For this reason we elected to perform our initial screen of chiral ligands in toluene. Treatment of silane **3.47** with the requisite rhodium-catalyst in toluene, furnished the desired tricyclic adduct **3.48** in a diminished yield of 30%. Whilst the efficiency of this transformation is significantly lower, we hoped that we could identify a ligand which in addition to providing high enantiomeric excess would also increase the efficiency of this transformation.

Finally, it is important to note that there is another catalytic component which could act as a ligand on the active catalyst.[30] The above hypothesis hinges on the assumption that one or both of the diene ligands (cod, Np) disassociate from the rhodium-metal, allowing the acetonitrile to coordinate. It is plausible that one of these ligands is coordinated to the metal in the active species. The past decade has witnessed increased exploitation of chiral diene ligands in a plethora of asymmetric transformations.[31]

Of particular interest is the research of Hayashi, which demonstrated that chiral diene-rhodium complexes can mediate transformations that are inactive with rhodium-phosphine catalysts.[32] For example, the asymmetric arylation of *n*-tosylarylimine **3.57** occurred upon treatment with phenylboroxin (**3.58**) and a (***R,R***)-**Ph-bod***-rhodium complex to provide tosylamide **3.59** in excellent yield and enantioselectivity (96%, 98% *ee*, eqn. (3.14)). In contrast, treatment with a phosphine-rhodium complex provided the desired amide in a diminished 28% yield and 31% enantioselectivity. The increasing utilisation of chiral dienes in asymmetric transition-metal catalysis has been facilitated by the chiral dienes developed in the research groups of Carreira (**Carreira's Ligand**) and Carnell (**L2**).[33-34] These dienes

are synthesised efficiently *via* reliable protocols, and as a consequence **Carreira's Ligand** is now available from commercial sources.





(*R*,*R*)-Ph-bod* **Carreira's Ligand** **L2**

Figure 3.4 Chiral diene ligands

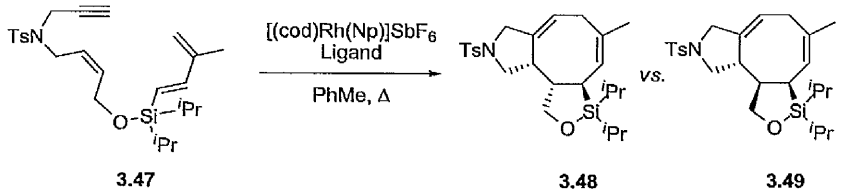
3.4.3 Initial Studies and Optimisation of the Asymmetric TST [(4+2+2)] Cycloisomerisation

Before instigating the synthesis of (+)-epoxydictymene, the feasibility of **approach A** was investigated on a model system. Substrate **3.47** was selected as a suitable substrate since the racemic transformation demonstrated higher efficiency for diene-enynes with *trans*-alkene geometry and the nitrogen tether facilitates a concise construction of the substrate. Table 3.1 describes our initial efforts towards developing an asymmetric [(4+2+2)] carbocyclisation through the addition of chiral ligands.[36] In concurrence with the original findings, the addition of (*S*)-BINAP failed to provide the desired octadiene (entry 2).[24] Encouragingly, modification of the catalyst by the addition of (*S*)-QUINAP ligand provided the desired 5,8,5-tricyclic adduct in 4% enantiomeric excess, albeit in poor yield (entry 3). Undoubtedly, the

levels of enantiocontrol observed in this transformation are poor, nevertheless this example represents a significant improvement toward the enantioselective reaction, since it is the first example where we have of selectively modified the active catalyst through installing a tuneable ligand.

Significantly, the success of the catalytic turnover of the transformation utilising a fluctuating mono/bidentate ligand is in keeping with our earlier hypothesis that mono and bidentate ligands may behave differently in this transformation. This is unsurprising when we examine the substrate for the transformation, which is capable of occupying many of the coordination sites on the rhodium-centre. Disappointingly, the addition of **(*S*)-^{i}Pr-Phox** retarded the reaction (entry 4). At this junction, we decided to focus our attention on screening alternative classes of ligands.

Table 3.1 Optimisation of the asymmetric rhodium-catalysed TST [(4+2+2)] cycloisomerisation reaction of silane **3.47**[a]

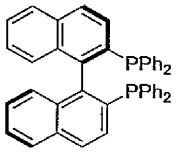


3.47 **3.48** **3.49**

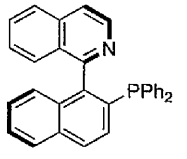
ds ≥19:1

Entry	Ligand[b]	Yield (%)	% *ee*[c]
1	-	30	-
2	**(*S*)-BINAP**[d]	n/r	-
3	**(*S*)-QUINAP**	~20[e]	4
4	**(*S*)-*i*Pr-Phox**	n/r	-
5	**Diene**[f]	n/r	2
6	**L3**	~20[e]	6
7	**L4**	"	25

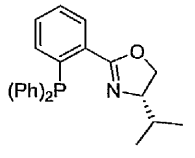
[a] All reactions were carried out on a 0.5 mmol scale. 20 mol% catalyst used. [b] 20 mol% ligand used, unless otherwise specified. [c] Enantioselectivity was determined by HPLC of the crude reaction mixture. [d] 10% mol dimer used. [e] based on ^{1}H NMR. [f] [(diene)Rh(cod)] catalyst used.



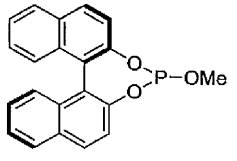
(*S*)-BINAP



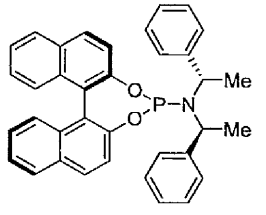
(*S*)-QUINAP



(*S*)-iPr-Phox



L3



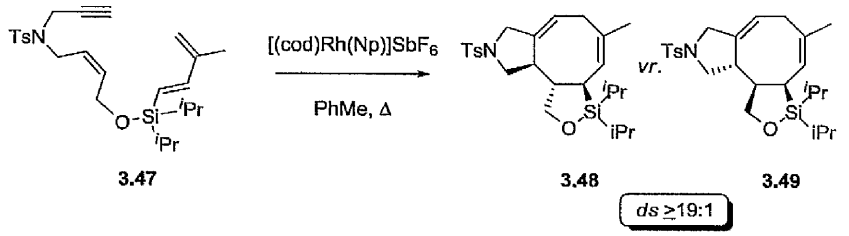
L4

Figure 3.5 Chiral ligands screened in the rhodium-catalysed TST [(4+2+2)] carbocyclisation transformations

Disappointingly, treatment of silane **3.47** with a chiral diene-rhodium complex provided the desired 5,8,5-tricyclic compound with no observable enantioselectivity (entry 5). The chiral catalyst was synthesis *via* the protocol described by Wender to prepare the $[(cod)Rh(Np)]SbF_6$ catalyst, substituting naphthalene for **Carreira's Ligand**. The addition of BINOL derived phosphate **L3** provided compound **3.48** with a modest 6% enantiomeric excess (entry 6).

Gratifyingly, the modification of the catalyst by the addition of phosphoramidite **L4** afforded adduct **3.48** in 25% enantiomeric excess (entry 7). Whilst both yield and degree of enantioinduction in this transformation are poor, we were encouraged by this result since it represents the first example of an asymmetric [(4+2+2)] for the construction of carbon octadienes. Conceptually, the success of the phosphoramidite ligand is encouraging since these ligands are modular in nature.[36] Furthermore, in contrast to phosphine ligands, phosphoramidite can be synthesised in an efficient manner, allowing the expedient construction of libraries of analogues. These two factors allow the systematic tuning of phosphoramidite ligands to optimise both yield and enantiomeric induction.

Table 3.2 Optimisation of the asymmetric rhodium-catalysed TST [(4+2+2)] cycloisomerisation reaction of silane **3.47**[a]

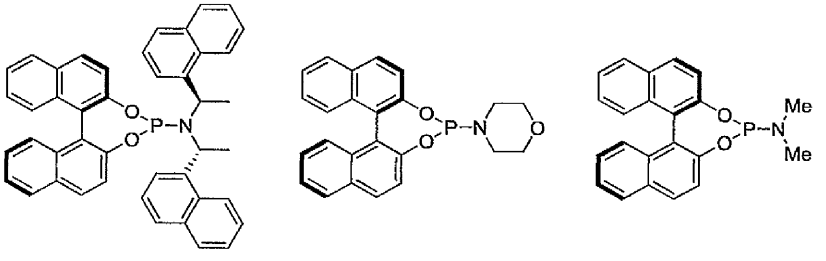


3.47 **3.48** **3.49**

ds ≥19:1

Entry	Ligand[b]	% *ee*[c]
1	**L2**	25
2	**L4**	12
3	**L5**	22
4	**L6**	30

[a] All reactions were carried out on a 0.1 mmol scale. 20 mol% catalyst used. [b] 20 mol% ligand used. [c] Enantioselectivity was determined by HPLC of the crude reaction mixture.



L4 **L5** **L6**

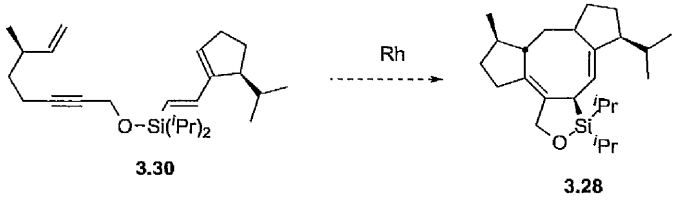
Figure 3.6 Chiral Phosphoramidite ligands screened in the rhodium-catalysed TST [(4+2+2)] carbocyclisation transformations

A plethora of BINOL derived phosphoramidite ligands are available from commercial sources. As such, our initial investigation focused on examining the influence that changing the amine component of the ligand has on the levels of enantioselectivity in the transformation. Table 3.2 describes the screen of chiral phosphoramidite ligands performed on substrate **3.47**. Surprisingly, more sterically encumbered naphthalene ligand **L4** affords octadiene **3.48** with slightly diminished levels of enantioinduction (entry 2). Replacing the amine component of the phosphamidite ligand with a morpholine ring furnished the desired product in

comparable enantiomeric excess (entry 3). A moderate increase in enantiomeric excess was observed utilizing the BINOL-dimethyl ligand **L6** (entry 4). Overall, changing the amine component of the ligand had little influence on the observed enantioselectivity.

At this juncture, we decided that further optimisation would be performed on substrate **3.29** since model systems often behave in a different manner to the complex intermediates of target directed synthesis. Specifically, the diene component of alcohol **3.29** is more sterically encumbered than substrate **3.47**, and the stereogenic centre adjacent to the alkyne provides further complication. We believe these factors may influence the observed enantiocontrol, affecting the steric congestion of the transisition state.

3.5 Approach B: Diastereoinduction within the Rhodium-Catalysed Silicon-Tethered [(4+2+2)] Cycloisomerisation Reaction



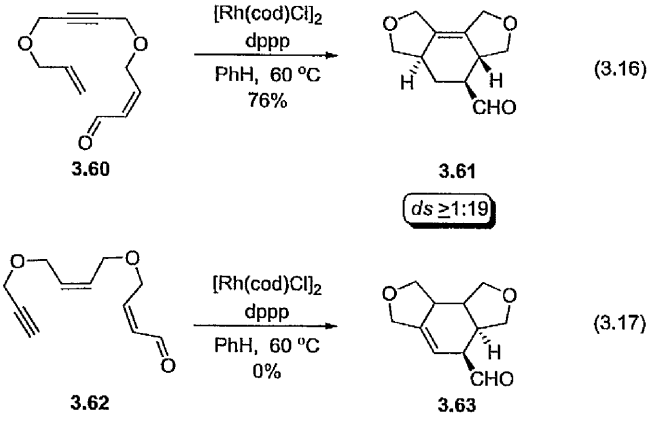
3.30 **3.28** (3.15)

The central transformation in the synthesis of (+)-epoxydictymene *via* **approach B** is a diastereoselective TST [(4+2+2)] cycloisomerisation, with the necessary stereochemistry induced from the methyl stereogenic center at C^1 (eqn. (3.15)). At the outset of our research we were heedful of two major obstacles with

this strategy. First, the cycloisomerisation of substrates of the type **3.30** has not previously been disclosed. Secondly, it is imperative that the reaction proceeds with diastereoinduction to obtain an optically active sample of the natural product.

3.5.1 Rhodium-Catalysed Silicon-Tethered [(4+2+2)] Cycloisomerisation Reaction

Fundamentally, the successful synthesis of (+)-epoxydictymene *via* **approach A** hinges upon the accomplishment of the cycloisomerisation of substrate **3.30**. Whilst, the analogous rhodium-catalysed [(4+2+2)] is an excellent transformation, the isomerisation of silane **3.30** has not been investigated. It is worthy to note, that changing the connectivity of unsaturated moieties can drastically alter the reactivity profile of the cycloisomerisation reaction. Indeed within our group, attempts to develop a rhodium-catalysed dienynes [(2+2+2)] carbocyclisation analogous to the transformation described in chapter 2 proved fruitless. For example, whilst subjecting dienyne **3.60** to a rhodium-dppp complex, provides tricyclic **3.61** in good yield and excellent diastereocontrol (76%, *ds* ≥19:1, eqn. (3.16)), subjecting dienyne **3.62** to the same reaction conditions fails to provide any of the desired isomer **3.63** (eqn. (3.17)).



(3.16)

(3.17)

3.5.2 Diastereoinduction: Historic Reference

The second crucial feature in the successful synthesis of (+)-epoxydictymene *via* **approach B** is that the key [(4+2+2)] cycloisomerisation proceeds with high levels of diastereoinduction. Sections 1.5 (chapter 1) provides a comprehensive review of the progress made within the field of diastereoinduction in rhodium-catalysed [m+n+o] carbocyclisations. In addition, during chapter 2, section 2.5 we described the impact our research group has made in this arena within rhodium-catalysed [(2+2+2)] carbocyclisations. In summary, a stereogenic centre adjacent to an unsaturated moiety can influence the conformation of the resultant metallacycle by affecting the diastereotopic face which the rhodium coordinates through steric encumbrance. Consequently, installing an enantiomerically enriched stereocenter at this position, results in optically active cyclic products.

The degree of diastereoinduction is greatest when the rhodium-centre can only coordinate to the unsaturated moiety *via* a single trajectory. This is easier to achieve for unsaturated moieties with a single π-bond (for example, alkenes); in this instance, the rhodium-metal can coordinate to either face of the π-orbital and blocking one of these faces through steric hindrance has an enormous effect. In comparison, the coordination of rhodium to unsaturated moieties containing multiple π-orbitals (e.g. alkynes) can occur from several faces; therefore blocking a single face would still allow the rhodium to coordinate from several other planes. Based on the above assumptions, we predict that cycloisomerisation of compound **3.29** would result in a mixture of diastereoisomers, since the methyl group at C^1 will have minimal influence on the metallacycle formation. Consequently, we proposed

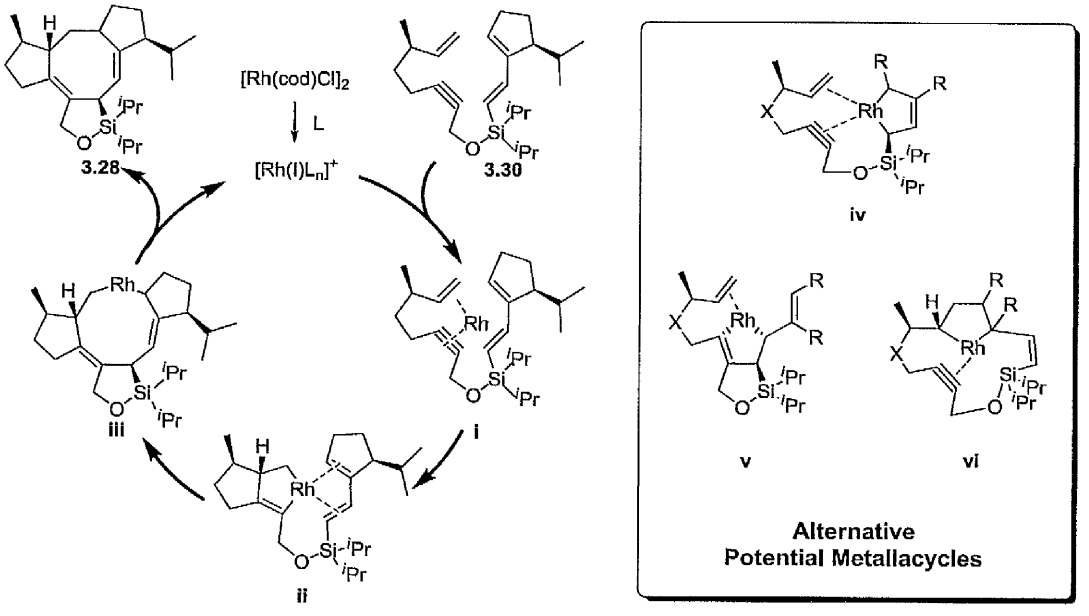
intermediate **3.30** as an alternative substrate for the cycloisomerisation reaction (*c.f.* Scheme 3.5).

3.5.3 Catalytic Cycle Rationale

Intrinsically, the successful diastereoinduction in transition metal-catalysed higher-order carbocyclisations is dependent upon which catalytic cycle is dominant during the transformation. Importantly, the unsaturated motif adjacent to the stereocenter must coordinate to the rhodium-centre during or before the diastereo-determining step. The general catalytic cycle for a carbocyclisation reaction (Scheme 1.1, Chapter 1) depicts two unsaturated moieties that initially coordinate to the rhodium-centre and subsequently undergo oxidative addition. In a three component reaction, the two π-components that initially coordinate dictate which catalytic cycle is operative in the transformation. Scheme 3.6 describes a possible catalytic cycle arising from the cycloisomerisation of substrate **3.30**. The coordination of the 1,6-enyne unit and subsequent oxidative addition affords metallabicyclopentene **ii**. Carbometallation of the diene moiety and reductive elimination furnishes cyclic adduct **3.28** and regenerates the active catalyst. If the reaction proceeds through the depicted catalytic cycle we would predict that tricyclic **3.28** would be obtained in high enantiomeric excess, since the alkene adjacent to the influential methyl stereogenic centre is coordinated to the rhodium-centre prior to the diasteroselectivity-determining event.

Scheme 3.6 also describes three alternative metallacycles resulting from the oxidative additions between different π-components. In the case of metallacycles **iv**

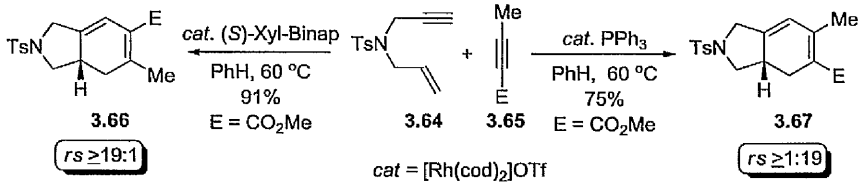
and **v** we postulate that no diastereoinduction will be observed. Interestingly, metallacycle **vi** is a macrocyclic compound. Whilst rhodium-catalysted carbocyclisations of macrocyclic compounds have been disclosed, diasteroinduction in these systems has not been reported, as such, it is difficult to predict the outcome of this transformation. Nevertheless the diastereo-determining step has not occurred, so according to our own hypothesis we would hope to observe diastereoinduction *via* this pathway.



Scheme 3.6 Possible catalytic cycle of the TST [(4+2+2)] cycloisomerisation of substrate **30** and alternative metallacycles

It is important to note that previous work preformed within our research group has demonstrated that the modification of a catalytic system can influence the dominant catalytic cycle in higher-order carbocyclisation transformations. In 2010, the Evans group disclosed the first example of a regiodivergent rhodium-catalysed [(2+2)+2] carbocyclisation for the construction of bicyclohexadiene (Scheme 3.7).[37]

The judicious choice of ancillary ligand facilitated the construction of complementary bicyclohexadiene regioisomers. The authors reasoned that the employment of a bidentate *vs.* a monodentate ligand affects the dominant catalytic cycle and subsequently the cyclic adduct formed. These transformations are described in greater detail in Chapter 1, Section 1.4.



Scheme 3.7 Regiodivergent rhodium-catalysed [(2+2)+2] carbocyclisation for the construction of bicyclohexadiene

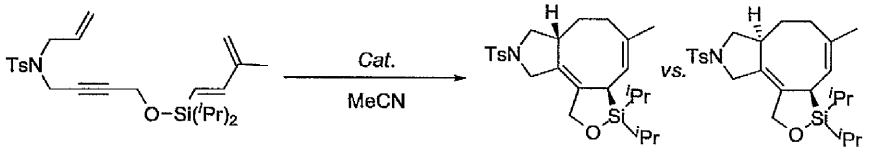
These seminal findings could have significant influence within our current research. Significantly, *if* high levels of enantioinduction are not observed during the carbocyclisation of substrate **3.29**, then the modification of the active catalyst with different ligands *may* allow us to access a different catalytic cycle, resulting in higher diastereoinduction.

3.5.4 Initial Studies and Optimisation of the Alternative TST [(4+2+2)] Cycloisomerisation

Prior to commencing the synthesis of the natural product, we elected to investigate the feasibility of the key carbocyclisation transformation of **approach B** on a model system. Tosylamine **3.68** was selected as a suitable substrate since nitrogen tethered diene-yne-enes undergo cycloisomerisation in the analogous TST carbocyclisation with high efficiency. Table 3.3 describes the preliminary

optimisation of the asymmetric rhodium-catalysed TST [(4+2+2)] cycloisomerisation reaction of silane **3.68**.

Table 3.3 Optimisation of the asymmetric rhodium-catalysed TST [(4+2+2)] cycloisomerisation reaction of silane **3.68**[a]



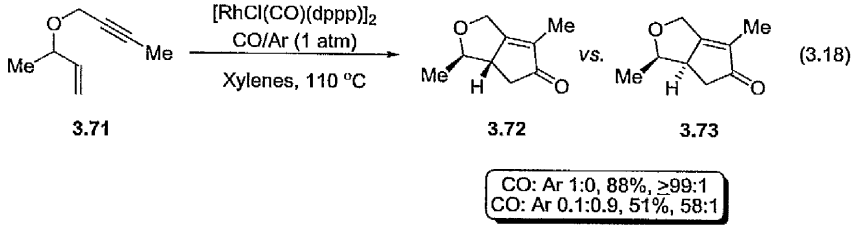
3.68 **3.69** **3.70**

Entry	Cat.[b]	Temp / °C	atm.	Yield / %	*ds*[c] major:minnor
1	[(cod)Rh(Np)]SbF_6	110	Ar	-	-
2	$[Rh(cod)Cl]_2$	"	"	-	-
3	$[Rh(cod)Cl]_2$, dppp	"	"	-	-
4	$[Rh(cod)Cl]_2$	132	CO	41%	10:1

[a] All reactions were carried out on a 0.1 mmol scale. [b] 10 mol% catalyst used.
[c] Diastereoselectivity was determined by ^1H NMR of the crude reaction mixture.

Taking heed from the previously reported rhodium-catalysed TST-[(4+2+2)] cycloisomerisation of diene-ene-eynes **3.20** and **3.23**, we began our current exploration with the catalytic systems that had furnished optimum reactivity. The attempted cyclisation of **3.68** with Wender's [(cod)Rh(Np)]SbF_6 catalyst in acetonitile, failed to afford the desired cyclisation product (entry 1).[38] Utilising $[Rh(cod)Cl]_2$ as an alternative pre-catalyst was also unsuccessful (entry 2). By analogy to the previously described rhodium-catalysed *inter*molecular [(2+2+2)] cycloisomerisation of dienynes (*c.f.* chapter 2) we reasoned that the addition of phosphine ligands *could* provide optimum activity. Disappointingly, these conditions also failed to afford the desired cyclic compound (entry 3).

Previous research within the Evans group disclosed the rhodium-catalysed Pauson-Khand reaction of 1,6-enynes.[39] Crucial to the success of this transformation was performing the reaction under one atmosphere of carbon-monoxide, with CO/Argon mixture resulting in both diminished yield and selectivity (eqn. (3.18)). For example, 1,6-enyne **3.71** undergoes Pauson-Khand annulation when treated with the required rhodium-catalyst under one atmosphere of CO to provide **3.72** in good yield and excellent enantiomeric excess (88%, ≥99:1, eqn (3.18)). Conversely, subjecting substrate **3.71** to the same catalyst under one atmosphere of a mixture of CO:Ar provided **3.72**: **3.73** in 51% yield as a 58:1 mixture of diastereoisomers. The authors postulate that the concentration of CO changes the composition of the active catalyst. Consequently, we designated to perform the reaction under an atmosphere of carbon monoxide (entry 4). Gratifyingly, diene-yne-ene **3.68** underwent the desired isomerisation to furnish tricycles **3.69** and **3.70** in 41% yield. The diastereoselectivity of the transformation is 10:1 however the major diastereoisomer has not yet be identified. (^{1}H NMR analysis). Attempts to assign the relative stereochemistry of the mojor diasteroisomer *via* X-ray crystalography is on going. Significanly, in our synthsis of (+)-epoxydictymene either diastereoisomer can be utilised as the stereogenic centre adjacent to the silicon tether is subsequently removed.



This novel transformation represents an exciting development in rhodium-catalysed [(4+2+2)] carbocyclisation, as this reaction facilitates the formation of alternative octadienes. Not only is this a significant development toward the synthesis of (+)-epoxydictymene, but this denotes an exciting development in higher-order cycloisomerisations, allowing access to alternative 5,8- natural products. At this juncture, we elected to investigate the influence of a substituent adjacent to the alkene before further optimisation. As such it was decided futher screening would be undertaken on substrate **3.30**.

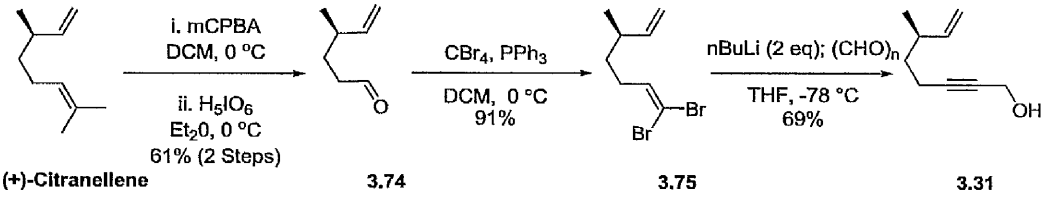
3.6 Substrate Synthesis

3.6.1 Synthesis of Fragment 3.31

Our strategy toward the construction of (+)-epoxydictymene began by simultaneously investigating the feasibility of **approaches A** and **B**. The divergent nature of the planned synthesis made this possible, with the two carbocyclisation precursors constructed from the coupling of silane **3.33** and either alcohol **3.31** or **3.32**. The synthesis of the alcohol fragments **(3.31 & 3.32)** diverged from the common intermediate **3.62**, a previously reported aldehyde.

The construction of key aldehyde **3.74** was achieved *via* a two-step protocol from commercially available (+)-β-citronellene (scheme 3.7).[40] The selective epoxidation of the more electron rich alkene, followed by oxidative cleavage of the expoxide upon treatment with periodic acid, provided key intermediate **3.74** in 61%

(2 steps). It is worthy to note that aldehyde **3.74** can also be synthesised in a single transformation *via* ozonolysis of the more substituted olefin.[41] Practically, we found the two-step protocol to be more reliable on a larger scale. The volatility and relative instability of the aldehyde dictated that this intermediate was utilised immediately in the next reaction.



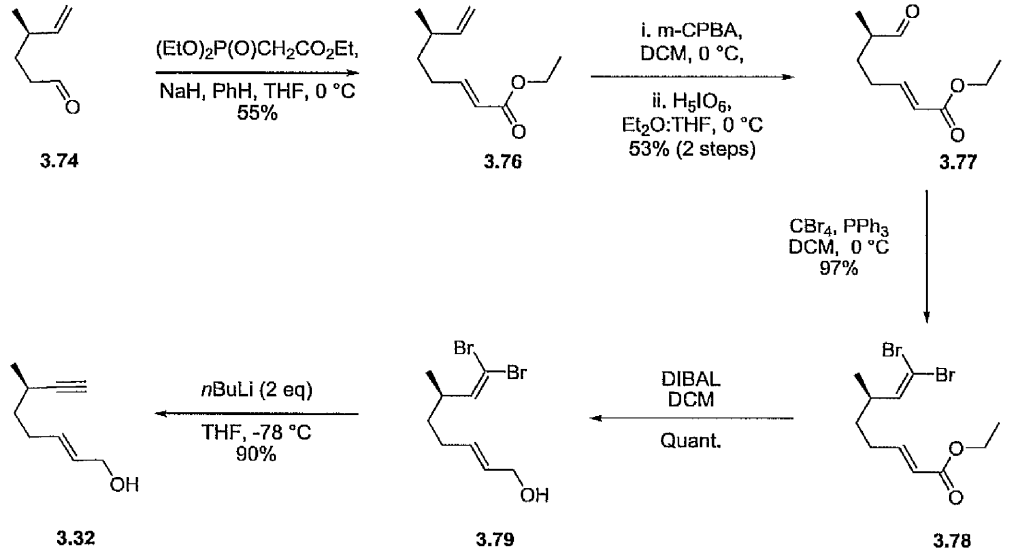
Scheme 3.8 Synthesis of fragment **3.31**

To complete the synthesis of fragment **3.31**, aldehyde **3.74** was subjected to Corey-Fuchs two-step protocol for the construction of the acetylenes.[42] Subjecting aldehyde **3.74** to the dibromo-ylide, prepared *in situ* from the exposure of carbon tetrabromide to triphenylphosphine, provided adduct **3.75** in excellent yield (91%). Treatment of dibromide **3.75** with two equivalents of *n*BuLi and the subsequent addition of paraformaldehyde provided alcohol **3.31** in 69%. In summary, fragment **3.31** was obtained from commercially available source in 4 linear steps and 38% yield.

3.6.2 Synthesis of Fragment 3.32

Scheme 3.9 decribes the synthesis of alcohol **3.32** from key aldehyde intermediate **3.74**. The construction of fragment **3.32** advanced with a Horner-Wadsworth-Emmons transformation.[43] Treatment of key aldehyde **3.74** with the deprotonated phosphonate provided enal **3.76** in 55% yield and complete E/Z

selectivity (by ^{1}H NMR). Utilising a benzene and tetrahydrofuran solvent mixture was found to be optimal to obtain the required *trans*-geometry.



Scheme 3.9 Synthesis of alcohol **3.32**

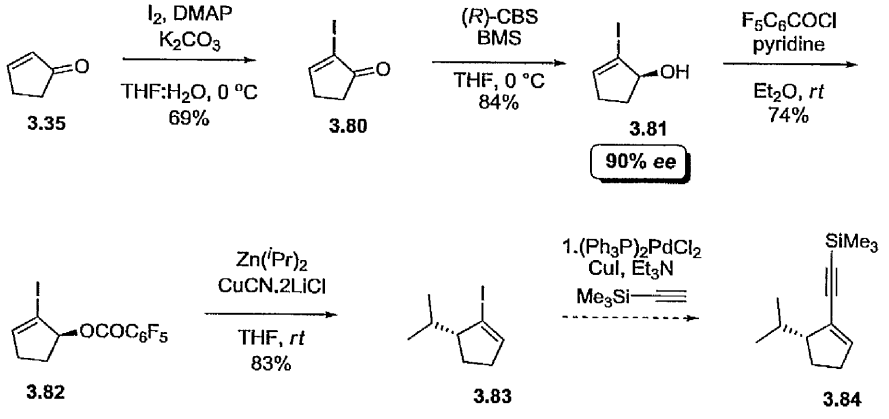
The selective epoxidation of the terminal alkene of **3.76** followed by epoxide cleavage, provided key intermediate **3.77** in 53% (2 steps). In analogy to the construction of aldehyde **3.74**, the selective epoxidation is determined by the differing electronics of the olefins. The intervening epoxide was obtained as an inconsequential 6:1 mixture of diastereoisomers. The resultant aldehyde (**3.77**) was subjected to Corey-Fuchs protocol and the conjugated ester reduced with DIBAL-H to provide alcohol **3.32** in 63% yield (three steps). Overall fragment **3.32** was obtained from a commercially available source in 8 linear steps and 15% yield.

3.6.3 Synthesis of Fragment 3.33

Scheme 3.10 decribes the construction of intermediate **3.83** from comercially avalable 2-cyclopentenone. The construction of fragment **3.33** began with the

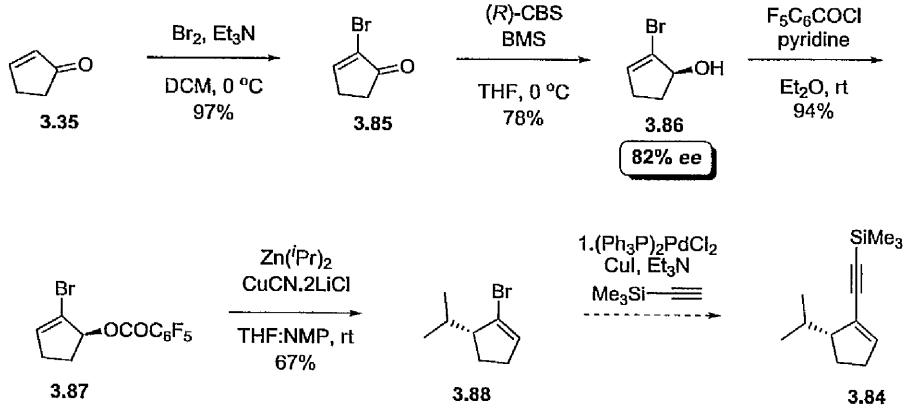
installation of the halide, required for a late stage coupling. The iodine moiety was introduced *via* a Baylis–Hillman type pathway to provide adduct **3.80** in 69% yield.[44] A Corey-Bakshi-Shibata (CBS) reduction was utilised to install the stereocentre, providing alcohol **3.81** in 84% yield and 82% enantiomeric excess (determined *via* HPLC).[45] The optical purity of compound **3.81** was increased *via* a recrystallisation, to provide alcohol **3.81** in 90% enantiomeric excess. Confirmation of the stereochemistry was achieved through the derivatisation with (*R*)/(*S*)-Mosher's acid chloride reagent and analysis of the ^{1}H NMR spectra *via* Mosher's advanced substitution protocol (Appendix 3.1).[46]

The requisite allylic benzoate moiety for the imminent S_N2' reaction was installed through treatment of optically active alcohol **3.81** with the acid chloride, DMAP and pyridine to provide benzoate **3.82** in 74% yield. The required isopropyl moiety was installed through a copper catalysed S_N2' reaction established within the Knochel group.[19-20] Treatment of compound **3.82** with a pre-treated solution of diisopropylzinc and CuCN.2LiCl proceeded to afford **3.83** in 83% yield. Crucial to the success of the transformation was the prolonged drying of the copper cyanide and lithium chloride solid under reduced pressure before the addition of THF.



Scheme 3.10 Effort towards the synthesis of fragment **3.33**

To complete the synthesis of fragment **3.33** the diene-silane motif remained. We identified a Sonogashira coupling followed by a zirconium addition as a viable route for the installation of this moiety. Disappointingly, treating iodide **3.83** under standard reaction conditions provided the desired acetylene **3.83** in poor yield (20% *via* crude ^{1}H NMR). A plethora of different conditions were investigated too little avail, including various bases and alternative palladium catalysts. We postulated that the stability of the iodine compound was responsible for the lethargic reactivity, with the decomposed iodide preventing the successful coupling of the two-components. In response we proposed an alternative route towards the construction of adduct **3.33**, involving the installation of an alternative halide.



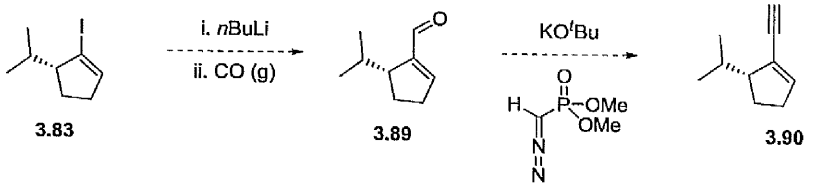
Scheme 3.11 Alternative route towards the synthesis of fragment **3.33**

Scheme 3.11 describes the alternative route towards the construction of fragment **3.33**. Treatment of commercially available cyclopentenone **3.35** with bromine and Et_3N provided bromide **3.85** in 97% yield.[47] The oxidation of enone **3.85** with (*R*)-CBS reagent afforded the optically active alcohol **3.86** in 78% yield and 82% enantiomeric excess. The absolute confirmation of alcohol **3.87** was determined through Mosher's procedure (Appendix 3.2), with the enantiomeric

excess of alcohol **3.86** was established *via* HPLC analyses of a 4-nitrobenzoate derivative.

The esterification of alcohol **3.86** afforded ester **3.87** in an improved 94% yield. Subjecting optically active benozate **3.87** to the optimal to copper-catalysed S_N2' conditions reaction resulted in complete conversion. Utilising a THF and NMP solvent mixture was found to be crucial, providing bromide **3.88** in 67% yield. Subjecting bromide **3.88** to standard Sonagashira coupling conditions failed to provide the desired acetylene compound.

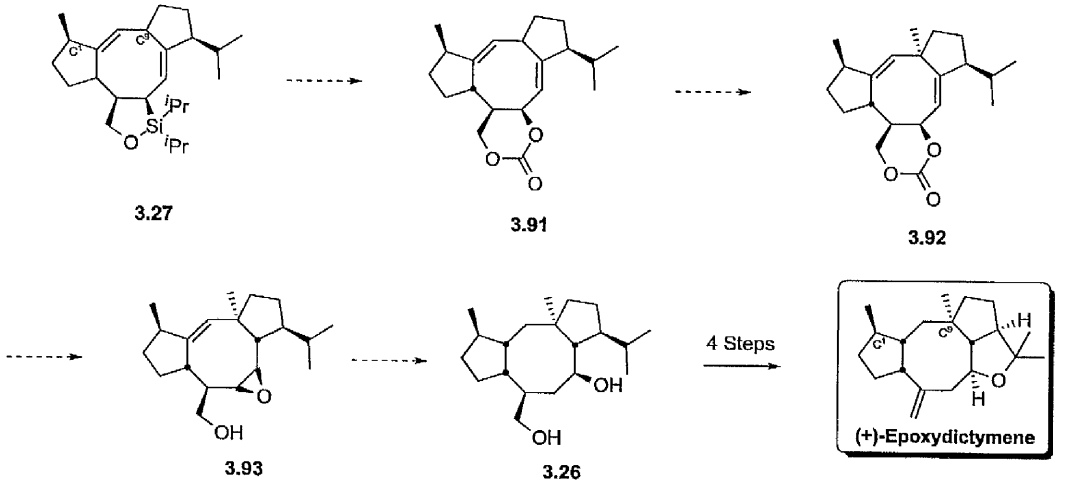
At this juncture an alternate route to compound **3.33** was proposed. Treatment of iodo-**3.83** with butyl lithium would result in halogin lithium exhange, subsequent capture by carbon monoxide or a CO equivilent would provide compound **3.89**. Subjecting aldehyde **3.89** to Seyferth-Gilber homologation conditions would afford acetylene **3.90**. Future work will focus on the realisation of ths fragment.



Scheme 3.12 Proposed alternative route towards intermediate **3.90**

3.7 End Game Strategies

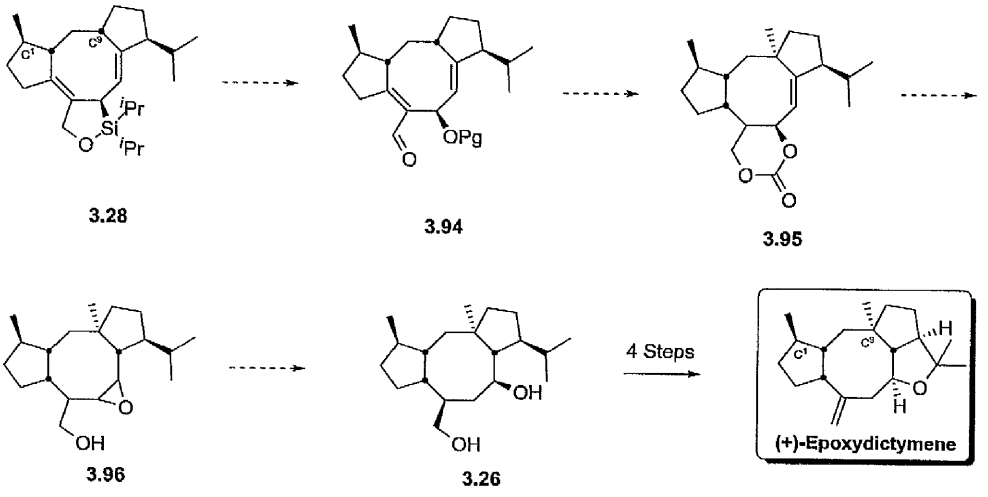
The proposed routes to complete the formal synthesis of (+)-epoxydictymene are outlined below. Advanced intermediates **3.27** and **3.28** are isomers and consequently the final synthetic transformations will differ in each approach.



Scheme 3.13 Approach A: Final synthetic transformations in the synthesis of (+)-epoxydictymene

Scheme 3.13 describes the transformation proposed to obtain (+)-epoxydictymene from advanced intermediate **3.27**. Cleavage of the TST *via* Woerpel's modification of a Tamao-Fleming oxidation should afford a diol, which in turn can be converted to the cyclic carbonate **3.91**.[49] At this stage we propose to install the final stereocenter, the quaternary methyl group, at the doubly allylic C^9 to provide intermediate **3.92**. It is likely that the angular methyl group at C^9 of cyclic carbonate **3.92** will promote a syn-oxidative addition by palladium. The succeeding stereospecific reduction, alkene isomerisation and directed epoxidation should then afford **3.93**. Regiospecific ring opening of the epoxide and directed hydrogenation of

the remaining trisubstituted olefin should provide **3.26** and complete the formal synthesis of (+)-epoxydictymene.

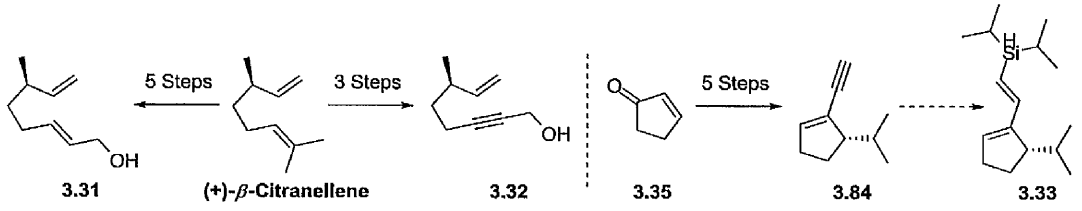


Scheme 3.14 Approach B: Final Synthetic transformations in the synthesis of (+)-epoxydictymene

Scheme 3.14 delineates a proposed route to (+)-epoxydictymene from advanced intermediate **3.28**. Treating tetracyclic **3.28** to Woerpel's modification of a Tamao-Fleming oxidation should afford the diol. A protection, mono-deprotection, oxidation sequence would then provide enone **3.94**. Stereioselective 1,4-reduction of enone and reduction of the resultant aldehyde would afford a second diol intermediate. From here the diol can be converted to the cyclic carbonate **3.95**, It is observed that the installation of the quaternary methyl at C^9 group route is more challenging than in **approach A** as intermediate **3.95** is not doubly allylic. The final sequence of transformations, an oxidative addition of palladium, reduction, epoxidation and an epoxide ring opening should proceed in an analogous manor as described for **approach A** to complete the formal synthesis of (+)-epoxydictymene.

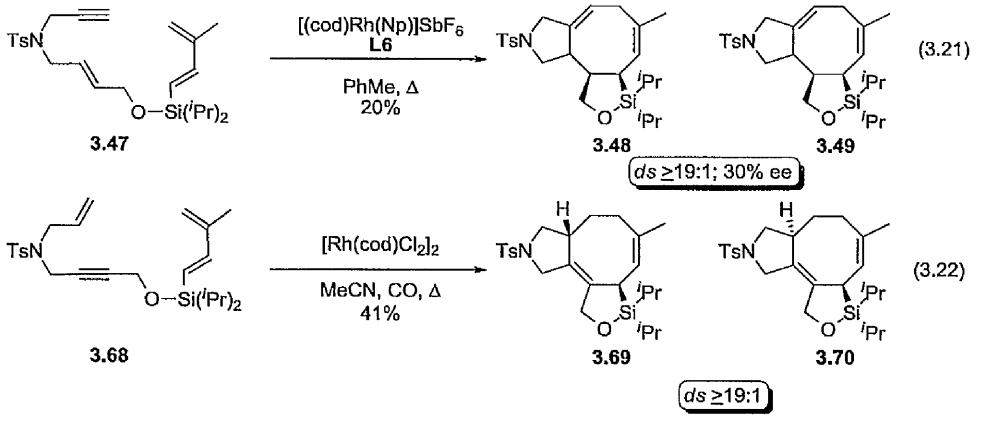
3.8 Conclusion

In conclusion, we have completed the synthesis of fragments **3.31** and **3.32** in 4 steps (38% overall yield) and 8 steps (15% overall yield), respectively (Scheme 3.15). Efforts to complete the synthesis of fragment **3.33** are ongoing. Our initial route proved unsuccessful and an alternative course has been proposed and is currently being investigated.



Scheme 3.15 Summary and Outlook

Gratifyingly, preliminary studies on model systems investigating the validity of approaches **A** and **B** provided encouraging results. These investigations represent the first examples of an asymmetric diene-eneyn [(4+2+2)] cycloisomerisation and a novel rhodium-catalysed [(4+2+2)] cycloisomerisation.



3.9 Experimental

3.9.1 General

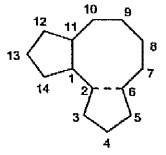
All reactions were performed in oven-dried (125 °C) or flame-dried glassware under an inert atmosphere of argon unless otherwise specified. Syringes were oven-dried (125 °C) and then cooled in a desiccator. The following reaction solvents were dried using an alumina column solvent system: toluene (PhMe), diethyl ether (Et_2O) and dichloromethane (DCM) were dried over alumina column solvent system using the method of Grubbs.[50] The following reaction solvents were distilled from the indicated drying agents: tetrahydrofuran (THF) (sodium, benzophenone), Hexanes (CaH_2), benzene (PhH) (sodium) and acetonitrile (MeCN) (CaH_2). Triethylamine (Et_3N) was distilled from CaH_2. All starting material and reagents were purchased from Acros, Aldrich, Alfa Aesar, Fluka, and Strem chemical companies and were used without further purification unless noted otherwise. Analytical thin layer chromatography (TLC) was performed on Merck 60 F_{254} precoated silica-gel plates. Visualisation was accomplished with a UV light and/or a $KMnO_4$, or iodine. Flash column chromatography (FCC) was performed by the method of Still with Merck Silica-gel 60 (230-400 mesh). Solvents for extraction and FCC were technical grade. Reported solvent mixtures for both TLC and FCC were volume/volume mixtures. Infrared spectra (IR) were obtained on a Perkin-Elmer spectrum one series FTIR spectrophotometer. Peaks are reported in cm^{-1} with the following relative intensities: vs (very strong), s (strong), m (medium), w (weak). The Liverpool University Mass Spectroscopy Centre and EPSRC National Spectrometry Centre, Swansea, recorded Mass spectra. High resolution electron-

impact electrospray (ESI) mass spectra were obtained on a Micromass LCT Mass spectrometer and LTQ Orbitrap XL. The specific rotation was measured with a PerkinElmer Model 343 Plus polarimeter.

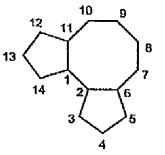
^{1}H-NMR and ^{13}C-NMR were recorded on a Bruker DRX-500 MHz NMR spectrometer in the indicated deuterated solvents. For ^{1}H-NMR, $CDCl_3$ and C_6D_6 were set to 7.26 ppm ($CDCl_3$ singlet) and 7.16 (C_6D_6 singlet) respectively and for ^{13}C-NMR, CDC^{13} and C_6D_6 were set to 77.16 ppm ($CDCl_3$ center of triplet) and 128.06 ppm (C_6D_6 center of triplet) respectively. All values for ^{1}H-NMR and ^{13}C-NMR chemical shifts for deuterated solvents were obtained from Cambridge Isotope Labs. Data are reported in the following order: chemical shift in ppm (δ) multiplicity, which are indicated by br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), h (heptet), m (multiplet)); assignment of 2nd order pattern, if applicable; coupling constants (*J*, Hz); integration. All ^{13}C-NMR spectra were reported using the descriptor (o) and (e) referring to whether the peak is odd or even, respectively, and correlate to an attached proton test (ATP) experiment.

All high-performance liquid chromatography (HPLC) were obtained using a Hewlett-Packard 1100 series HPLC equipped with a variable wavelength UV detector (set to 254 nm or 280 nm as appropriate). The instrument was fitted with a Rockland Technologies, Inc. Rx-Sil (Zorbax®, 4.6mm x 25cm) column.

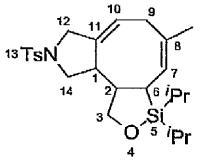
3.9.2 Nomenclature



bicyclo[9.3.0.]tetreadecane



tricyclo[9.3.0.$0^{2,6}$]tetreadecane



3.48

5,5-Diisopropyl-8-methyl-13-(phenylsulfonyl) -4-oxa,5-sila,13-aza-tricyclo[9.3.0.$0^{2,6}$] tetreadeca-7,10-diene

All tricyclic compound were named with using IUPAC Nomenclature of Organic Chemistry in accordance with the Von Baeyer system for naming polycyclic compounds.[51] For example, the main rings and bridge provide the core bicyclic skeleton. Numbering starts from the bridge head *via* the largest ring, placing the second bridge head at the lowest value. The second bridge head is identified by stating the number of bridging atoms, along with the two atoms to which the bridge is attached in superscript. Finally, heteroatoms, unsaturation and substituents are denoted by reference to the location and the appropriate description.

In the case of compound **3.48** the core ring system is bicyclo[9.3.0]tetreadecane. The second bridge head is identified by [$0^{2,6}$] (tricyclo[9.3.0.$0^{2,6}$]tetreadecane). Finally, the description of the compound is completed by the reference to the heteroatom's (oxygen = oxa, nitrogen = aza, silicon = sili), unsaturation (7,10-diene) and substituents (isopropyl and methyl) to provide the title 5,5-Diisopropyl-8-methyl-13-(phenylsulfonyl)-4-oxa,5-sila,13-aza-tricyclo[9.3.0.02,6]tetreadeca-7,10-diene.

3.9.3 Experimental Procedures

3.9.3.1 General Experimental Procedures

i. General procedure for the synthesis of substrates

To a stirred solution of eneyne (2 eq) in DCM (0.25 M) was added NBS (1.3 eq) in portions. The resultant solution was stirred for ca. 10 minutes at room temperature then added to a round-bottom flask containing **3.71** (1 eq), DMAP (0.15 eq), Triethylamine (3 eq) and DCM (0.25 M) *via* cannula. The resultant solution was stirred overnight at rt. The reaction mixture was concentrated *in vacuo* onto silica gel. Purification via FCC on silica gel (eluting with 2.5-10% Et_2O/Pentane gradient) provided the diene-ene-yne compound.

ii. General procedure for type A [(4+2+2)] cycloisomerisation

A 10 mL sealed tube was charge with **diene-ene-yne** (0.1 mmol) and [(cod)RhNp]SbF_6 (12.0 mg, 0.02 mmol) and **L4** (12.0 mg, 0.022 mmol). PhMe (0.25 M) was added under a stream of N_2 *via* syringe. The sealed tube was then heated in a 110 °C oil bath for ca. 16 hr. Concentration *in vacuo* and subsequent purification by FCC on silica gel (eluting with 5-20% Et_20/Pentane gradient) provided the tricyclic compound.

iii. General procedure for type B [(4+2+2)] cycloisomerisation

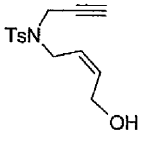
A 10 mL sealed tube was charge with **3.68** (0.1 mmol) and $[Rh(cod)Cl_2)_2]$ (0.01 mmol). MeCN (0.04 M) was added under a stream of N_2 *via* syringe. The atmosphere was purged with CO (x3). The sealed tube was then heated in a 132 °C oil bath for ca. 16 hr. Concentration *in vacuo* and subsequent purification by FCC on silica gel (eluting with 5-20% Et_20/Pent gradient) provided the tricyclic compound.

iii. General procedure for the synthesis of Moshers ester

To a stirred solution of allyl alcohol (1 eq) in dry pyridine (0.1 M) was added (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride (0.015 mL, 0.081 mmol) at 0 °C under argon. After being stirred for 48 h at the same temperature, the reaction mixture was partitioned between ethyl acetate (5 mL) and water (5 mL). The phases were separated and the combined extracts dried over anhydrous $MgSO_4$, filtered and evaporated under *vacuo*. Purification by flash chromatography over silica-gel (eluting with 10% EtOAc-hexanes) afforded the Mosher ester.

3.9.3.2 Experimental Procedures

(*Z*)-N-(4-hydroxybut-2-enyl)-4-methyl-N-(prop-2-ynyl)benzenesulfonamide[13]



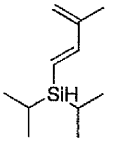
3.97

To a stirred solution of N-allyl-N-(4-(tert-butyldimethylsilyloxy)but-2-ynyl)-4-methylbenzene-sulfonamide (4.92 g, 12.5 mmol) in THF (125 mL) at 0 °C was added TBAF (1 M solution in Hexanes, 12.5 mL, 12.5 mmol) drop-wise. After 30 min the reaction was quenched by the addition of saturated aqueous NH_3Cl (125 mL), extracted with Et_2O (3 x 125 mL) and concentrated *in vacuo*. Purification *via* FCC on silica gel (eluting with 30% Et_2O/Hexanes) provided the title compound **3.97** (2.51 mg, 9.00 mmol, 72%) as a colourless, viscous oil.

^{1}H NMR (500 MHz, C_6D_6): δ 7.73 (d, J = 8.5 Hz, 2H), 7.31 (d, J = 8.5 Hz, 2H), 5.91-5.85 (m, 1H), 5.54-5.48 (m, 1H), 4.22 (t, J = 5.9 Hz, 2H), 4.10 (d, J = 2.4 Hz, 2H), 3.91 (d, J = 7.4 Hz, 2H), 2.43 (s, 3H), 2.07 (t, J = 2.5 Hz, 1H), 1.55 (br s, 1H).

IR (Neat): 3451 (w), 3260 (w), 2928 (w), 2119 (w), 1340 (s), 1154 (s), 658 (vs) cm^{-1}.

(*E*)-diisopropyl(3-methylbuta-1,3-dienyl)silane[13]



3.98

In the glove box and in the absence of light, a 100 mL one-neck round-bottom flask equipped with a magnetic stir bit and subaseal was charged with $Cp_2Zr(H)Cl$ (5.54 g, 21.6 mmol). DCM (40 mL) was added via syringe. To this mixture was added 2-methylbut-1-en-3-yne (2.06 mL, 21.5 mmol) via syringe. The resultant solution was stirred for ca. 30 minutes at rt, at which time the reaction became homogeneous. The reaction mixture was then cooled with an ice bath and quenched by the addition of iodine (5.54 g, 21.8 mmol) in portions. The resulting solution was then warmed to rt and stirred for 1 hr. The reaction was diluted with pentane and washed with saturated

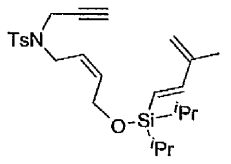
aqueous $Na_2S_2O_3$ (100 mL, 5%), dried with $MgSO_4$ and concentrated *in vacuo* (no heat). The light-sensitive crude vinyl iodide (3.09, 15.9 mmol, 74%) was carried onto the next reaction without further purification.

In the absence of light, a 250 mL three-necked round-bottom flask equipped with a thermometer was charged with crude vinyl iodide (3.09g, 14.3). Et_2O (100 mL) was added *via* syringe and the resultant solution was cooled to ca. –78 °C. ^{t}BuLi (1.7 M solution in pentane, 17.9 mL, 28.7 mmol) was added drop-wise *via* syringe, keeping the temperature below –60 °C. The orange solution was stirred at this temperature for two hours, at which time diisopropylchlopsilane (2.69 mL, 15.8 mmol) was added drop-wise *via* syringe. The reaction was then allowed to slowly warm to room temperature. The reaction mixture was filtered through a silica gel plug and subsequently washed with pentane and concentrated *in vacuo*. The resulting oil was purified by Kugelrohr distillation (15 mmHg, 90 °C) to afford the title compound **3.98** as a colourless oil (1.96 g, 10.8 mmol, 75%).

^{1}H NMR (500 MHz, C_6D_6): δ 6.77 (d, J = 18.9 Hz, 1H), 5.73 (dd, J = 18.9, 4.6 Hz, 1H), 5.08 (s, 1H), 5.03 (s, 1H), 3.65 (d, J = 3.9 Hz, 1H), 1.85 (s, 3H), 1.03-1.00 (m, 14H).

IR (Neat): 2942 (m), 2865 (m), 2099 (m), 1685 (w), 999 (m), 827 (vs), 802 (vs) cm^{-1}

N-((*Z*)-4-(diisopropyl((*E*)-3-methylbuta-1,3-dienyl)silyloxy)but-2-enyl)-4-methyl-N-(prop-2-ynyl)benzenesulfonamide[13]



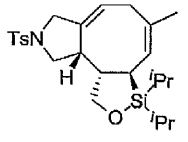
3.47

Compound **3.47** (0.77 g, 2.42 mmol, 77%) was prepared by general procedure **i** from **3.72** (1.15 g, 6.29 mmol) and was isolated as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.3 Hz, 2H), 6.74 (d, J = 19.3 Hz, 1H), 5.84-5.76 (m, 1H), 5.66 (d, J = 19.3 Hz, 1H), 5.41-5.36 (m, 1H), 5.11 (s, 1H), 5.03 (s, 1H), 4.31 (d, J = 4.9 Hz, 2H), 4.07 (d, J = 2.3 Hz, 2H), 3.87 (d, J = 6.7 Hz, 2H), 2.43 (s, 3H), 1.97 (t, J = 2.3 Hz, 1H), 1.84 (s, 3H), 1.06-0.98 (m, 14H).

IR (Neat): 3311 (w), 2943 (m), 2865 (m), 2010 (w), 1349 (m), 1161 (vs), 993 (m), 812 (s), 658 (vs) cm^{-1}.

5,5-Diisopropyl-8-methyl-13-(phenylsulfonyl)-4-oxa,5-sila,13-aza-tricyclo [9.3.0.0^{2,6}] tetreadeca-7,10-diene[13]



3.48

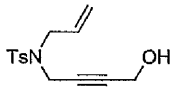
Compound **3.68** (14.0 mg, 0.03 mmol, 30% yield) was prepared by general procedure **ii** from **3.47** (46.0 mg, 0.1 mmol) and was isolated as a colourless oil.

^{1}H NMR (500 MHz, C_6D_6): δ 7.67 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 5.50 (d, J = 2.0 Hz, 1H), 5.26 (d, J = 9.9 Hz, 1H), 4.05 (dd, A or ABX, J_{AB} = 9.3 Hz, J_{AX} =

5.9 Hz, 1H), 3.79 (d, A of AB, J = 13.2 Hz, 1H), 3.50 (dd, B of ABX, J_{AB} = 13.2, J_{BX} = 2.1 Hz, 1H), 3.36-3.34 (m, 1H), 3.29 (dd, A of ABX, J_{AB} = 9.3, J_{BX} = 2.7 Hz, 1H), 3.26 (dd, J = 11.1, 9.4 Hz, 1H), 3.05 (dd, B of ABX, J_{AB} = 9.3, J_{BX} = 7.7 Hz, 1H), 2.97 (d, A of AB, J = 20.0 Hz, 1H), 2.64 (dd, B of ABX, J_{AB} = 20.0 Hz, J_{BX} = 2.6 Hz, 1H), 2.42 (s, 3H), 2.32-2.25 (m, 1H), 2.17 (dd, B of ABX, J_{AB} = 13.2 Hz, J_{BX} = 9.8 Hz, 1H), 1.72 (s. 3H), 1.09-0.95 (m, 14H).

IR (Neat): 2945 (m), 2861 (m), 1345 (vs), 1091 (m), 829 (m), 818 (s) cm^{-1}

N-allyl-N-(4-hydroxybut-2-ynyl)-4-methylbenzenesulfonamide[25]



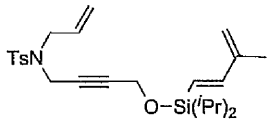
2.99

To a stirred solution of N-allyl-N-(4-(tert-butyldimethylsilyloxy)but-2-ynyl)-4-methylbenzene-sulfonamide (2.98 g, 7.57 mmol) in THF (75 mL) at 0 °C was added TBAF (1 M solution in Hexanes, 7.57 mL, 7.57 mmol) drop-wise. After 30 min the reaction was quenched by the addition of saturated aqueous NH_3Cl (75 mL), extracted with Et_2O (3 x 75 mL) and concentrated *in vacuo*. Purification *via* FCC on silica gel (eluting with 30% Et_2O/Hexanes) provided the title compound **3.99** (1.73 mg, 6.20 mmol, 82%) as a colourless, viscous oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 5.71 (ddt, J = 16.9, 10.3, 6.5 Hz, 1H), 5.29-5.21 (m, 2H), 4.08 (s, 2H), 3.97 (s. 2H), 3.8 (d, J = 6.5 Hz, 2H), 2.42 (s, 3H), 1.11 (br s, 1H).

IR (Neat): 3511 (bw), 2922 (w), 1598 (w), 1343 (m), 1326 (m), 115 (vs) cm^{-1}.

(*E*)-N-allyl-N-(4-(diisopropyl(3-methylbuta-1,3-dienyl)silyloxy)but-2-ynyl)-4-methylbenzenesulfonamide



3.68

Compound **3.68** (390 mg, 1.24 mmol, 72% yield) was prepared by general procedure **i** from **2.73** (235 mg, 1.70 mmol) and was isolated as a colourless oil.

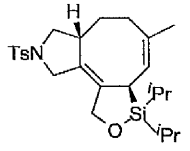
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, J = 8.2 Hz, 2H), 7.27 (d, J = 8.2 Hz, 2H), 6.75 (d, J = 19.3 Hz, 1H), 5.72 (ddt, J = 16.7, 10.2, 6.5 Hz, 1H), 5.63 (d, J = 19.3 Hz, 1H), 5.28-5.21 (m, 2H), 5.13 (s, 1H), 5.06 (s, 1H), 4.11 (s, 2H), 4.08 (s, 2H), 3.80 (d, J = 6.5, 2H), 2.40 (s, 3H), 1.85 (s, 3H), 1.05-0.98 (m, 14H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 150.34 (o), 143.45 (e), 143.28 (e), 136.21 (e), 132.11 (e), 132.11 (o), 129.48 (o), 127.90 (o), 120.75 (o), 199.92 (e), 118.57 (e), 84.26 (e), 77.40 (e), 51.81 (e), 49.13 (e), 36.26 (e), 21.59 (o), 17.88 (o), 17.42 (o), 17.38 (o), 12.43 (o).

IR (Neat): 2941 (w), 2866 (m), 1645 (w), 1352 (s), 992 (s), 823 (m) cm^{-1}

HRMS (ES $[M+Na]^+$ calcd for $C_{25}H_{37}NO_3NaSiS$ 482.2161, found 482.2467.

5,5-Diisopropyl-8-methyl-13-(phenylsulfonyl)-4-oxa,5-sila,13-aza-tricyclo[9.3.0.0^{2,6}]tetreadeca-1,7-diene



3.69

Compound **3.69** (18.6 mg, 0.04 mmol, 41% yield) was prepared by general procedure **iii** from **3.68** (46.0 mg, 0.1 mmol) and was isolated as a colourless oil.

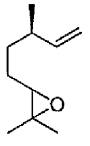
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 5.73 (s, 1H), 4.58 (d, A of AB, J = 16.3 Hz, 1H), 4.47 (d, B of AB, J = 16.3 Hz, 1H), 3.46 (d, A of ABX, J = 10.1, 8.0 Hz, 1H), 3.39 (d, A of AB, J = 9.7 Hz, 1H), 2.96 (d, B of AB, J = 9.7 Hz, 1H), 2.84 (dd, B of ABX, J = 10.1, 6.5 Hz, 1H), 2.20 (d, A of AB, J = 17.1 Hz, 1H), 2.08 (app. sept, J = 7.1 Hz, 1H), 1.78 (B of AB, J = 17.1 Hz, 1H), 1.72 (s, 3H), 1.13-0.93 (m, 14H), 0.75 (d, J = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 150.50 (e), 143.76 (e), 133.56 (e), 129.80 (o), 129.34 (e), 127.62 (o), 119.60 (o), 112.16 (e), 73.83 (e), 56.41 (e), 53.93 (e), 46.68 (e), 41.30 (e), 41.27 (o), 23.31 (o), 21.69 (o), 17.39 (o), 17.01 (o), 15.15 (o), 13.26 (o), 13.11 (o).

IR (Neat): 2863 (m), 1144 (w), 1461 (w), 1345 (m), 1152 (s).

HRMS (EI $[M+Na]^+$ calcd for $C_{25}H_{37}NO_3{}^{23}NaSiS$ 482.2161, found 482.2164.

2,2-Dimethyl-3-((*R*)-3-methylpent-4-enyl)oxirane[40]



3.100

(–)-β-Citronellene (15.0 mL, 83.0 mmol) was dissolved in DCM (830 mL) and cooled to 0 °C. To this stirred solution was added mCPBA (28.5 g, 83.0 mmol) and the resultant mixture stirred for 2 hr at the same temperature. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (400 mL) and saturated aqueous Na_2SO_3 (400 mL). The reaction mixture was then vigorously stirred for an

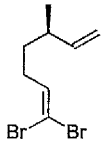
additional 15 min, and the layers were separated. The organic layer was then washed with saturated aqueous $NaHCO_3$ (400 mL), NaOH (400% 1N) dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purified by FCC on silica gel (eluting with 1-5% EtOAc/Hexanes gradient) provided the title compound **3.100** as a colourless oil (12.1 g, 78.0 mmol, 95%).

$[\alpha]_D^{20}$ –1.86 (*c* 4.5, Et_2O), lit. $[\alpha]_D^{20}$ –5.3 (*c* 4.1, Et_2O),

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.72-5.63 (m, 1H), 4.99-4.92 (m, 2H), 2.70 (app. H, J = 2.8 Hz, 1H), 2.18-2.14 (m, 1H), 1.53-1.48 (m, 3H), 1.42-1.34 (m, 1H), 1.30 (d, J = 1.0 Hz, 3H), 1.25 (d, J = 1.1 Hz, 3H), 1.00 (d, J = 6.8 Hz, 3H).

IR (Neat): 2959 (m), 1457 (m), 1377 (s), 1216 (w), 995 (m), 910 (vs), 872 (w) cm^{-1}.

(*R*)-4-methylhen-5-enal



3.75

To a stirred 0 °C suspension of periodic acid (6.0 g, 26.1 mmol) in Et_2O (125 mL) were added epoxide **3.100** (3.7 g, 23.7 mmol) in Et_2O (30 mL).[40] After 3 h, periodic acid (0.5 g, 2.37 mmol) was added. After the suspension was stirred for a total of 5 h, the reaction mixture was filtered through Celite® and washed with saturated aqueous $NaHCO_3$ (100mL), and saturated aqueous Na_2S0_3 (100mL, 5%). The combined aqueous washes were back-extracted with Et_2O (100mL), the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by FCC in silica gel (eluting with 10% Et_2O:pentane) afforded the corresponding aldehyde as

colourless oil (1.7 g, 15.3 mmol, 64%), which was used immediately without further purification.

To a stirred solution of tetrabromomethane (7.5 g, 22.7 mmol) in DCM (70 mL) at 0 °C was added triphenylphoshine (11.9 g, 45.5 mmol) in portions. After the mixture had been stirred for 30 min at 0 °C, the orange solution was cooled to -78 °C and a solution of aldehyde **3.74** (1.7 g, 15.6 mmol) in DCM (30 mL) was added drop-wise. After stirring for 1 hr, the reaction mixture was poured into pre-cooled (at 0 °C) and stirred Hexanes (85 mL). The precipitates were filtered off, and the filtrate was concentrated *in vacuo*. Purified by FCC on silica gel (eluting with 1-5% EtOAc/Hexanes gradient) afforded **3.75** as a colourless oil (3.8 g, 14.3 mmol, 94%).

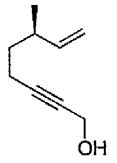
$[\alpha]_D^{20}$ –3.2 (*c* 1.00, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.38 (t, *J* = 7.3 Hz, 1H), 5.66 (ddd, *J* = 17.6, 10.1, 7.5 Hz, 1H), 5.01-4.95 (m, 2H), 2.17-2.03 (m, 3H), 1.44-1.39 (m, 2H), 1.01 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 143.86 (o), 138.87 (e), 113.53 (e), 88.75 (e), 37.50 (e), 34.62 (e), 31.05 (e), 20.26 (o).

IR (Neat): 2958 (w), 1054 (m), 995 (m), 797 (s), 750 (m) cm^{-1}.

(*R*)-6-methyloct-7-en-2-yn-1-ol



3.31

To a solution of dibromide **3.75** (3.0 g, 11.2 mmol) in THF (85 mL) at –78 °C was added nBuLi (2.5M, 12.48 mL, 31.2 mmol) down the side of the flask over a period of 3 min. After 1 hr, the cold bath was removed for 1 hr, and then the reaction mixture was recooled to –78 °C and paraformaldehyde (1.4 g, 44.8 mmol) was added in one portion. The reaction mixture was allowed to warm slowly to room temperature over a period of 3 hr. After 1 hr, Et_2O (100 mL) and water (100 mL) were added, and the aqueous layer was separated and extracted with Et_2O. The combined extracts were washed with saturated aqueous NaCl (100 mL), dried over $MgSO_4$, concentrated *in vacuo*. Purification *via* FCC on silica gel (eluting with 30% Et_2O:Hexanes) afforded **3.31** as an colourless oil (1.1 g, 1.77 mmol, 69%).

$[\alpha]_D^{20}$ –7.4 (*c* 0.80, $CHCl_3$).

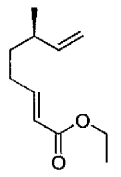
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.64 (app. quint., J = 8.8 Hz, 1H), 5.01-4.94 (m, 2H), 4.26-4.24 (m, 2H), 2.29-2.14 (m, 3H), 1.56 (s, 1H), 1.57-1.45 (m, 2H), 1.00 (d, J = 6.8 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 143.61 (o), 113.63 (e), 86.58 (e), 78.48 (e), 51.59 (e), 37.05 (o), 35.32 (e), 20.06 (o), 16.74 (e).

IR (Neat): 3329 (bw), 225 (w), 1013 (s), 912 (s) cm^{-1}.

HRMS (EI $[M+NH_4]^+$ calcd for $C_9H_{14}O$ 156.1383, found 156.1383.

(*R*,*E*)-Ethyl 6-methylocta-2,7-dienoate



3.76

Triethyl phosphinoacetate (13.9 mL, 69.6 mmol) was added drop-wise to a suspension of sodium hydride (2.8 g, 69.6 mmol) in PhMe (200 mL), at 0 °C. After the evolution of H_2 was complete, a solution of the aldehyde **3.74** (6.3 g, 55.7 mmol) in THF (100 mL) was added *via* cannula and the reaction mixture was stirred at 0 °C for 1 h and at room temperature for 2.5 hr. After quenching with saturated aqueous NaCl (300 mL), the layers were separated and the aqueous phase was extracted with Et_2O (400 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification *via* FCC (eluting with 10% EtOAc/Hexanes) provided **3.76** as a yellow oil (5.6 g, 30.8 mmol, 55 %).

$[\alpha]_D^{20}$ –5.83 (*c* 1.00, $CHCl_3$).

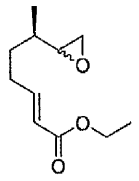
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.95 (dt, *J* = 15.7, 7.0 Hz, 1H), 5.80 (dt, *J* = 15.7, 1.5 Hz, 1H), 5.65 (ddd, *J* = 17.9, 9.9, 7.5 Hz, 1H), 4.99-4.93 (m, 2H), 4.17 (q, *J* = 7.2 Hz, 2H), 2.23-2.11 (m, 3H), 1.44 (app. q, *J* = 7.5 Hz, 2H), 1.28 (t, *J* = 7.2, 3H), 1.00 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.77 (e), 149.26 (o), 143.82 (o), 121.30 (o), 113.35 (e), 60.14 (e), 37.33 (o), 34.68 (e), 29.9 (e), 20.19 (o), 14.28 (o).

IR (Neat): 2963 (w), 2930 (w), 1720 (vs), 1654 (m), 118 (s), 1046 (s), 912 (s) cm^{-1}.

HRMS (EI $[M+H]^+$ calcd for $C_{11}H_{19}O_2$ 183.1380, found 182.1380.

(6*R*,*E*)-Ethyl 6-(oxiran-2-yl)hept-2-enolate



3.101

Compound **3.76** (6.4 g, 35.3 mmol) was dissolved in DCM (350 mL) and cooled to 0 °C. To this stirred solution was added mCPBA (12.2 g, 35.3 mmol). After 10 min at the same temperature, the reaction was allowed to warm to room temperature. After 14 h at the same temperature, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (200 mL) and saturated aqueous Na_2SO_3 (200 mL). The reaction mixture was then vigorously stirred for an additional 1 hr, and the layers were separated. The organic layer was then washed with saturated aqueous $NaHCO_3$ (200 mL), dried over anhydrous $MgSO_4$, concentrated *in vacuo*. Purification *via* FCC on silica gel (eluting with 1-5% EtOAc/Hexanes) provided the title compound **3.101** as a colourless oil (*ds* = 6:1, 6.0g, 30.3 mmol, 86%). (Major diastereoisomer depicted by *, minnor diastereoisomer depicted by $^+$)

$[\alpha]_D^{20}$ 4.66 (*c* 1.01, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.00-6-91 (m, 5H)*$^+$, 5.84 (dd, *J* = 15.7, 1.4 Hz)$^+$, 5.83 (dd, *J* = 15.6, 1.3 Hz, 4H)*, 4.19 (dq, *J* = 7.1, 1.2 Hz, 10H)*$^+$, 2.78-2.76 (m, 4H)*, 2.73-2.70 (m, 6H)*$^+$, 2.55-2.54 (m, 4H)*, 2.48-2.67 (m, 1H)$^+$, 2.33-2.30 (m, 2H)$^+$, 2.27 (app hex, *J* = 7.0 Hz, 8H)*, 1.74-1.69 (m, 1H)$^+$, 1.62-1.55 (m, 4H)*, 1.52-1.40 (m, 6H)*$^+$, 1.39-1.32 (m, 1H)$^+$, 1.30(t, *J* = 7.1 Hz, 15H)*$^+$, 1.05 (dd, *J* = 6.7, 0.9 Hz, 2H)*, 0.97 (dd, *J* = 7.0, 1.1 Hz, 3H)$^+$.

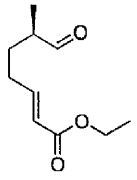
^{13}C NMR (125 MHz, $CDCl_3$): δ 166.86 (e)*, 166.84 (e)$^+$, 149.97 (o)$^+$, 148.68 (o)*, 121.79 (o)$^+$, 121.65 (o)*, 60.37(e)$^+$, 60.37 (e)*, 56.95 (o)$^+$, 56.70 (o)*, 46.87 (e)*,

45.81 (e)$^+$, 35.96 (o)$^+$, 35.62 (o)*, 33.17 (e)$^+$, 31.86 (e)*, 29.80 (e)*, 29.73 (o)$^+$, 16.93 (o)*, 15.93 (o)$^+$, 14.41 (o)*, 13.58(o)$^+$.

IR (Neat): 2963 (m), 2926 (w), 1717 (vs), 1266 (s), 1179 (s), 869 (m), 828 (m) cm^{-1}.

HRMS (EI $[M+H]^+$ calcd for $C_{11}H_{19}O_3$ 199.1329, found 199.1329

(6*R*,*E*)-Ethyl 6-methyl-7-oxohept-2-enolate



3.77

To a stirred 0 °C suspension of periodic acid (7.56 g, 33.2 mmol) in Et_2O (160 mL) were added epoxide **3.101** (5.98 g, 30.2 mmol) in Et_2O (40 mL).[40] After 3 h, periodic acid (0688 mg, 3.02 mmol) was added. After the suspension was stirred for a total of 5 h, the reaction mixture was filtered through Celite® and washed with saturated aqueous $NaHCO_3$ (100mL), and saturated aqueous Na_2S0_3 (100mL, 5%). The combined aqueous washes were back-extracted with Et_2O (100mL), the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by FCC in silica gel (eluting with 10% Et_2O:pentane) afforded **3.77** as colourless oil (847 mg, 14.6 mmol, 49%), which was used immediately without further purification.

$[\alpha]_D^{20}$ –3.87 (*c* 1.00, $CHCl_3$).

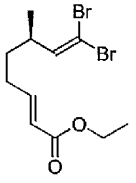
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.62 (d, *J* = 1.7 Hz, 1H), 6.91 (dt, *J* = 15.6, 6.9 Hz, 1H), 5.83 (dt, *J* = 15.6, 1.5 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.41-2.34 (m, 1H), 2.27-2.22 (m, 1H), 1.93-1.86 (m, 1H), 1.54-1.46 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 204.33 (o), 166.55 (e), 147.71 (o), 147.71 (o), 122.27 (o), 60.38 (e), 45.61 (o), 29.45 (e), 28.70 (e), 14.36 (o), 13.51 (o).

IR (Neat): 2979 (w), 2936 (w), 1716 (vs), 1654 (m), 1173 (s) cm^{-1}.

HRMS (EI $[M+H]^+$ calcd for $C_{10}H_{18}O_3$ 1851172, found 185.1169

(*R*,*E*)-ethyl 8,8-dibromo-6-methylocta-2,7-dienoate



3.78

To a stirred solution of tetrabromomethane (4.81 g, 14.5 mmol) in DCM (46 mL) at 0 °C was added triphenylphoshine (7.60 g, 29.0 mmol) in portions. After the mixture had been stirred for 30 min at 0 °C, the orange solution was cooled to -78 °C and a solution of aldehyde **3.77** (1.78 g, 9.66 mmol) in DCM (19 mL) was added drop-wise. After stirring for 1 hr, the reaction mixture was poured into pre-cooled (at 0 °C) and stirred Hexanes (60 mL). The precipitates were filtered off, and the filtrate was concentrated *in vacuo*. Purified by FCC on silica gel (eluting with 1-5% EtOAc/Hexanes gradient) afforded **3.78** as a colourless oil (3.20 g, 9.41 mmol, 97%). $[\alpha]_D^{20}$ –1.24 (*c* 1.00, $CHCl_3$).

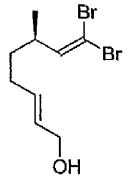
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.91 (dt, J = 15.6, 6.9 Hz, 1H), 6.15 (d, J = 9.5 Hz, 1H), 5.81 (dt, J = 15.6, 1.5 Hz, 1H), 4.16 (q, J = 7.2 Hz, 2H), 2.50-2.44 (m, 1H), 2.18 (q, J = 7.5 Hz, 2H), 2.21-1.43 (m, 2H), 1.26 (t, J = 7.2 Hz, 3H), 1.01 (d, J = 6.7 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.54 (e), 148.40 (o), 143.5 (o), 121.76 (o), 88.52 (e), 60.45 (e), 38.10 (e), 34.38 (o), 30.08 (o), 19.48 (e), 14.32 (e).

IR (Neat): 2964 (w), 2929 (w), 1716 (vs), 1655 (m), 1165 (s), 1045 (s), 765 (s) cm^{-1}.

HRMS (EI $[M+Na]^+$ calcd for $C_{11}H_{16}O_2Br_2Na$ 360.9415, found 360.9410

(6*R*,*E*)-8,8-Dibromo66-methylocta-2,7-diene-1-ol



3.79

To a solution of **3.78** (1.0 g, 2.94 mmol) in DCM (12 mL) at –78 °C was added DIBAL-H (1 M solution in Hexanes 8 mL) over 2 hr. The resultant solution wad stirred at this temperature for 1 hr, before the addition of saturated aqueous NH_4Cl (50 mL) and sodium potassium tartrate (50 mL, 30%). The organic layer were collected, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification *via* FCC on silica gel (eluting with 1-5% EtOAc/Hexanes) provided **3.79** as a colourless oil. (859 mg, 2.88 mmol, 98%)

$[\alpha]_D^{20}$ –4.0 (*c* 1.00, $CHCl_3$)

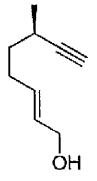
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.17 (d, J = 9.5 Hz, 1H), 5.66 (t, J = 3.9 Hz, 2H), 4.09 (s, 2H), 2.47 (app. H, J = 7.3 Hz, 1H), 2.07-2.04 (m, 2H), 1.49-1.32 (m, 2H), 1.32 (br. s, 1H), 1.01 (d, J = 6.7 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 144.03 (o), 132.43 (o), 129.63 (o), 87.75 (e), 63.83 (e), 37.98 (e), 35.53 (o), 29.96 (o), 19.33 (e).

IR (Neat): 3319 (bw), 2925 (m), 2851 (w), 1089 (m), 969 (vs), 846 (m) cm^{-1}.

HRMS (CI $[M+Na]^+$ calcd for $C_9H_{14}Br_2O$ 318.9309, found 318.9302

(*R*,*E*)-6-methyloct-2-en-7-yn-1-ol



3.32

To a solution of dibromide **3.79** (121 mg, 0.41 mmol) in THF (3 mL) at –78 °C was added nBuLi (2.5 mL, 0.50 mL, 0.50 mmol) down the side of the flask over a period of 3 min. After 1 hr, the cold bath was removed for 1 hr, and then the reaction mixture was recooled to –78 °C and water (1 mL) was added in one portion. The reaction mixture was allowed to warm slowly to room temperature over a period of 3 hr. After 1 hr, Et_2O (5 mL) and water (5 mL) were added, and the aqueous layer was separated and extracted with Et_2O. The combined extracts were washed with saturated aqueous NaCl (5 mL), dried over $MgSO_4$, concentrated *in vacuo*. Purification *via* FCC on silica gel (eluting with 30% Et_2O:Hexanes) afforded **3.31** as an colourless oil (51.0 mg, 0.36 mmol, 90%).

$[\alpha]_D^{20}$ –23.0 (*c* 0.56, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.71-5.70 (m, 2), 4.11 (s, 2H), 2.49-2.44 (m, 1H), 2.29-2.23 (m, 1H), 2.21-2.16 (m, 1H), 2.68 (d, J = 2.4 Hz, 1H), 1.59-1.51 (m, 2H), 1.28 (br s, 1H), 1.21 (d, J = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 132.33 (e), 129.55 (e), 87.850 (e), 68.52 (e), 63.75 (e), 36.02 (e), 29.83 (e), 25.15 (o), 20.88 (o).

IR (Neat): 3329 (b, m), 2932 (m), 1671 (w), 971 (s) cm^{-1}.

HRMS (EI $[M+NH_4]^+$ calcd for $C_9H_{14}O$ 156.1383, found 156.1386.

2-Iodocyclopent-2-enone[42]

3.80

To a stirred solution of cyclopent-2-enone (10.0 mL, 119 mmol) in THF (55 mL):H_2O (55 mL) was added K_2CO_3 (19.8 g, 143 mmol), iodine (45.4 g, 179 mmol) and DMAP (2.92 g, 23.8 mmol). Upon completion, the reaction mixture was diluted with EtOAc (10 mL) and washed with saturated aqueous $Na_2S_2O_3$ (20 mL) and HCl (20 mL, 0.1 M) successively. The mixture was subsequently extracted with EtOAc and dried over $MgSO_4$, before concentration *in vacuo*. Purification *via* FCC on silica gel (eluted with 10% EtOAc/Hexanes) afforded **3.80** (17.1 g, 8.24 mmol, 69%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (app. quin, J = 2.8 Hz, 1H), 6.20 (dt, J = 5.7, 2.2 Hz, 1H), 2.69 (app. hept. J = 2.3 Hz, 2H), 2.36-2.34 (m, 2H).

IR (Neat): 2923 (w), 1698 (vs), 1649 (m), 1179 (s), 827 (w) cm^{-1}.

(*R*)-2-Iodocyclopent-2-enol

3.81

To a solution of (*R*)-CBS (0.48 mL, 0.48 mmol) in THF (20 mL) at 0 °C were added simultaneously over 0.5 h solutions of ketone **3.80** (1.00 g, 4.81 mmol) in THF (6 mL) and borane tetrahydrofuran complex (2.88 mL, 2.88 mmol). The reaction mixture was stirred at 5 °C for 30 min, after which aqueous buffer (30 mL, pH 7)

was added, followed by H_2O_2 (5 mL, 30%). After being stirred for 20 min EtOAc (100 mL) was added and the solution was washed successively with HCl (100 mL, 1 M), H_2O (100 mL), saturated aqueous $NaHCO_3$ (100 mL), and saturated aqueous NaCl (100mL) and then dried ($MgSO_4$). Purification *via* FCC on silica gel (eluted with 40% EtOAc/Hexanes) provided **3.81** as a colourless oil (848 mg, 4.04 mmol, 84%).

SFC (Screen OD-H, 0.1% TFA in MeOH;EtOH, 212 nm, flow rate 4 mL/min, 42 °C): (*S*)-isomer *t*R 2.50 min (major), (*R*)-isomer *t*R 2.77 min (minor).

$[\alpha]_D^{20}$ –2.85 (*c* 1.00, CH_2Cl_2), lit $[\alpha]_D^{20}$ +21.0 (*c* 1.18, CH_2Cl_2),

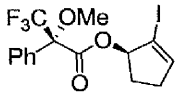
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.30 (s, 1H), 4.71-4.68 (m, 1H), 2.53-2.44 (m, 1H), 2.37-2.28 (m, 2H), 1.91-1.82 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 142.75 (o), 100.34 (e), 82.38 (o), 32.87 (e), 31.55 (e).

IR (Neat): 3207 (bm), 2911 (w), 2849 (w), 1603 (w), 1432 (w), 1069 (s), 808 (m) cm^{-1}.

HRMS (CI $[M+H]^+$ calcd for $C_5H_7O_1I_1$ 209.9536, found 209.9532

(*S*)-((*R*)-2-iodocyclopent-2-enyl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate



2.102

Compound **2.102** (31.0 mg, 0.07 mmol, 81% yield) was prepared by general procedure **iii** from **3.81** (19.0 mg, 0.09 mmol) and was isolated as a colourless oil.

$[\alpha]_D^{20}$ –43.9 (*c* 1.01, $CHCl_3$).

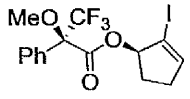
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59 (app. t, J = 3.4, 2H), 7.42-7.40 (m, 3H), 6.48-6.47 (m, 1H), 5.95-5.92 (m, 1H), 3.66 (d, J = 0.9 Hz, 3H), 2.52-2.42 (m, 2H), 2.37-2.31 (m, 1H), 1.83-1.80 (m, 1H), 1.56 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.29 (e), 147.22 (o), 132.05 (e), 129.72 (o), 128.49 (o), 127.79 (e), 122.21 (e), 90.53 (o), 86.59 (e), 55.70 (o), 33.26 (e), 30.11 (e).

IR (Neat): 2949 (w), 1743 (vs), 1605 (w), 1166 (vs), 717 (s) cm^{-1}.

HRMS (CI $[M+Na]^+$ calcd for $C_{15}H_{14}O_3F_3{}^{23}NaI$ 448.9838 found 448.9836.

(*R*)-((*R*)-2-iodocyclopent-2-enyl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate



2.103

Compound **2.103** (55.0 mg, 0.13 mmol, 81% yield) was prepared by general procedure **iii** from **3.81** (34.0 mg, 0.16 mmol) and was isolated as a colourless oil.

$[\alpha]_D^{20}$ −156.5 (*c* 1.00, $CHCl_3$).

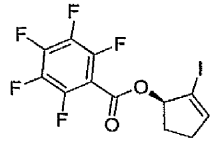
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59-7.58 (m, 2H), 7.42-7.41 (m, 3H), 6.23 (t, J = 2.5 Hz, 1H), 5.97-5.95 (m, 1H), 3.56 (s, 3H), 2.59-2.50 (m, 2H), 2.41-2.36 (m, 1H), 1.83-1.80 (m, 1H), 1.56 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.26 (e), 138.65 (o), 132.05 (e), 129.72 (e), 18.46 (o), 127.43 (o), 124.46 (e), (e), 122.16 (e), 118.31 (e), 83.50 (0), 55.56 (o), 30.97 (e), 30.06 (e).

IR (Neat): 2949 (w), 2850 (w), 1743 (vs), 1605 (w), 1021 (vs), 1011 (vs), 716 (s) cm^{-1}.

HRMS (EI $[M+NH_4]^+$ calcd for $C_9H_{14}O$ 156.1383, found 156.1341.

(*R*)-2-Iodocyclopent-2-enyl 2,3,4,5,6-pentafluorobenzoate



3.82

To a solution of alochol **3.81** (2.08 g, 9.88 mmol) in dry Et_2O (55 mL) was added pyridine (1.04 mL, 12.8 mmol), DMAP (121 mg, 0.98 mmol) and 2,3,4,5,6-pentafluorobenzoyl chloride (1.85 ml, 12.8 mmol). The resulting suspension was stirred at room temperature for 2 hr before poured into saturated aqueous NH_4Cl (55 mL). The mixture was extracted with Et_2O (3 x 55 mL). The combined organic phase was washed with saturated aqueous $NaHCO_3$ solution, saturated aqueous NaCl, dried over $MgSO_4$ and concentrated *in vacuo*. Purification *via* FCC on silica gel (eluting with 10% DCM:pentane) afforded **3.82** as a white solid (3.0 g, 7.31 mmol, 74%).

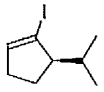
$[\alpha]_D^{20}$ –6.9 (*c* 1.00, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.54-6.53 (m, 1H), 6.00-5.97 (m, 1H), 2.61-2.53 (m, 2H), 2.43-2.34 (m, 1H), 2.07-2.00 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 158.783 (e), 146.62-144.19 (m, e), 144.49-142.17 (m, e), **90.60** (e), 87.10 (o), 33.27 (e), 30.22 (e).

IR (Neat): 2946(w), 1733 (s), 1494 (s), 1218 (vs), 995 (s), 820 (m) cm^{-1}.

(*R*)-1-iodo-5-isopropylcyclopent-1-ene



3.83

A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet and a rubber septum, was charged with a solution of lithium chloride (0.57 g, 13.3 mmol) and cyanocopper (0.60 g, 6.66 mmol) in THF (8 mL). The solution was cooled at 0 °C in an ice bath and then added diisopropylzinc (10.7 mL, 10.7 mmol). The mixture was stirred at 0 °C for 10 min. The ice bath was removed then the solution of **3.82** (1.8 g, 4.44 mmol) in THF (50 mL) was added dropwise at 25 °C. The resulting mixture was stirred at 25 °C for 12 h before poured into saturated aqueous NH_4Cl (10 mL, contained 25 % of aqueous NH_3). The mixture was extracted with Et_2O (3 x 25 mL). The combined ethereal phase was washed with saturated aqueous NaCl (25 mL) and dried over $MgSO_4$. Purification *via* FCC on silica gel (eluting with pentane) provided **3.83** (0.87 mg, 3.7 mmol, 83%) as a colourless oil.

$[\alpha]_D^{20}$ –2.1 (*c* 1.02, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.14 (q, J = 2.3 Hz, 1H), 2.73-2.68 (m, 1H), 2.33-2.20 (m, 2H), 2.09-2.03 (m, 1H), 1.86-1.78 (m, 1H), 1.75-1.69 (m, 1H), 0.95 (d, J = 7.0 Hz, 3H), 0.69 (d, J = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 139.92 (o), 101.59 (e), 57.67 (o), 33.98 (e), 29.41 (o), 21.51 (e), 21.13 (o), 14.97 (e).

IR (Neat): 2955 (s), 2922 (vs), 1605 (w), 1463 (m), 808 (m) cm^{-1}.

HRMS (CI $[M+H+]^+$ calcd for $C_8H_{13}I$ 236.0056, found 236.0056.

2-Bromocyclopent-2-enone[47]

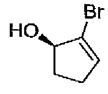
3.85

To a stirred solution of cyclopent-2-enone (2.60 mL, 31.7 mmol) in DCM (80 mL) 0 °C, was added a solution of bromine (1.63 mL, 31.7 mmol) in DCM (80 mL) drop-wise over 30 min. The solution was stirred at 0 °C for 1.5 hr and then triethylamine (7.37 mL, 52.9 mmol) was added drop-wise. The mixture was stirred at room temperature for 1.5 h for quenching by the addition of HCl (50 mL 3%). The organic layer was extracted and washed with saturated aqueous NaCl (50mL), dried over anhydrous $MgSO_4$. The reaction mixture was concentrated *in vacuo* onto silica gel. Purification via FCC on silica gel (eluted with 10% EtOAc/Hexanes) provided **3.85** as a white solid (4.67g, 29.1 mmol, 97%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (t, J = 2.9 Hz, 1H), 2.73 (dt, J = 4.5, 2.9 Hz, 2H), 2.57-2.55 (m, 2H).

IR (Neat): 3055 (w), 2922 (w), 1704 (vs), 1585 (s), 1001 (s) 660 (m) cm^{-1}.

(*R*)-2-Bromocyclopent-2-enol



3.86

To a solution of (*R*)-CBS (1.62 mL, 1.62 mmol) in THF (60 mL) at 0 °C were added simultaneously over 0.5 h solutions of ketone **3.85** (2.60 g, 16.2 mmol) in THF (20 mL) and borane tetrahydrofuran complex (9.69 mL, 9.69 mmol). The reaction mixture was stirred at 5 °C for 30 min, after which aqueous buffer (80 mL, pH 7)

was added, followed by H_2O_2 (20 mL, 30%). After being stirred for 20 min EtOAc (100 mL) was added and the solution was washed successively with HCl (100 mL, 1 M), H_2O (100 mL), saturated aqueous $NaHCO_3$ (100 mL), and saturated aqueous NaCl (100mL) and then dried ($MgSO_4$). Purification *via* FCC on silica gel (eluted with 40% EtOAc/Hexanes) provided **3.81** as a colourless oil (2.05 mg, 12.6 mmol, 78%).

$[\alpha]_D^{20}$ –27.6 (*c 2.40*, $CHCl_3$), lit. $[\alpha]_D^{20}$ +27.7 (*c* 2.39, $CHCl_3$),

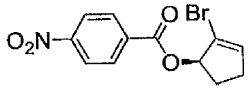
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (t, J = 3.0 Hz, 1H), 4.38-4.72 (m, 1H), 2.51-2.39 (m, 2H), 2.33-2.37 (m, 1H), 2.01 (br s, 1 H), 1.89 (ddt, J = 13.6, 9.0, 4.5 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 134.32 (o), 125.02 (e), 79.46 (o), 31.95 (e), 30.41 (e).

IR (Neat): 3207 (bs), 2911 (w), 1603 (w) cm^{-1}.

HRMS (CI $[M+NH_3]^+$ calcd for $C_5H_{14}O_1N_1Br_1$ 180.0019, found 180.0019

(*R*)-1-((2-bromocyclopent-2-enyloxy)methyl)-4-nitrobenzene[55]



2.104

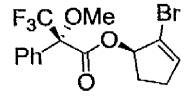
To the solution of (*R*)- **3.86** (6.52 mg, 0.04 mmol) in dry DCM (0.5 mL) added DMAP (4.89 mg, 0.04 mmol) and 1-(chloromethyl)-4-nitrobenzene (8.92 mg, 0.05 mmol). The resulting suspension was stirred at 25 °C for 2 h before concentrating *in vacuo*. Purification *via* FCC on silica gel (eluting with 10% Et2O:Hexanes) afforded the title compound **2.104** as a white solid (10.9 mg, 0.04 mmol, 87% yield).

HPLC (Chiralcel AD-H, 0.5% *i*-PrOH in hexane, 254 nm, flow rate 0.8 mL/min, 25 °C): (*S*)-isomer *t*R 49.37 min (major), (*R*)-isomer *t*R 52.60 min (minor).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.30 (d, J = 8.8 Hz, 2H), 8.24 (d, J = 8.8 Hz, 2H), 6.53 (s, 1H), 5.94-5.93 (m, 1H), 2.63-2.51 (m, 2H), 2.47-2.40 (m, 1H), 2.05-1.98 (m, 1H).

IR (Neat): 3114 (w), 2923 (w), 2859 (w), 1717 (vs), 1608 (m), 1522 (s), 1347 (s), 715 (vs) cm^{-1}.

(*S*)-((*R*)-2-iodocyclopent-2-enyl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate



3.105

Compound **3.105** (8.5 mg, 0.22 mmol, 72% yield) was prepared by general procedure **i** from **3.86** (49.0 mg, 0.30 mmol) and was isolated as a colourless oil.

$[\alpha]_D^{20}$ –47.8 (*c* 1.01, $CHCl_3$).

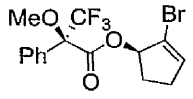
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (t, J = 3.5 Hz, 2H), 7.42-7.40 (m, 3H), 6.23 (t, J = 2.4 Hz, 1H), 5.95 (dt, J = 7.7, 3.2 Hz, 1H), 3.65 (d, J = 1.2 Hz, 3H), 2.54-2.40 (m, 2H), 2.36-2.29 (m, 1H), 1.86-1.80 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.26 (e), 138.64 (o), 132.00 (e), 129.72 (o), 127.36 (o), 126.77 (o), 124.47 (e), 122.18 (e), 118.33 (e), 83.51 (o), 55.56 (e), 30.97 (o), 30.07 (o).

IR (Neat): 2860 (w), 1735 (s), 1652 (m), 1494 (vs), 1219 (vs), 1162 (w) cm^{-1}.

HRMS (CI $[M+Na]^+$ calcd for $C_{15}H_{14}O_3F_3{}^{23}NaBr$ 402.9956 Found 402.9971

(*R*)-((*R*)-2-bromocyclopent-2-enyl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate



3.106

Compound **3.106** (109 mg, 0.288 mmol, 72% yield) was prepared by general procedure **i** from **3.86** (65.0 mg, 0.40 mmol) and was isolated as a colourless oil.

$[\alpha]_D^{20}$ –178.4 (*c* 1.00, $CHCl_3$).

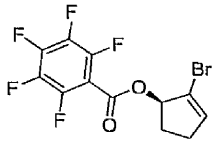
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60-7.58 (m, 2H), 7.43-7.40 (m, 3H), 6.23 (t, *J* = 2.5 Hz, 1H), 5.98-5.95 (m, 1H), 3.56 (s, 3H), 2.59-2.50 (m, 2H), 2.42-2.35 (m, 1H), 2.04-1.98 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.26 (e), 138.65 (o), 131.99 (e), 129.72 (o), 128.46 (o), 127.73 (o), 124.46 (e), 122.17 (e), 118.32 (e), 83.50 (o), 55.56 (o), 30.97 (e), 30.06 (e).

IR (Neat): 2951 (w), 1744 (s), 1620 (w), 1165 (vs), 922 (m), 715 (s) cm^{-1}.

HRMS (CI $[M+Na]^+$ calcd for $C_{15}H_{14}O_3F_3{}^{23}NaBr$ 402.9956 Found 402.9956.

(*R*)-2-Bromocyclopent-2-enyl 2,3,4,5,6-pentafluorobenzoate



3.87

To a solution of alochol **3.81** (1.73 g, 10.6 mmol) in dry Et_2O (60 mL) was added pyridine (1.12 mL, 13.8 mmol), DMAP (129 mg, 1.06 mmol) and 2,3,4,5,6-pentafluorobenzoyl chloride (1.99 ml, 13.8 mmol). The resulting suspension was

stirred at room temperature for 2 hr before poured into saturated aqueous NH_4Cl (60 mL). The mixture was extracted with Et_2O (3 x 60 mL). The combined organic phase was washed with saturated aqueous $NaHCO_3$ solution, saturated aqueous NaCl, dried over $MgSO_4$ and concentrated *in vacuo*. Purification *via* FCC on silica gel (eluting with 10% DCM:pentane) afforded **3.87** as a white solid (3.56 g, 9.98 mmol, 94%).

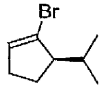
$[\alpha]_D^{20}$ –16.1 (*c* 1.00, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.29 (t, J = 2.5 Hz, 1H), 5.98 (dt, J = 7.7, 3.3 Hz, 1H), 2.62-2.52 (m, 2H), 2.43-2.37 (m, 1H), 2.09-2.03 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 158.76 (e), 146.50-144.42 (m, e), 144.42-14231 (m, e), 138.89 (o), 138.77-136.76 (m, e), 118.26 (o), 30.96 (e), 30.27 (e).

IR (Neat): 2950 (w), 1735 (vs), 1652 (m), 1494 (vs), 1219 (vs), 1162 (m) cm^{-1}

(*R*)-1-bromo-5-isopropylcyclopent-1-ene



3.88

A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet and a rubber septum, was charged with a solution of lithium chloride (0.57 g, 13.3 mmol) and cyanocopper (0.60 g, 6.66 mmol) in THF (8 mL). The solution was cooled at 0 °C in an ice bath and then added diisopropylzinc (10.7 mL, 10.7 mmol). The mixture was stirred at 0 °C for 10 min. The ice bath was removed then the solution of **3.87** (1.8 g, 4.44 mmol) in THF:NMP (1:1, 50 mL) was added dropwise at 25 °C. The resulting mixture was stirred at 25 °C for 12 h before poured into saturated aqueous NH_4Cl (10 mL, contained 25 % of aqueous NH_3). The mixture was

extracted with Et_2O (3 x 25 mL). The combined ethereal phase was washed with saturated aqueous NaCl (25 mL) and dried over $MgSO_4$. Purification *via* FCC on silica gel (eluting with pentane) provided **3.88** (0.64 g, 4.1 mmol, 67%) as a colourless oil.

$[\alpha]_D^{20}$ –2.9 (*c* 1.03, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.88 (q, *J* = 2.3 Hz, 1H), 2.76-2.72 (m, 1H), 2.27-2.20 (m, 2H), 2.14-2.08 (m, 1H), 1.91 (ddt, A of ABX, *J* = 13.8, 9.3, 5.7 Hz, 1H), 1.74 (ddt, B of ABX, *J* = 13.8, 8.6, 5.6 Hz, 1H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.74 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 131.19 (o), 125.85 (e), 54.91 (o), 31.47 (e), 28.45 (o), 22.24 (e), 20.81 (o), 15.23 (e).

IR (Neat): 2954 (s), 2932 (vs), 1628 (w), 1563 (m) cm^{-1}.

HRMS (CI $[M+H+]^+$ calcd for $C_8H_{13}I$ 188.0201, found 188.0234.

3.10 References

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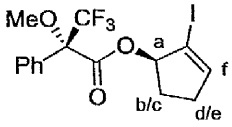
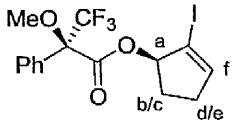
3.12 Appendix 1



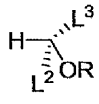
(*S*)-Mosher ester



(*R*)-Mosher ester

Assignment	δ (*S*)-Mosher ester [ppm]	δ (*R*)-Mosher ester [ppm]	$\Delta\delta^{SR}$ [ppm]
b	1.82	2.00	-0.18
c	2.47	2.55	-0.08
d	2.34	2.39	-0.05
e	2.47	2.55	-0.08
f	6.48	6.23	0.25

$\Delta\delta^{SR} = \delta^{S} - \delta^{R}$
$\Delta\delta^{SR} = + = L^2$
$\Delta\delta^{SR} = - = L^3$



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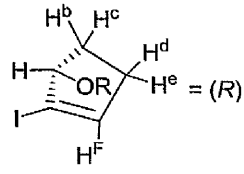
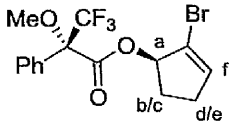


= (*R*)

3.13 Appendix 2



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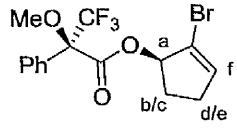
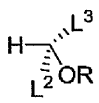


(*R*)-Mosher ester

Assignment	δ (*S*)-Mosher ester [ppm]	δ (*R*)-Mosher ester [ppm]	$\Delta\delta^{SR}$ [ppm]
b	1.83	2.01	-0.18
c	2.47	2.56	-0.09
d	2.33	2.39	-0.06
e	2.47	2.56	-0.09
f	6.23	6.23	0

$\Delta\delta^{SR} = \delta^{S} - \delta^{R}$
$\Delta\delta^{SR} = + = L^2$
$\Delta\delta^{SR} = - = L^3$



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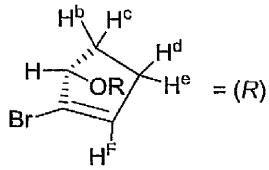

= (*R*)