Metal-Catalysed Desymmetrizations of *Meso*-Compounds



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A thesis submitted for the degree of

Doctor of Philosophy

Trinity 2019

Declaration

This thesis describes the work carried out in the Chemistry Research Laboratory, Oxford, between February 2016 and July 2019 under the supervision of Prof. Stephen Fletcher, and at Vertex Pharmaceuticals (Europe) Ltd, Abingdon, between April 2018 and June 2018 under the supervision of Dr. Robert Pullin. This thesis is a result of my own work, except when stated otherwise, and has not been submitted for any other degree at this or any other university.

Reece Jacques

Acknowledgements

Firstly, I would like to thank Steve for the opportunity to work in the group and all his supervision and support throughout my DPhil. Whenever I needed synthesis help, project ideas or someone to have a beer with, Steve was always there.

Thanks also to Rob Pullin who went above and beyond the usual expectations of an industrial supervisor, and thanks to all those at Vertex who welcomed me during my time there.

The Fletcher group has been a fantastic place to work over these last 3 and a half years and I would like to thank Rob, Elias, Chus, Nisha, Thomas, Alex H, Mireia, Philipp, Lucy, Sarah, Alex B, Wieland, Elena, Sedef, Joseph and many others old and new for all the pub trips, tequila and karaoke nights. An honourable mention to part II's Ivan and Josh for lifting the atmosphere in G4 to new heights in my final year. Thanks also to close friends Butler, Danny, Dave, Tom, Mus and Nada for always being around for good times.

I wouldn't even have the opportunity to write this if it wasn't for the support given to me from my parents. They have supported every decision I have made over the years and backed me all the way.

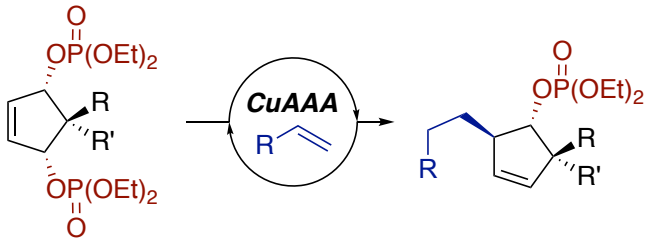
My thesis is full of chemistry and big words, but Jade has contributed more than can be written on paper. Thanks for always being there for me good times and bad.

A final thanks to the SBM CDT for funding and giving me the chance to study in Oxford.

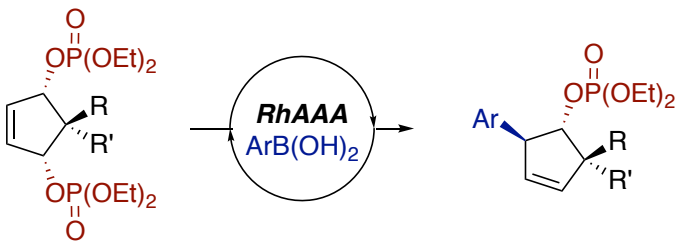
Abstract

The work contained in this thesis describes transition metal-catalysed desymmetrizations of a diverse range of *meso*-bisphosphates to afford enantiopure compounds with multiple contiguous stereocenters. The projects focus on the resolution of pro-quaternary centers in the *meso*-substrates, as these desymmetrizations are underrepresented in organic synthesis.

The first part of the thesis demonstrates the copper-catalysed asymmetric allylic alkylation of cyclic and acyclic *meso*-bisphosphates using alkylzirconium nucleophiles. The reaction was applied to increasingly complex starting materials, allowing access to products with up to 3 contiguous stereocenters and all-carbon quaternary centers with high enantioselectivity. Unsymmetrical bisphosphates were investigated to allow insight on the reaction mechanism and also underwent kinetic resolution successfully.



In the second part, rhodium-catalysed asymmetric allylic arylation was applied to *meso*-bisphosphates using boronic acid nucleophiles, which expanded on previous asymmetric sp^2-sp^3 couplings developed in the Fletcher group. Although the reaction was limited in substrate scope, high enantioselectivity was obtained. In addition, cyclic thiophosphates were investigated as electrophiles in a range of catalytic transformations.



List of Abbreviations

º	Degrees
*	Star
α	Alpha
AAA	Asymmetric allylic alkylation
AAAr	Asymmetric allylic arylation
Ac	Acetyl
ACA	Asymmetric conjugate addition
Ad	Adamantyl
Ar	Aryl
BINOL	1,1'-Bi-2-naphthol
BINAP	(2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl)
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
BQ	*para*-Benzoquinone
C_3-TunePhos	1,13-Bis(diphenylphosphino)-7,8-dihydro-6*H*-dibenzo [f,h] [1,5] dioxonin
Cl-MeO-BIPHEP	5,5′-Dichloro-2,2′-bis(diphenylphosphino)-6,6′-dimethoxy-1,1′-biphenyl
cod	1,5-Cyclooctadiene
coe	*cis*-Cyclooctene
COSY	Correlation spectroscopy
CPA	Chiral phosphoric acid
CPME	Cyclopentyl methyl ether
CuAAA	Copper-catalysed asymmetric allylic alkylation
CuAAC	Copper-catalysed azide-alkyne cycloaddtion
CuACA	Copper-catalysed asymmetric conjugate addition
Cy	Cyclohexyl
d	Doublet (NMR)
dd	Doublet of doublets (NMR)
ddd	Doublet of doublets of doublets (NMR)
DABCO	(1,4-Diazabicyclo[2.2.2]octane)

DCE	1,2-Dichloroethane
DIAD	Diisopropyl azodicarboxylate
DM-SEGPHOS	5,5′−Bis[di(3,5-xylyl)phosphino]-4,4′-bi-1,3-benzodioxole
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMSO	Dimethyl sulfoxide
DOSY	Diffusion-ordered spectroscopy
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dppp	1,3-Bis(diphenylphosphino)propane
dr	Diastereomeric ratio
DTBM-SEGPHOS	5,5′-Bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole
DYKAT	Dynamic kinetic asymmetric transformation
E	Entgegen
ee	Enantiomeric excess
eq	Equivalents
Et	Ethyl
ESI	Electrospray ionization
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
GC	Gas chromatography
GII	Grubbs Catalyst® 2^{nd} Generation
HFIP	Hexafluoroisopropanol
HMBC	Heteronuclear multiple bond correlation spectroscopy
HPLC	High-performance liquid chromatography
HRMS	High-resolution mass spectrometry
HSQC	Heteronuclear single quantum correlation spectroscopy
*i*Bu	Isobutyl
*i*Pr	Isopropyl
IR	Infrared
J	Coupling constant (Hz)

Josiphos	2-((Diphenylphosphino)ferrocenyl)ethyldicyclohexylphosphine
LUMO	Lowest unoccupied molecular orbital
M	Molarity
m	Multiplet (NMR)
Me	Methyl
Me-DUPHOS	1,2-Bis(2,5-dimethylphospholano)benzene
MeOH	Methanol
MeO-MOP	2-(Diphenylphosphino)-2′-methoxy-1,1′-binaphthyl
Mes	Mesityl
mmol	millimoles
MonoPhos®	(3,5-Dioxa-4-phosphacyclohepta[2,1-a:3,4-a′]dinaphthalen-4-yl) dimethylamine
Ms	Methanesulfonyl
m/z	Mass to charge ratio
nbd	Norbornadiene
NHC	*N*-heterocyclic carbene
NLE	Non-linear effect
NMO	N-Methylmorpholine N-oxide
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect spectroscopy
Ns	Nosyl
*n*Pr	Normal-propyl
p	Pentet (NMR)
PIDA	(Diacetoxyiodo)benzene
Pin	Pinacol
Ph	Phenyl
PhMe	Toluene
Phth	Phthalate
PivOH	Pivalic acid
P-Phos	2,2′,6,6′-Tetramethoxy-4,4′-bis(diphenylphosphino)-3,3′-bipyridine
PPL	Porcine pancreatic lipase
ppm	Parts per million
PTFE	Polytetrafluoroethylene

PyBOX	Pyridine-2,6-bis(oxazoline)
q	Quartet (NMR)
R	Rectus
RhAAAr	Rhodium-catalysed asymmetric allylic arylation
rr	Regioisomeric ratio
S	Sinister
s	Singlet (NMR) or Strong (IR)
SEGPHOS	5,5′-Bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole
SFC	Supercritical fluid chromatography
S_N2	Bimolecular nucleophilic substitution
S_N2'	Bimolecular nucleophilic substitution with allylic rearrangement
S_N2''	Bimolecular nucleophilic substitution with bishomoallylic rearrangement
sp^2	Orbital hybridisation: 2:1 p:s character
sp^3	Orbital hybridisation: 3:1 p:s character
t	Triplet (NMR)
TaniaPhos	1-Dicyclohexylphosphino-2-[α-(dimethylamino)-2-(dicyclohexylphosphino)benzyl]ferrocene
TaoPhos	3-(Diphenylphosphaneyl)-2'-(hydroxy(2-(trimethylsilyl)phenyl)methyl)-[1,1'-binaphthalen]-2-ol
*t*AmOH	*tert*-Amyl alcohol
TBDPS	*tert*-Butyldiphenylsilyl
TBME	*tert*-Butyl methyl ether
*t*Bu	*tert*-Butyl
*t*BuOH	*tert*-Butanol
TC	Thiophene-2-carboxylate
Tf	Trifluoromethanesulfonate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
tmdBH	Methylpentanediolborane
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
TOL-BINAP	2,2′-*p*-Tolyl-phosphino-1,1′-binaphthyl

W	Watt
Xylyl-P-Phos	2,2′,6,6′-Tetramethoxy-4,4′-bis(di(3,5-xylyl)phosphino)-3,3′-bipyridine
Z	Zusammen

Contents

1 Catalytic Intermolecular Desymmetrizations to Form All-Carbon Quaternary Centers – An Introduction **1**

1.1 All-Carbon Quaternary Centers via Addition/Coupling Desymmetrizations **3**

1.1.1 Cross Coupling 3

1.1.2 C-H Activation 5

1.1.3 Opening of Small Rings 9

1.1.4 Cyclopropenes 10

1.1.5 Cycloadditions 15

1.1.6 1,4-Additions 18

1.1.7 Conclusion 21

2 Desymmetrization of *Meso*-Bisphosphates via Cu-Catalysed Asymmetric Allylic Alkylation **23**

2.1 Asymmetric Allylic Alkylation **23**

2.2 Organometallic Nucleophiles in CuAAA **24**

2.2.1 Grignard Reagents 24

2.2.2 Organozinc Reagents 26

2.2.3 Organolithium Reagents 27

2.2.4 Organoaluminium/Organoboron Reagents 27

2.2.5 Organozirconium Reagents 28

2.3 Project Aims **30**

2.4 Results and Discussion **31**

2.4.1 Reaction Optimisation 31

2.4.2 Ring Size and Alkene Scope 36

2.4.3 Quaternary Centers 39

2.4.4 Other Substrates 45

2.4.5 Product Derivatisations 47

2.4.6 Kinetic Resolution of Cyclic Bisphosphates 48

2.4.7 Postulated Mechanism 51

2.4.8 Kinetic Resolution of Linear Bisphosphates 54

2.5 Conclusions and Future Work **60**

3 Desymmetrization of *Meso*-Bisphosphates via Rh-Catalysed Asymmetric Allylic Arylation **63**

3.1 Rh-Catalysed Asymmetric Allylic Arylation **63**

3.2 Project Aims **67**

3.3 Results and Discussion **68**

3.3.1 Reaction Optimisation 68

3.3.2 Electrophile Scope 70

3.3.3 Nucleophile Scope 72

3.3.4 Desymmetrization of Cyclic Phosphates 75

3.4 Conclusions and Future Work **82**

4 Experimental Information 84

4.1 General Information 84

4.2 Chemicals 86

4.3 General Procedures 87

4.4 Experimental Procedures for Chapter 2 95

4.5 Experimental Procedures for Chapter 3 233

5 References 260

1 Catalytic Intermolecular Desymmetrizations to Form All-Carbon Quaternary Centers – An Introduction

All-carbon quaternary stereogenic centers are key structural motifs found in many biologically active natural products and can enhance the biological activity of small molecule drugs.[1–4] Conformational restraints in molecules bearing quaternary centers improve target binding by reducing the entropic penalty incurred when interacting with the active site of proteins.[5] Furthermore the absolute configuration of these stereogenic centers can also greatly influence the interaction with homochiral proteins.[6]

Despite these advantages all-carbon quaternary centers are underrepresented in pharmaceuticals, with most structures derived from natural products and chiral pool materials.[7] This reflects the synthetic challenge in synthesising molecules with quaternary centers, and in particular controlling the stereochemistry.[8,9] Significant efforts have been made to develop reliable, enantioselective synthetic methods towards quaternary centers, but a lack of approved drugs containing these motifs despite the obvious biological benefits shows new methods are highly sought after. Strategies in this field are limited by the all-carbon nature of these systems, meaning there are limited functional groups which can access these structures. Common strategies (Figure 1, left) use prochiral sp^2 carbons such as fully substituted enolates,[10,11] disubstituted carbenes[12,13] and tri/tetrasubstituted alkenes.[14] These functional groups are often sterically hindered, and enantiofacial discrimination can be difficult between 2 carbon substituents. In some cases compounds containing pre-existing quaternary centers can undergo

kinetic resolution to give the desired enantiomer, but these transformations are limited to 50% yield.[15]

Another strategy is to use a desymmetrization reaction. These reactions apply enantioselective protocols to symmetrical substrates, with theoretical yields of 100%.[16–19] Using these transformations on compounds which contain a preformed all-carbon quaternary center, whether prochiral or *meso*, offer an alternative to using prochiral sp^2 substrates (Figure 1.1, right).[20] This avoids the need of specific functional groups, allowing a wider range of reactions to be considered. In addition, bond forming events can occur at a distance from the congested quaternary center, allowing fragments which are sterically demanding or not compatible with methods involving a prochiral sp^2 center to be included.

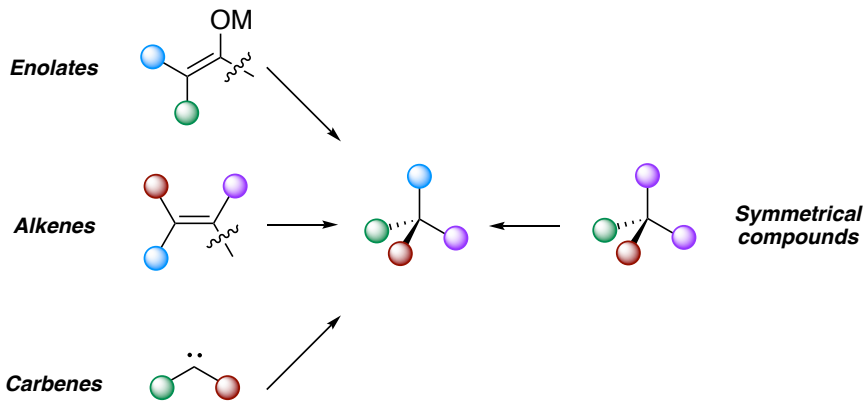


Figure 1.1. Strategies towards all-carbon quaternary centers.

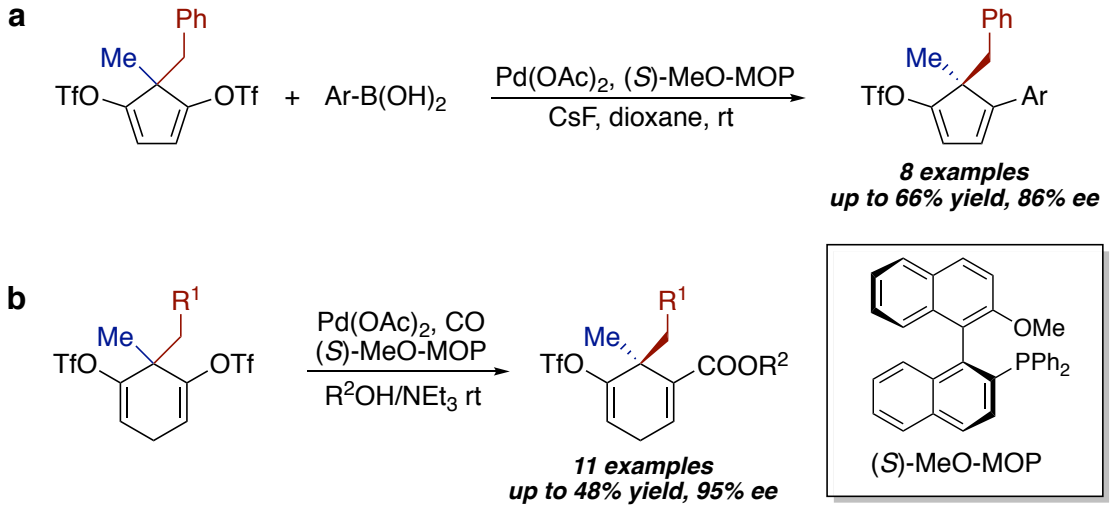
These advantages mean that developing catalytic enantioselective desymmetrizations of prochiral and *meso* compounds with preformed all-carbon quaternary centers is currently an active, exciting area of research. Many desymmetrizing intramolecular reactions exist with preformed all-carbon quaternary centers, but the focus of this introduction will be intermolecular desymmetrizations via addition or coupling reactions, which are underrepresented in this field.

1.1 All-Carbon Quaternary Centers via Addition/Coupling Desymmetrizations

1.1.1 Cross Coupling

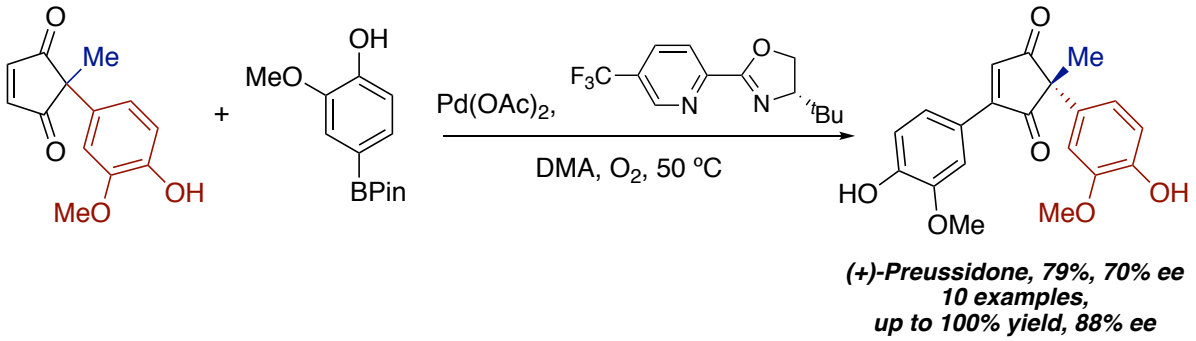
The development of transition metal catalysed cross coupling reactions has transformed the way that synthetic chemists construct carbon-carbon bonds, resulting in the awarding of the 2010 Nobel Prize in Chemistry to the pioneers of these reactions.[21–23] These valuable and robust transformations have been adapted for asymmetric catalysis very successfully and applications in the formation of quaternary centers via desymmetrization have followed.[24]

The Willis group reported the desymmetrizing Suzuki-Miyaura coupling of a prochiral cyclopentadiene bistriflate with moderate enantioselectivity. The use of the monodentate MeO-MOP ligand with $Pd(OAc)_2$ allowed a variety of aryl boronic acids to be coupled, whilst resolving the pro-quaternary center substituted with a methyl and benzyl group (Scheme 1.1 a).[25] A related system was applied by the Willis group in 2010 to a 6 membered ring analogue of the bistriflate in a desymmetrizing carbonylation reaction. Again resolution of the pro-quaternary center could be achieved, but yields suffered as a result of bis-carbonylation (Scheme 1.1 b).[26]



Scheme 1.1. a) Desymmetrization of cyclopentadiene bistriflates via Suzuki-Miyaura coupling. **b)** Desymmetrization of cyclohexadiene bistriflates via Pd-catalysed carbonylation.

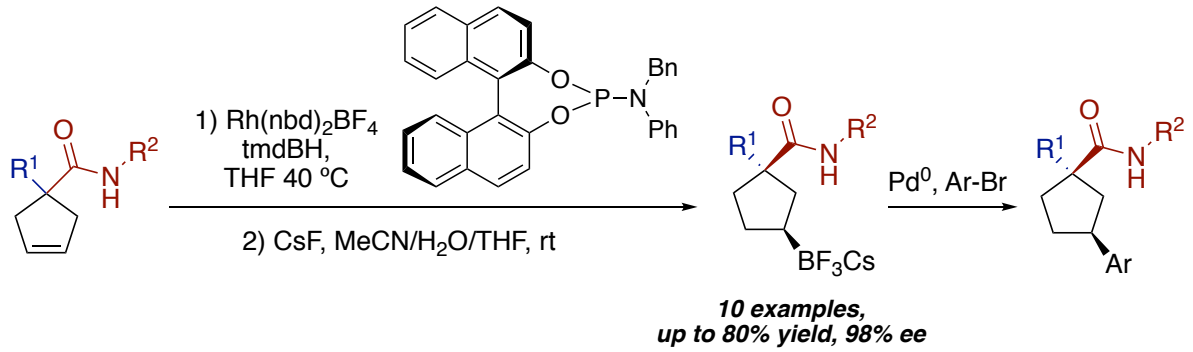
An oxidative Heck coupling from the Lee group was shown to be effective in resolving the pro-quaternary center of cyclopentene-1,3-dione derivatives. Using Pd^{II} catalysis with PyOX ligands under an O_2 atmosphere, conditions pioneered by Sigman,[27] allowed coupling of arylboroxine and pinacol boronic esters with moderate ee, which could be applied to the synthesis of (+)-preussidone in 79% yield and 70% ee (Scheme 1.2).[28]



Scheme 1.2. Oxidative Heck coupling of cyclopentane-1,3-dione derivatives.

The Takacs group applied a directed, enantioselective hydroboration to prochiral cyclopentenes with a amide substituent with up to 94% ee using rhodium-phosphoramidite catalysis. The pro-quaternary center was tolerant of multiple substituents including a CF_3 group. Conversion of the boronate ester products into trifluoroborate salts then allowed

stereoretentive Suzuki-Miyaura coupling with variety of aryl halides with good yields (Scheme 1.3).[29]

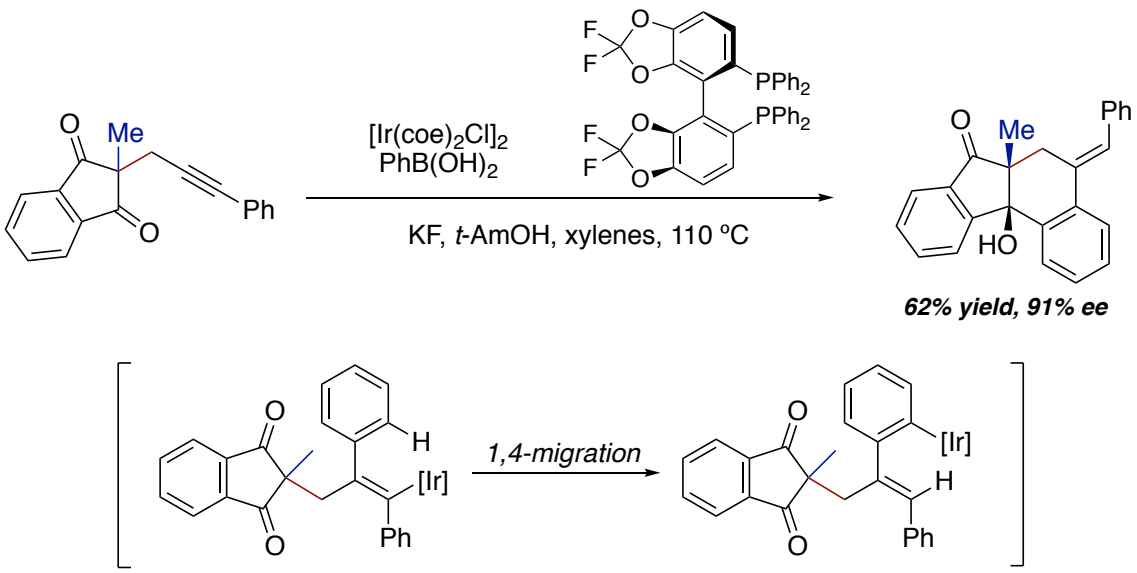


Scheme 1.3. Desymmetrizing hydroboration followed by Suzuki-Miyaura coupling.

1.1.2 C–H activation

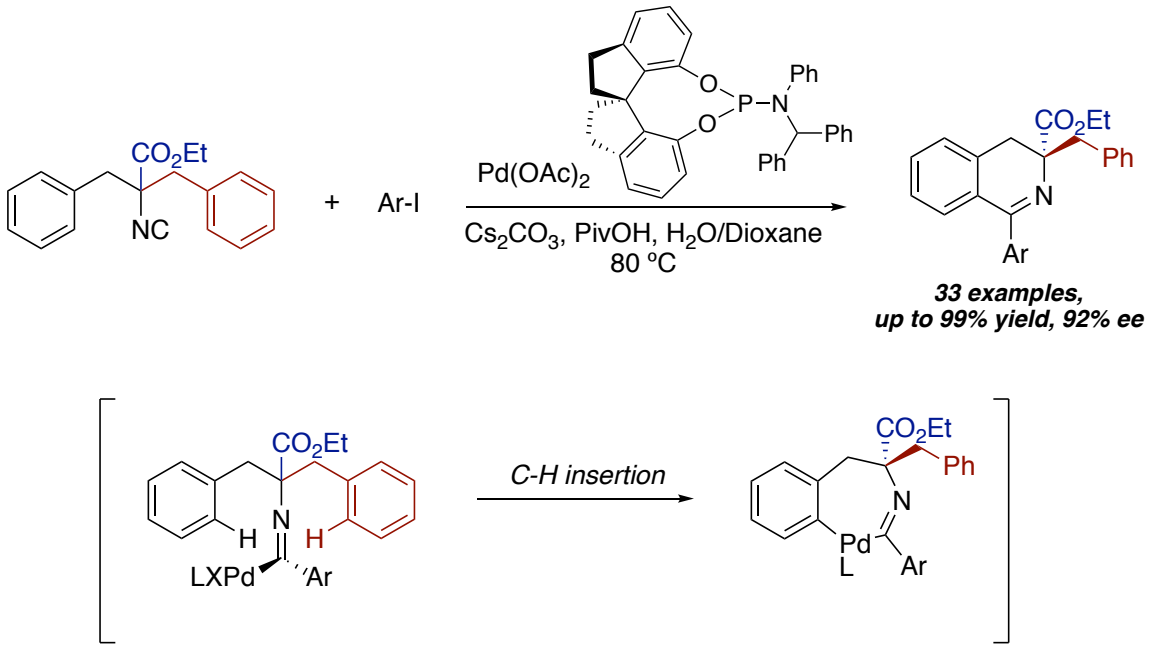
C–H activation has emerged as an extremely efficient way of constructing organic molecules. Rather than rely on functional groups to direct reactivity, inert C–H bonds can instead take on this role, allowing for elegant, economical transformations.[30,31] Recently more focus has been applied to catalytic enantioselective C–H functionalisations where symmetrical starting molecules have proven to be useful.[32,33]

Many C–H functionalisation reactions involve an sp^2 hybridised C-H bond which a transition metal catalyst can insert into. This is illustrated by an iridium-catalysed arylative cyclisation of symmetrical, alkynyl substituted 1,3 diones by Lam and co-workers. Insertion of an iridium-aryl species onto an alkyne followed by a 1,4-migration of the iridium species with an aryl C–H bond and subsequent 1,2-addition affords complex polycyclic products with high enantioselectivity (Scheme 1.4). [34]



Scheme 1.4. Iridium-catalysed arylative cyclisation of symmetrical alkynyl 1,3-diones.

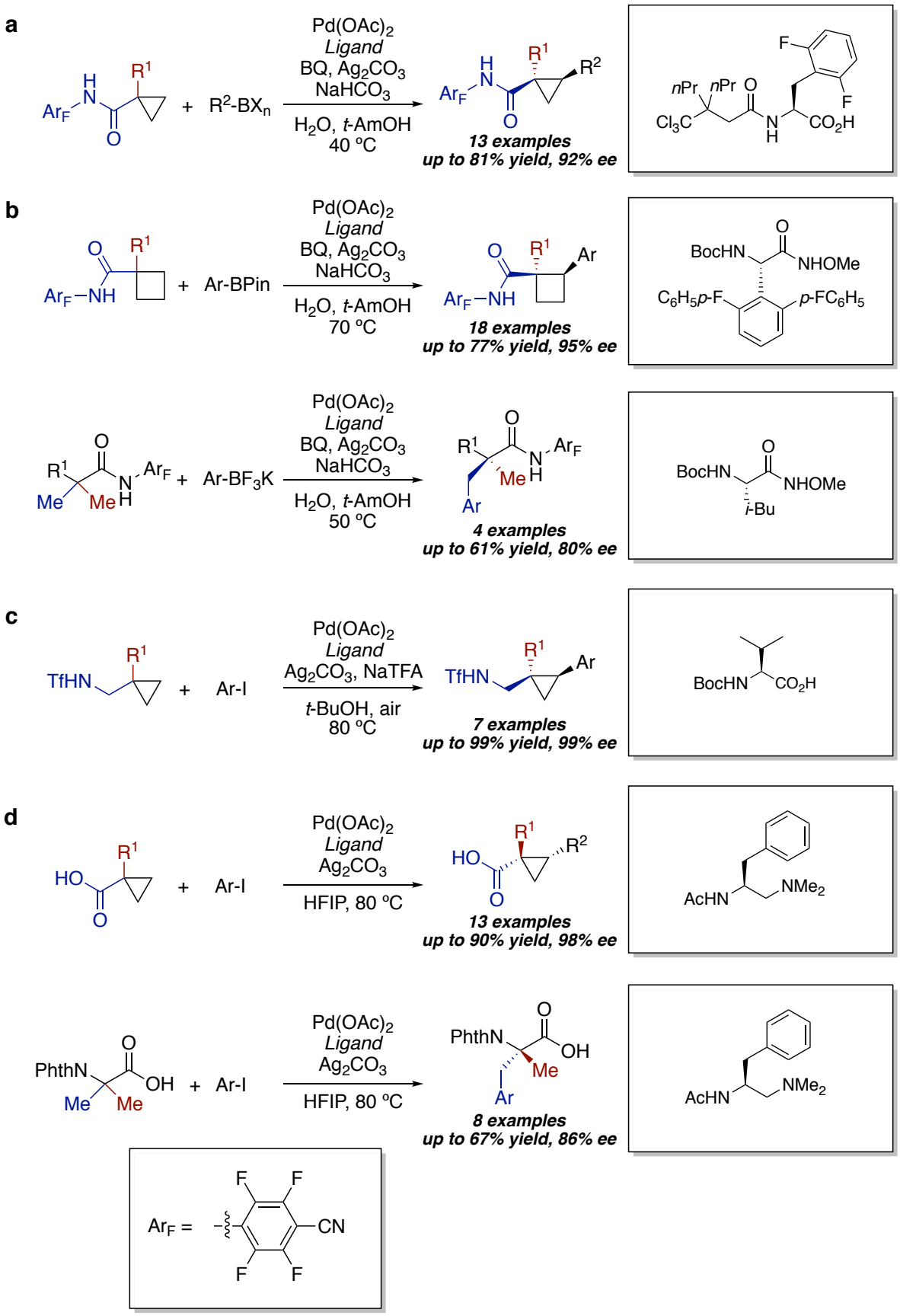
An example from the Zhu and You groups uses palladium catalysed C–H imidolyation of a symmetrical isocyanide with aryl iodides (Scheme 1.5). Insertion of palladium into the isocyanide followed by activation of an accessible sp^2 C–H bond and reductive elimination gives dihydroisoquinolines bearing an all-carbon quaternary center with excellent yields and enantioselectivities. The reaction was also shown to be tolerant of heterocyclic aryl iodides.[35]



Scheme 1.5. Desymmetrizing C–H imidoylation of symmetrical isocycanides.

Efforts towards enantioselective sp^3 C–H activation in desymmetrizations have also been successful. The group of Jin-Quan Yu has been particularly prolific in this area, using palladium catalysis to distinguish between enantiotopic sp^3 C-H substituents. Small strained rings in particular where C–H bonds have more s character and therefore more acidity are ideal candidates for sp^3 C–H activation.

The first of these reports in 2011 used an electron deficient amide substituted cyclopropane with $Pd(OAc)_2$ and an amino acid derived ligand to couple various sp^2 hybridised boron species to the cyclopropyl ring in up to 92% ee, giving cyclopropanes with all-carbon quaternary centers. The co-ordination of the acidic amide substituent facilitated C–H activation in this case (Scheme 1.6 a).[36] In 2014 a similar protocol was applied to cyclobutanes using a hydroxamic acid ligand with up to 95% ee. More interestingly the conditions were applied to related acyclic *gem*-dimethyl compounds with up to 80% ee in specific cases. To this day examples of intermolecular desymmetrizations of acyclic compounds are extremely limited and highlight future research opportunities (Scheme 1.6 b).[37] Methylamine substituted cyclopropanes can also be coupled to aryl iodides using Pd^{II}/Pd^{IV} catalysis with NBoc-Val as a ligand with high levels of enantioselectivity. An acidic NHTf moiety directs C–H activation in this reaction (Scheme 1.6 c).[38] With most previous examples requiring a directing group the enantioselective arylation of cyclopropanes with free carboxylic acids was achieved in 2018 using an ethylenediamine derived ligand. This protocol again uses Pd^{II}/Pd^{IV} catalysis with aryl iodides and can also be applied to acyclic *gem*-dimethyl compounds with a carboxylic acid and *N*-phthalimide substituents with good yields and moderate enantioselectivities of up to 86% (Scheme 1.6 d).[39]

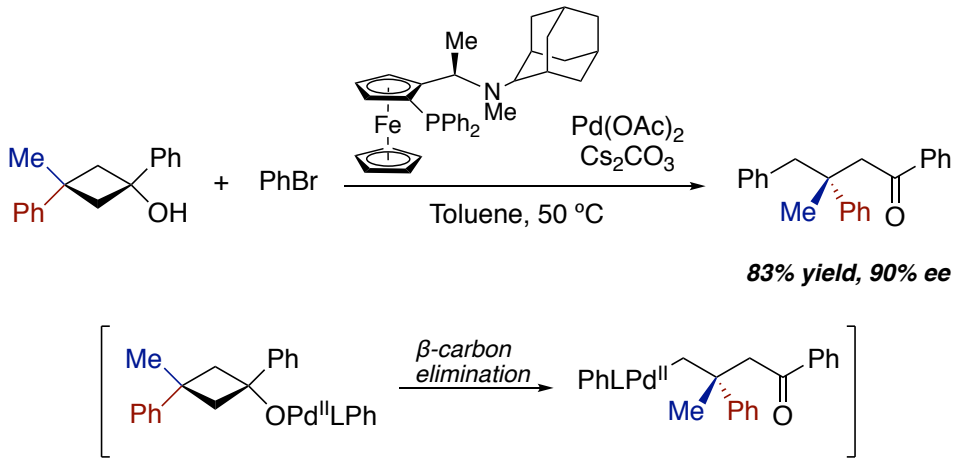


Scheme 1.6. All-carbon quaternary center forming desymmetrizations via C(sp^3)–H activation from the Jin-Quan Yu group. **a)** C–H activation of amide substituted cyclopropanes. **b)** C–H activation of amide substituted cyclobutanes. **c)** C–H activation of methylamine substituted cyclopropanes. **d)** C–H activation of carboxylic acid substituted cyclopropanes.

1.1.3 Opening of Small Rings

The release of ring strain when opening a 3 or 4 membered ring can be a major driving force for various reactions, such as nucleophilic addition and C-C bond insertions with transition metal complexes.[40] As a result these small rings have made ideal substrates for catalytic desymmetrizations.

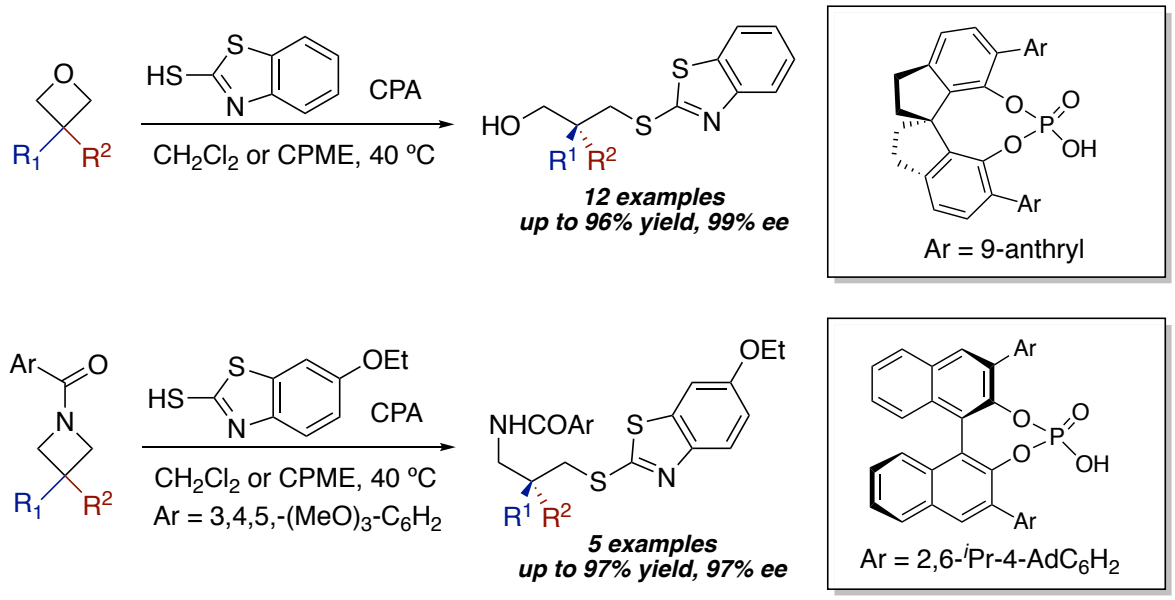
The enhanced ring strain of a cyclobutane with geminal substitution and the 1 and 3 positions was exploited by Uemura and co-workers using an enantioselective Pd-catalysed C-C bond cleavage with aryl bromides. Examples with quaternary centers were limited with one giving useful enantioselectivity. The reaction is believed to proceed via a Pd^{II} alkoxide intermediate, which undergoes a β-carbon elimination to open the ring to form a ketone. Subsequent reductive elimination affords the arylated product (Scheme 1.7).[41] This example is a rare case of an intermolecular desymmetrization of a *meso* compound with a preformed all-carbon quaternary center.



Scheme 1.7. Desymmetrizing C-C bond cleavage of a *tert*-cyclobutanol.

Small heterocycles have also been explored in ring opening desymmetrizations. The Sun group reported the chiral phosphoric acid (CPA) catalysed ring opening of *gem*-disubstituted oxetanes and azetidines using 2-mercaptobenzothiazole nucleophiles. DFT calculations

highlighted the bifunctional nature of the CPA catalyst which exploits hydrogen bonding interactions to bring the coupling partners together in a selective fashion (Scheme 1.8).[42,43]



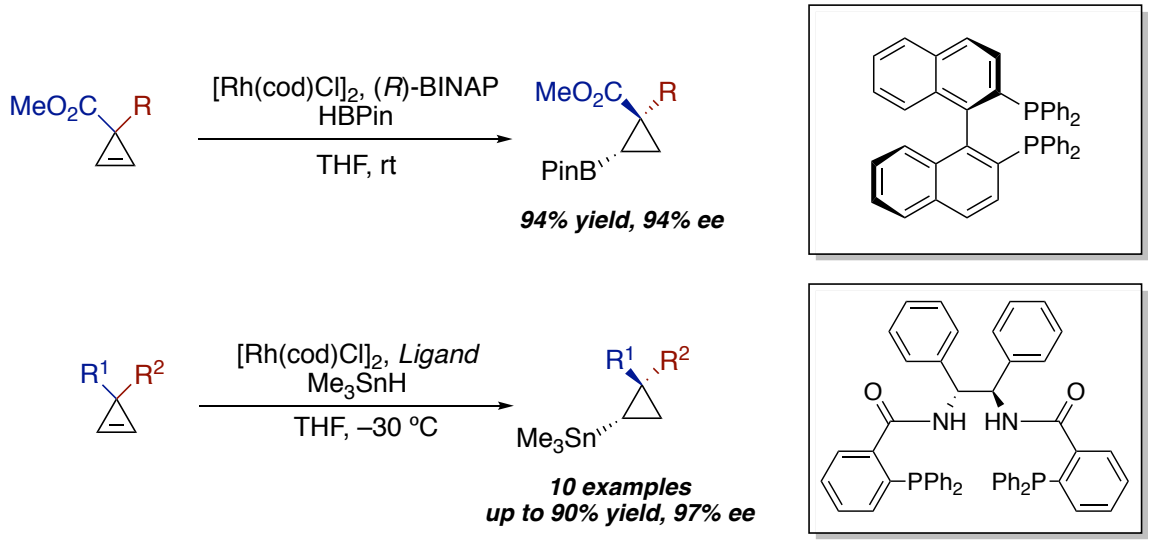
Scheme 1.8. CPA-catalysed ring opening of oxetanes and azetidines.

1.1.4 Cyclopropenes

A large portion of the literature concerning intermolecular desymmetrizations to form quaternary centers involve cyclopropenes. A prochiral cyclopropene with a pro-quaternary center is a classic substrate for desymmetrization due to synthetic accessibility and the range of transformations that can be carried out on these systems.[44] Reactions can generally be divided into hydrometallations, carbometallations and hydroacylation/alkylations. A wide range of catalysts have been investigated, including transition metals and rare-earth metals.

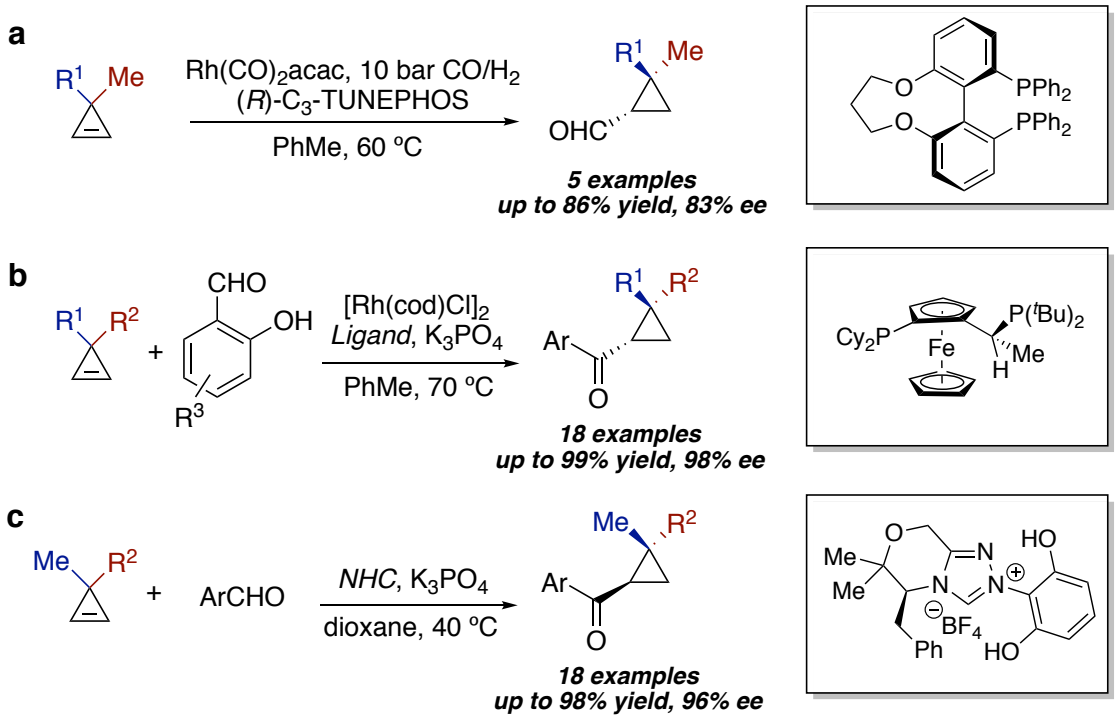
The first reports of desymmetrizations on cyclopropenes containing a pro-quaternary center are from Gevorgyan and co-workers, applying Rh-catalysed hydroboration followed by hydrostannation to these systems. Hydroboration required an ester directing group with BINAP as a ligand to achieve high diastereo- and enantioselectivity, whilst hydrostannation was more

tolerant of differing substitution at the 3 position using a stilbene derived Trost ligand (Scheme 1.9).[45,46] Further copper-catalysed hydroborations on related systems were later reported.[47,48]



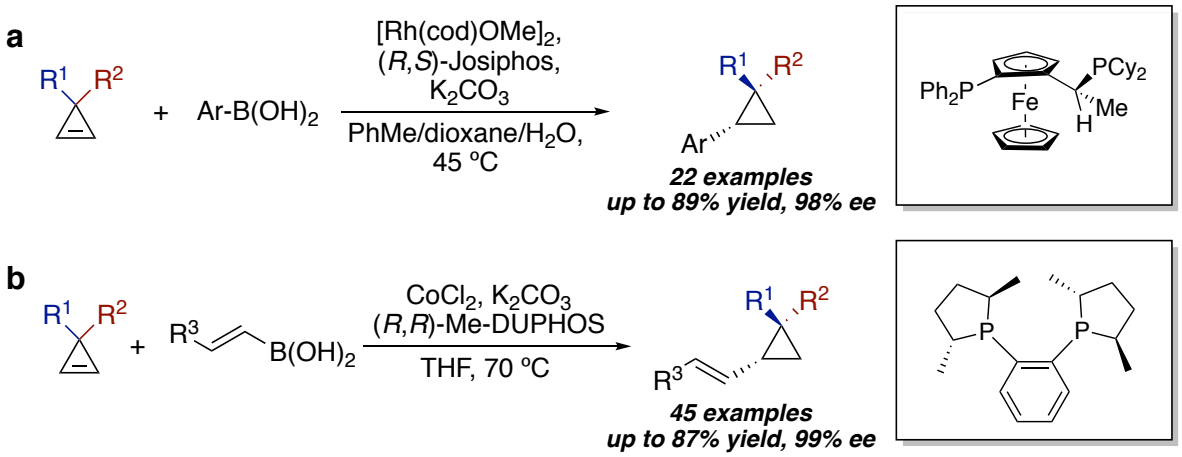
Scheme 1.9. Hydrometallation of cyclopropenes by Gevorgyan and co-workers.

Hydroacylation reactions have also been used to functionalise symmetrical cyclopropenes. These transformations have high atom economy and acylated products are useful for further functional group manipulations.[49] Rh-catalysed enantioselective hydroformylation of cyclopropenes was first reported in 2008 by Rubin and co-workers. $Rh(CO)_2acac$ with (*R*)-C_3-TUNEPHOS at 10 bar CO/H_2 afforded the formylated products with good yield, dr and up to 83% ee (Scheme 1.10 a).[50] The Dong group reported Rh-catalysed hydroacylation of cyclopropenes with salicylaldehydes and Josiphos ligands. A range of salicylaldehydes could be added to various unactivated cyclopropenes with high selectivities (Scheme 1.10 b).[51] The phenolic substituent of the aldehyde was required to accelerate the rate of hydroacylation relative to decarbonylation side product. NHC catalysis has also been shown to be effective in cyclopropene hydroacylation. Glorius and co-workers demonstrated the highly selective addition of benzaldehydes to cyclopropenes without the need for transition metal catalysis or *ortho* directing groups on the aldehyde coupling partner (Scheme 1.10 c).[52]



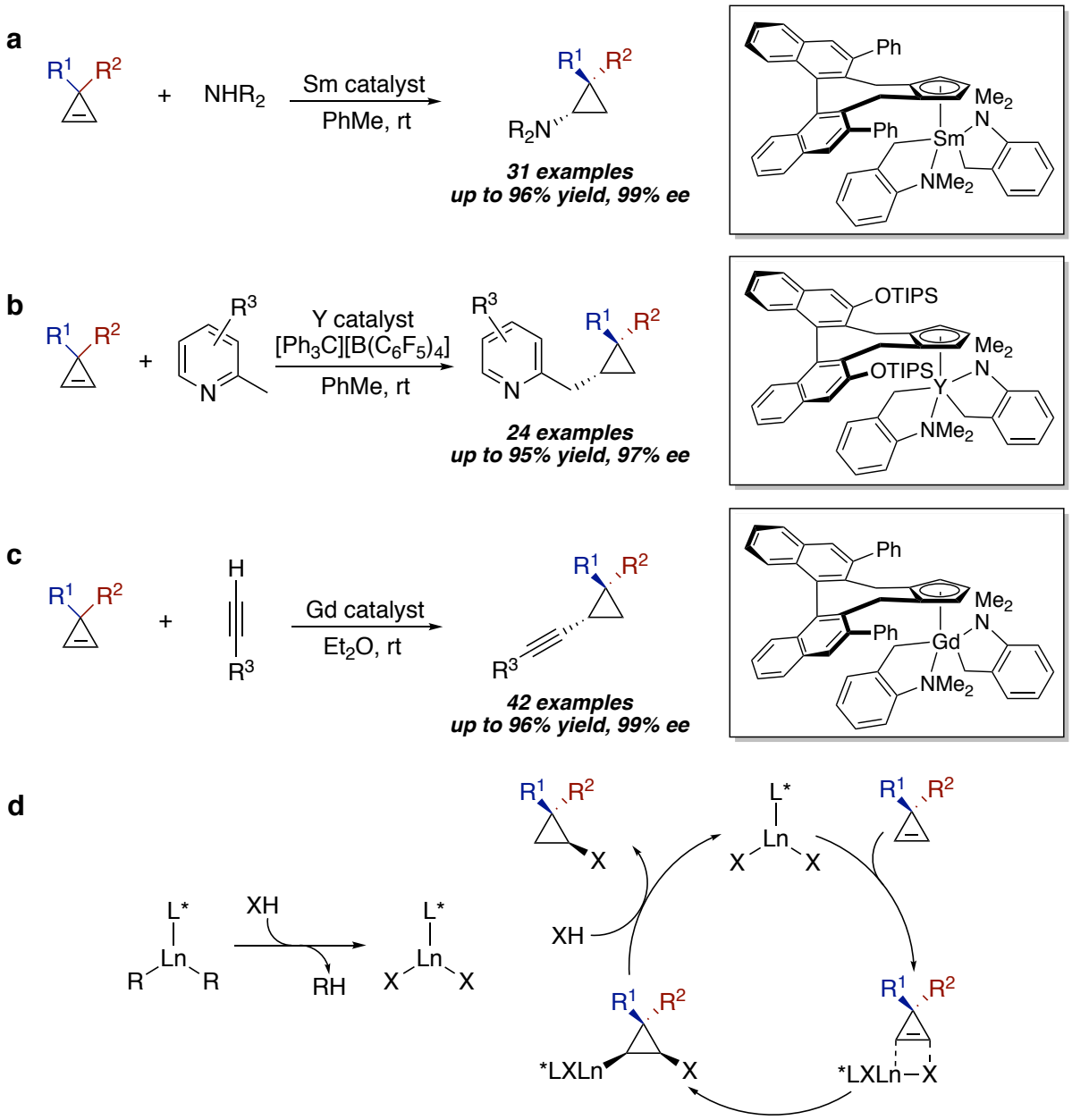
Scheme 1.10. Catalytic hydroacylation/formylation of *gem*-disubstituted cyclopropenes.

More recently the Marek group reported the rhodium-catalysed hydroarylation of cyclopropenes, allowing the enantioselective incorporation of aryl moieties on a cyclopropane ring using a Rh^{I} catalyst with (*R*,*S*)-Josiphos and readily available arylboronic acids. Enantioselectivities are good to excellent on a wide range of substrates, although heterocyclic boronic acids were generally less well tolerated (Scheme 1.11 a).[53] The Marek group also reported a copper-catalysed hydroallylation of prochiral cyclopropenes, with 2 enantioselective examples.[54] Meng and co-workers enabled the use of alkenylboronic acids in cyclopropene desymmetrization using cobalt catalysis and a DuPhos ligand (Scheme 1.11 b). The reaction allowed a diverse range of alkenyl substituents to be introduced and was tolerant of heterocyclic substituents such as a pyridine ring, however air sensitive cobalt catalysts required use of a glove-box.[55]



Scheme 1.11. a) Rh-catalysed hydroarylation of prochiral cyclopropenes using arylboronic acids by Marek. **b)** Co-catalysed hydroalkenylation of prochiral cyclopropenes using alkenylboronic acids by Meng.

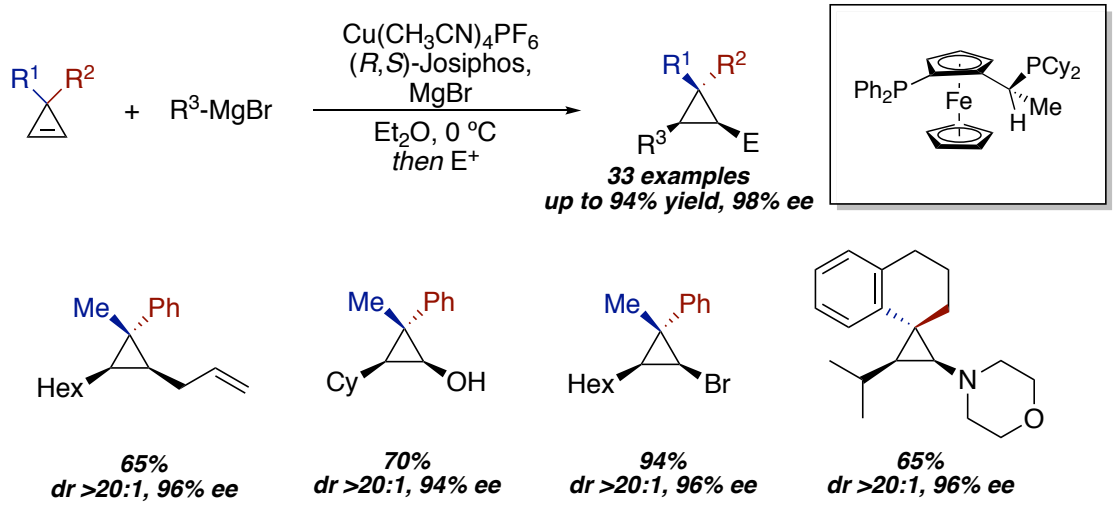
The use of rare-earth element metallations has allowed other functional groups to be added across the cyclopropene double bond. Hou and co-workers first reported the hydroamination of cyclopropenes using dialkylsamarium half-sandwich complexes. The chiral dialkylsamarium species is thought to react with an amine to prepare an amido substituted complex which can metallate the cyclopropene double bond giving *syn* addition of samarium and nitrogen, before quenching with the amine nucleophile. This reaction allows a large range of cyclopropenes with no co-ordinating groups to be hydroaminated with a diverse range of amine substituents in excellent ee and high diastereoselectivity (Scheme 1.12 a).[56] The Hou group then applied a similar protocol using a chiral yttrium half sandwich complex to add 2-methylpyridine derivatives across a cyclopropene via C-H activation of the 2-methyl substituent by the catalyst. Again high selectivities were achieved with a range of substrates (Scheme 1.12 b).[57] A chiral gadolinium half sandwich complex allowed hydroalkylnation of cyclopropenes in a similar fashion (Scheme 1.12 c).[58]



Scheme 1.12. Rare-earth half sandwich catalysts for cyclopropene desymmetrization from the Zhaomin Hou group. **a)** Hydroamidation of cyclopropenes. **b)** C-H activation 2-methylpyridine and subsequent hydroalkylation of cyclopropenes. **c)** Hydroalkynylation of cyclopropenes. **d)** Generic postulated mechanism for rare-earth metal-catalysed hydrometallation of cyclopropenes.

The use of organometallic nucleophiles to desymmetrize cyclopropenes has also been reported. The first enantioselective variant was reported by Fox and co-workers. Using a prolinol derived ligand in super-stoichiometric amounts and MeMgBr as a nucleophile, prochiral *gem*-disubstituted cyclopropenes could be alkylated with high enantioselectivity. The use of a reactive organometallic species also forms a metallocyclopropane product which can be trapped with a range of electrophiles.[59] This reaction was limited to the addition of just a methyl

group, and a co-ordinating alcohol group was required on the cyclopropene to achieve useful levels of selectivity. The first catalytic report came from the Marek group in 2015. Cu^{I} catalysis with a Josiphos ligand allowed an enantioselective carbometallation of the cyclopropene double bond with dialkylzinc reagents.[60] This work has since been expanded to use more diverse Grignard reagents, and a range of trapping protocols has allowed the formation of subsequent C-C, C-X, C-O and C-N bonds (Scheme 1.13).[61,62] The Marek group have also reported the use of alkenylaluminum reagents with this chemistry to expand the range of C-C bonds that could be formed.[63]



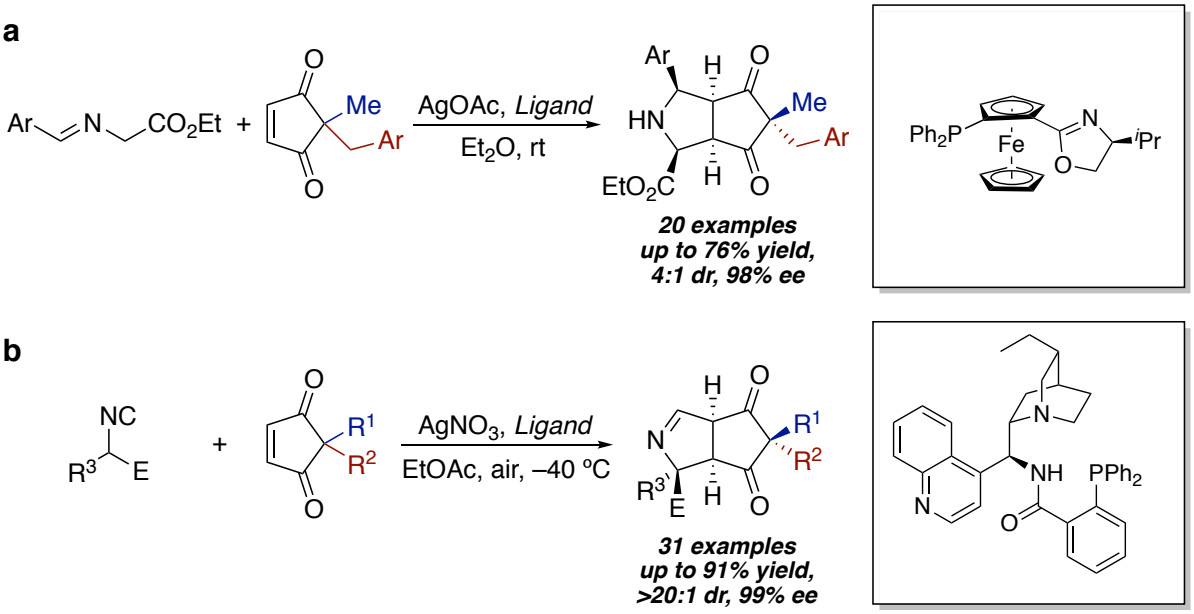
Scheme 1.13. Cu-catalysed desymmetrizing carbometallation of cyclopropenes with Grignard reagents by Marek and co-workers.

1.1.5 Cycloadditions

Cycloaddition reactions allow ring systems to be formed rapidly, with multiple bonds being formed in a single reaction. Many efforts have been made to make these reactions enantioselective,[64,65] and there are few examples of desymmetrizing cycloadditions to resolve a pro-quaternary center.

[3 + 2] cycloadditions to cyclopentenediones have enabled the enantioselective construction of complex bicyclic systems whilst controlling the stereochemistry at the 2-position of the dione.

Singh and co-workers first reported the silver-catalysed [3 + 2] cycloaddition of cyclopentenediones with azomethine ylides using ferrophox ligands to give highly substituted pyrrolidine structures (Scheme 1.14 a).[66] Enantioselectivity is high for a range of azomethine ylides and diones, but diastereoselectivity is generally between 3:1 to 4:1. In 2018 Oh and co-workers used cinchona alkaloid derived catalysts with $AgNO_3$ to facilitate the [3 + 2] cycloaddition of cyclopentenediones and isocyanoacetates with excellent diastereo- and enantioselectivity (Scheme 1.14 b).[67] α-substitution of the isocyanoacetates was necessary to achieve synthetically useful yields and ee.

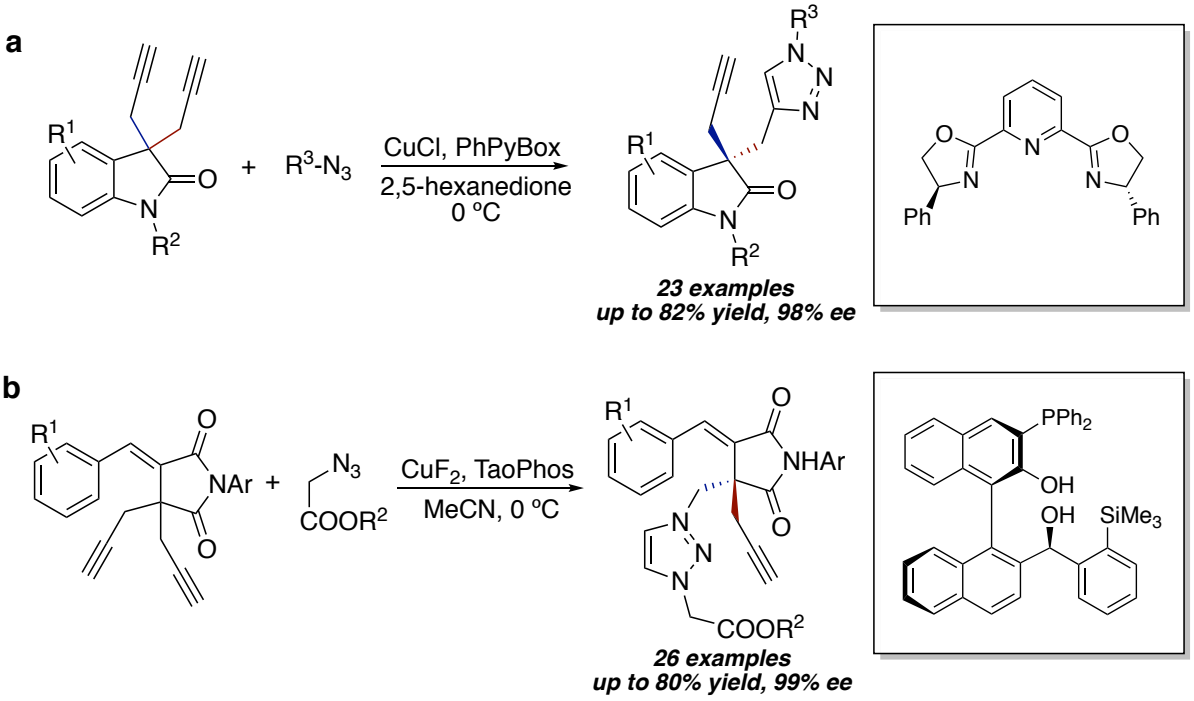


Scheme 1.14. a) Silver-catalysed desymmetrizing [3 + 2] cycloaddition of azomethine ylides and cyclopentenediones. **b)** Silver-catalysed desymmetrizing [3 + 2] cycloaddition of isocyanoacetates and cyclopentenediones.

Copper-catalysed azide-alkyne cycloadditions (CuAAC) have become ubiquitous across all areas of chemistry, from the synthesis of pharmaceuticals to systems chemistry and protein modification.[68] Asymmetric variants of the CuAAC reaction are rare, but there has been some application to quaternary center forming desymmetrizations.[69]

Terminal alkyne substituted quaternary oxindoles proved useful substrates for desymmetrization by CuAAC. The Zhou group demonstrated this using CuCl and a PhPyBox

ligand. Mono-triazole formation was well controlled and high enantioselectivities were observed for a range of substrates (Scheme 1.15 a).[70] Dione based solvents gave the best results, however no rationale was given for this observation. It is possible that the Lewis base properties of the dione could influence co-ordination chemistry. Terminal alkyne substituted quaternary malemides were also found the be suitable for asymmetric CuAAC chemistry. Using a CuF_2/TaoPhos catalyst was successful across a range of substrates (Scheme 1.15 b). A positive non-linear effect (NLE) was observed for this reaction, suggesting that a multi-nuclear species may be catalysing the reaction.[71]

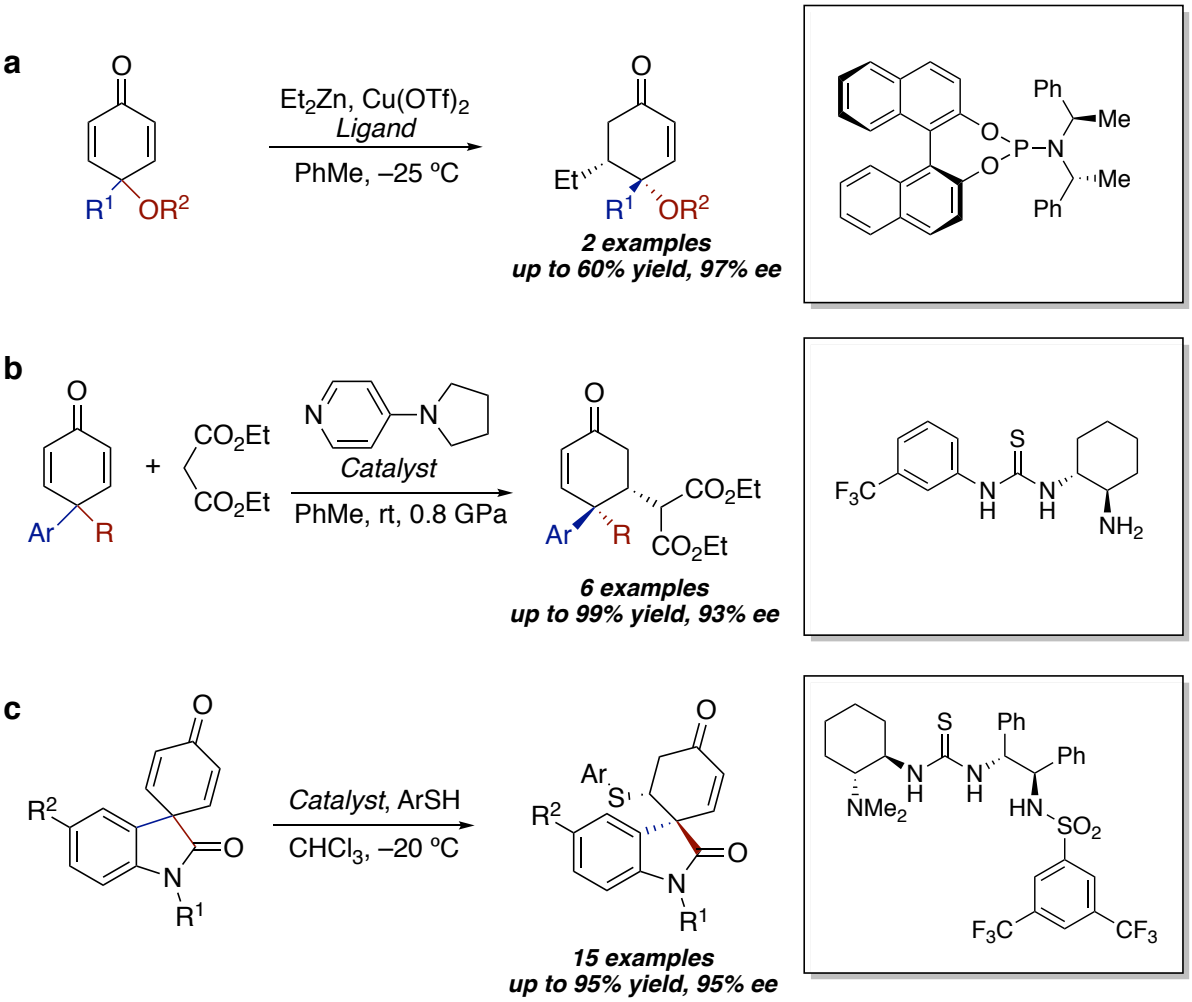


Scheme 1.15. a) CuAAC to desymmetrize quaternary oxindoles. **b)** CuAAC to desymmetrize quaternary malemides.

1.1.6 1,4-additions

Conjugate additions to α,β-unsaturated carbonyl compounds are one of the most developed reactions in intermolecular asymmetric catalysis.[72,73] A variety of nucleophiles have been adapted to use this chemistry and symmetrical substrates with pro-quaternary centers have been targeted with this methodology.

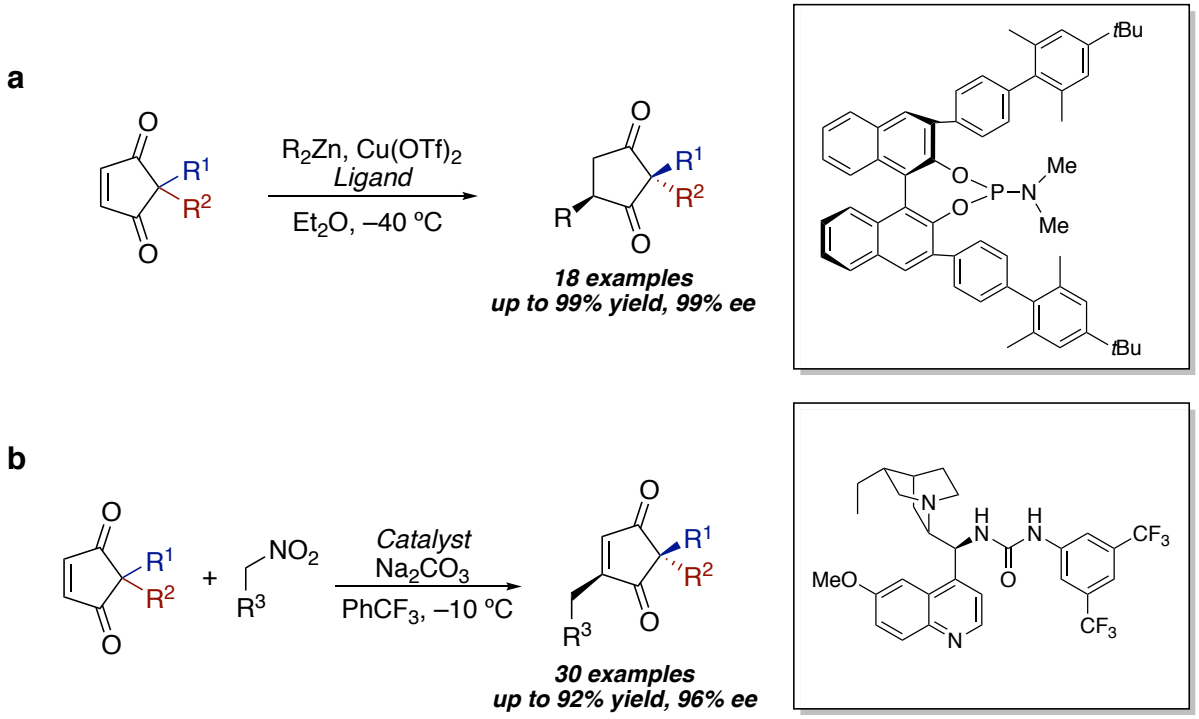
With asymmetric conjugate addition (ACA) to cyclohexenone derivatives already well established cyclohexanedienones were the first substrates to be examined in these desymmetrizations. Feringa and co-workers described the copper-catalysed addition of dialkylzinc reagents to these systems using the Feringa phosphoramidite ligand with up to 97% ee. An ether group is required in the 4-position to achieve enantioselectivity and bis-alkyl or bis-ether substitution was not tolerated (Scheme 1.16 a).[74] Chiral thiourea organocatalysis was shown to be effective in the desymmetrization of cyclohexanedienones with malonate nucleophiles by Kotsuki and co-workers. A range of substituents were tolerated on the dione, but extremely high, impractical pressures of approximately 8000 bar were required to achieve sufficient reaction rates (Scheme 1.16 b).[75] The formation of C-S bonds is also enabled by ACA,[76] as illustrated by the sulfa-Michael addition to oxindole-based spriocyclic cyclohexadienones by Wang and co-workers. High selectivities were obtained for a range of arylthiol nucleophiles but the scope of oxindole derivatives was limited (Scheme 1.16 c).[77]



Scheme 1.16. Desymmetrizations of cyclohexadienones by ACA. **a)** Copper-catalysed dialkylzinc addition by Feringa and co-workers. **b)** Organocatalysed malonate addition at high pressure. **c)** Sulfa-Michael addition to spriocyclic oxindoles.

Cyclopentene-1,3-diones have also been used desymmetrizations to form quaternary centers, their ease of synthesis allowing a wide range of pro-quaternary centers to be explored. The Mikami group first reported the desymmetrizing conjugate addition of dialkylzinc reagents to cyclopentene-1,3-diones using copper catalysis and phosphoramidite ligands (Scheme 1.17 a).[78] High enantioselectivities were attained for a range of substrates, and the enolate products were able to undergo trapping with electrophiles. This was highlighted in the formal syntheses of the cytokine inhibitors (+)-mandindoline A and B. Mukherjee and co-workers reported the first organocatalysed desymmetrization of cyclopentene-1,3-diones using deconjugated butenolides as nucleophiles with excellent enantioselectivities.[79] Modification of the thiourea

catalyst revealed a tridentate co-ordination mode which was crucial for high enantioselectivity to be attained. Later the Mukherjee group reported the enantioselective addition of nitroalkanes to cyclopentene-1,3-diones using a urea catalyst derived from a cinchona alkaloid (Scheme 1.17 b).[80] Subsequent E1cb elimination of the nitro group and keto-enol tautomerisation constituted a formal C(sp^2)-H alkylation. This also allowed a formal synthesis of (+)-mandindoline A and B. A similar protocol was developed by Enders and co-workers using a pyrazole nucleophile, however enantioselectivities were generally moderate.[81]



Scheme 1.17. a) Mikami and co-workers desymmetrization of cyclopentenediones using ACA. **b)** Organocatalysed nitroalkane addition/elimination by Mukherjee and co-workers.

1.1.7 Conclusion

The last 20 years have showcased a number of desymmetrizing coupling reactions which can resolve a pre-existing quaternary carbon stereocenter. Classic C-C bond forming methods such Suzuki-Miyaura coupling, 1,4-addition and cycloadditions have been exploited, as well as the opening of strained rings and functionalisation of cyclopropenes. In addition, the field of C-H activation has enabled some of the most remarkable desymmetrizations to date.

Despite these advances many opportunities still exist for future research. Nearly all of the examples shown demonstrate the desymmetrization of prochiral compounds, and intermolecular desymmetrizations of *meso*-compounds bearing all-carbon quaternary centers are extremely rare. Desymmetrizations of linear substrates are also limited. Asymmetric allylic alkylation (AAA), despite being a powerful tool in the enantioselective synthesis of C-C bonds, has also not been used in desymmetrizations to form quaternary centers.

The work contained in this thesis will focus on the intermolecular desymmetrization of complex *meso*-compounds to resolve pre-existing all-carbon quaternary centers using metal-catalysed AAA reactions, which will expand on a significantly underrepresented transformation in synthesis.

2 Desymmetrization of *Meso*-Bisphosphates via Cu-Catalysed Asymmetric Allylic Alkylation

Sections of this chapter are published in *Nat. Commun.*[82]

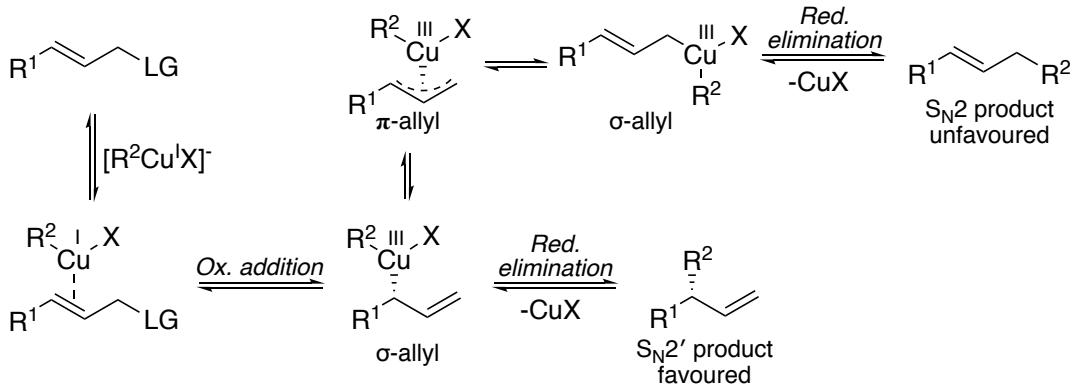
2.1 Asymmetric Allylic Alkylation

The asymmetric construction of C-C bonds is one of the most important transformations in organic chemistry, and are often key steps in the synthesis of complex natural products.[83] Asymmetric allylic alkylation (AAA) has proven to be one of the most versatile of these transformations and has been used extensively in synthesis.

Many metals have been applied in AAA, but the most studied is palladium, in what is commonly known as the Tsuji-Trost reaction. Pd-catalysed AAA has been successfully applied in the synthesis of many biologically active molecules,[84–88] but is limited to the addition of soft, stabilised nucleophiles with pK_a values of <25, restricting the variety of C-C bonds that can be formed by this strategy.

Copper-catalysed asymmetric allylic alkylation (CuAAA) allows the addition of unstabilised nucleophiles, normally via transmetallation of an organometallic species.[89–92] Allylic substitution can also give different regiochemical outcomes, but CuAAA generally favours *anti*-S_N2' addition, leading to branched products in linear systems.[93–95] This is rationalised by oxidative addition of a copper species being directed by orbital overlap of the d^{10} system in Cu^I

with the LUMO of the allylic substrate[96] and reductive elimination being fast for electron deficient copper catalysts, which is often the case in CuAAA (Scheme 2.1). It should be noted that the full mechanism of CuAAA with Cu^{I} catalysts is still debated, with a Cu^{III} intermediate proposed.[97–99] Identification of these species is limited to electron rich dialkylcopper reagents.[100] As with many cases in asymmetric catalysis there are examples which allow *syn* and/or S_N2 additions to occur, but specific conditions or chelating leaving groups are required.[101,102]



Scheme 2.1. Generally accepted mechanism of CuAAA, favouring S_N2' addition.

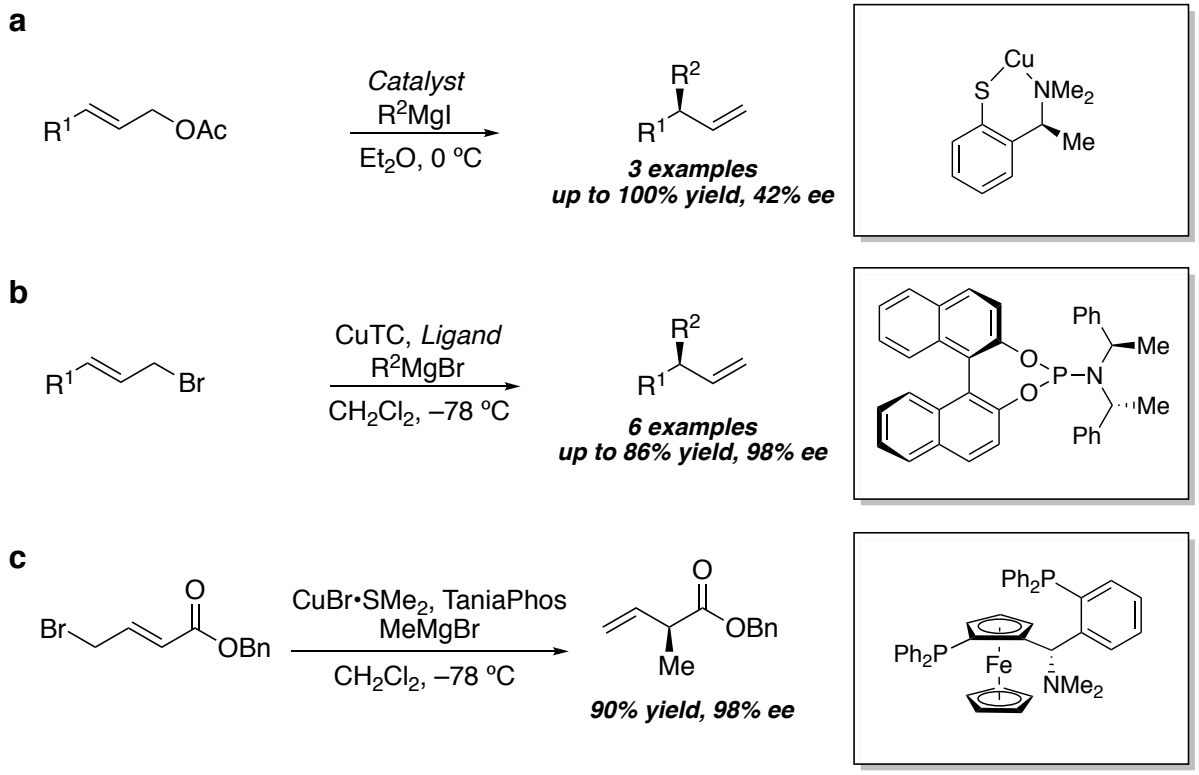
2.2 Organometallic Nucleophiles in CuAAA

A range of organometallic nucleophiles have been applied in enantioselective CuAAA, with advances over a 20-year period allowing high levels of regio- and stereocontrol. This chapter will highlight selected examples of C-C bond formation in CuAAA with a focus on applications to desymmetrization.

2.2.1 Grignard Reagents

The first class of hard, unstabilised nucleophiles applied to CuAAA were Grignard reagents,[83] one of the first organometallic reagents used in synthetic organic chemistry. In 1995 Bäckvall

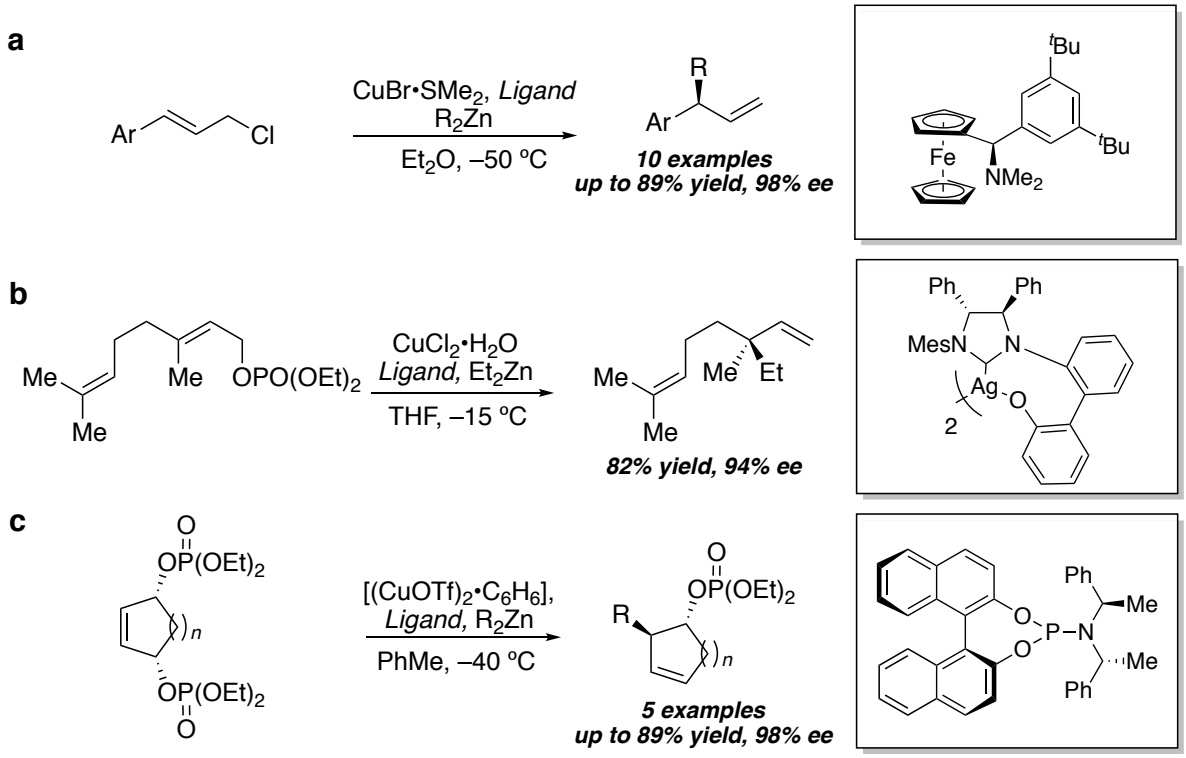
and co-workers reported the S_N2' selective addition of Grignard reagents to linear allylic acetates using an arenethiolatocopper complex (Scheme 2.2 a).[97,103] Branched products were obtained in excellent yields and regioselectivity, but enantioselectivity was generally modest, ranging from 28 to 42% ee. Further modifications to the catalyst in follow up studies improved the ee up to 64%.[104] Alexakis and co-workers first reported the use of bisphosphine ligands in CuAAA using linear allyl halides,[105] but had more success using phosphoramidite ligands developed by the Feringa group.[106,107] Regioselective addition of Grignard reagents was achieved with excellent enantioselectivities of >90% ee for the first time (Scheme 2.2 b). A similar protocol was applied to the synthesis of (*S*)-Naproxen.[108] Further approaches using bisphosphine ligands,[109,110] NHC ligands[111–113] and phosphine-phosphite[114] ligands have since been reported. Additions to more complex substrates have also been reported with Grignard reagents,[115–117] including halocrotonates by the Feringa group using TaniaPhos (Scheme 2.2 c).



Scheme 2.2. CuAAA with Grignard reagents. **a)** Arenethiolatocopper catalyst for additions to allylic acetates by Bäckvall. **b)** Phosphoramidite ligands used by Alexakis and co-workers. **c)** Feringa and co-worker's addition to halocrotonates.

2.2.2 Organozinc Reagents

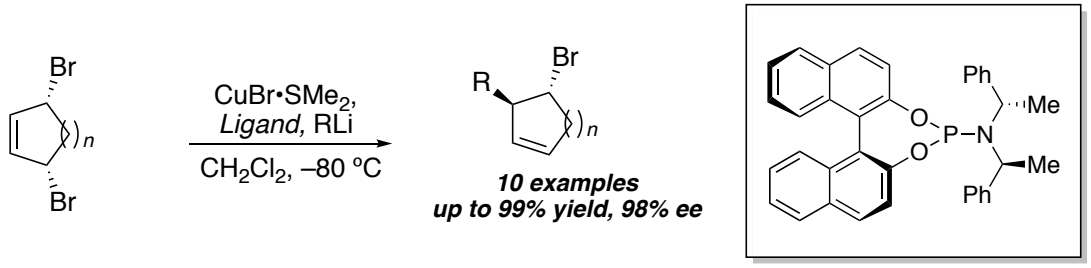
The first use of diorganozinc reagents in CuAAA was demonstrated in 1999 by the Knochel group using linear allylic chlorides and chiral ferrocene ligands.[118] The reaction was made highly enantioselective by increasing the steric bulk of the aryl substituent of the ligand (Scheme 2.3 a).[119] Further examples of allylic halide substitution with phosphoramidite ligands have since been published.[120,121] Allylic phosphates have also been shown to be compatible leaving groups with dialkylzinc reagents, as shown by the Hoveyda group.[122,123] The use of chiral sliver-NHC complexes, which undergo metal exchange with copper salts, have been effective in this chemistry, allowing additions to more elaborate substrates (Scheme 2.3 b).[124,125] The first desymmetrization reactions using CuAAA were reported by Gennari and co-workers, using dialkylzinc reagents to desymmetrize cyclic *meso*-bisphosphates.[126] The use of phosphoramidite ligands improved the selectivity of this chemistry, allowing 5, 6 and 7 membered rings to be desymmetrized with high ee (Scheme 2.3 c).[127]



Scheme 2.3. CuAAA with diorganozinc reagents. **a)** First use of diorganozinc nucleophiles in CuAAA with allylic chlorides by Knochel and co-workers. **b)** Cu-NHC catalysed additions to allylic phosphates by Hoveyda and co-workers. **c)** Desymmetrization of *meso*-bisphosphates by Gennari and co-workers.

2.2.3 Organolithium Reagents

Although organolithium reagents are used extensively in synthesis they have had limited use in asymmetric catalysis. Their high reactivity and basicity, coupled with their tendency to form aggregates, hindered progress in this field. Despite this, the Feringa group reported their use in CuAAA in 2011,[128] and could apply organolithium reagents in allylic substitutions to form quaternary centers.[129] More recently the Feringa group reported the desymmetrization of cyclic *meso*-dibromides with organolithium reagents to form cyclic alkyl bromides (Scheme 2.4).[130] Interestingly, the cycloheptene variant of this reaction undergoes a stereospecific ring contraction via what is believed to be a non-classical ion intermediate.[131]

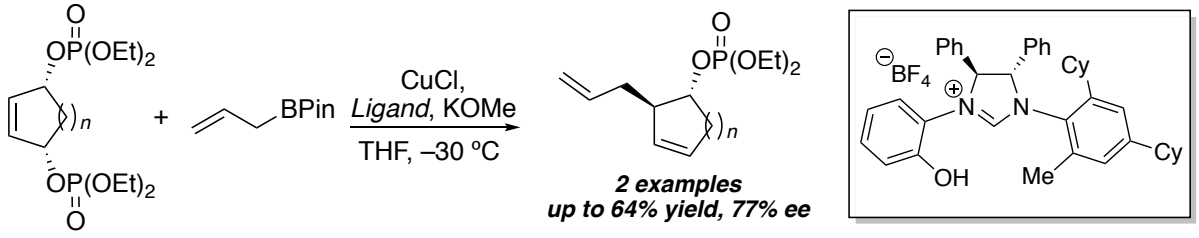


Scheme 2.4. Desymmetrization of *meso*-dibromides via CuAAA with organolithiums by Feringa and co-workers.

2.2.4 Organoaluminium/Organoboron Reagents

Organoaluminium nucleophiles have emerged as versatile reagents for CuAAA, especially combined with the use of NHC ligands. The Hoveyda group has pioneered the use of these nucleophiles in CuAAA, using them in a variety of allylic substitutions including those to form quaternary centers.[132–135] Organoboranes have also been applied in CuAAA and have allowed the introduction of aryl, alkenyl[136] and allenyl[137] substituents. More recently an example of S_N2'' substitution with allenyl boronates was demonstrated by the Hoveyda group.[138] The Sawamura group described the use of allyl boronates in the CuAAA of allylic phosphates. This

reaction could also be applied to *meso*-bisphosphates, but enantioselectivity was moderate (Scheme 2.5).[139]



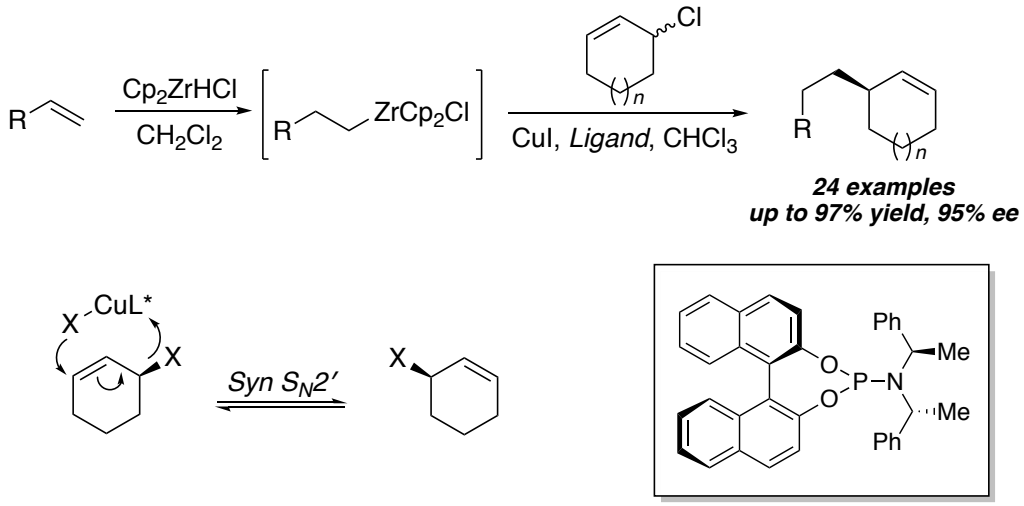
Scheme 2.5. Desymmetrization of *meso*-bisphosphates via CuAAA with allyl-BPin by Sawamura and co-workers.

2.2.5 Organozirconium Reagents

A wide variety of organometallic nucleophiles have been used in CuAAA, many with excellent yields, regio-, diastereo- and enantioselectivity. However, these transformations are largely limited to the introduction of aliphatic, unfunctionalized carbon chains. In addition, cryogenic temperatures are often required to tame the reactivity of these highly basic nucleophiles.

A solution to this issue is the use of organozirconium reagents, which can be applied in catalytic asymmetric transformations under mild conditions and facilitate the incorporation of useful functional groups in coupling reactions. The Fletcher group first used alkylzirconium nucleophiles in copper-catalysed ACA (asymmetric conjugate addition) to cyclic enones, allowing access to β-substituted ketones containing functional groups incompatible with other organometallic methods with excellent enantioselectivity at room temperature.[140,141] The alkylzirconium reagents were generated from readily available alkenes in situ via hydrometallation with Schwartz' reagent (Cp_2ZrHCl). Further advances have allowed ACA to linear enones.[142–144] The Fletcher group have also used organozirconium nucleophiles in CuAAA, using racemic cyclic allyl chlorides as electrophiles (Scheme 2.6).[145,146] The reaction proceeds via a DYKAT mechanism, where the CuI-phosphoramidite catalyst facilitates

racemisation of the allyl chloride substrate via an allyl iodide intermediate. Allylic substitution with alkylzirconium reagents afforded alkylated cyclohexene products with good functional group tolerance and enabled the synthesis of several natural products.



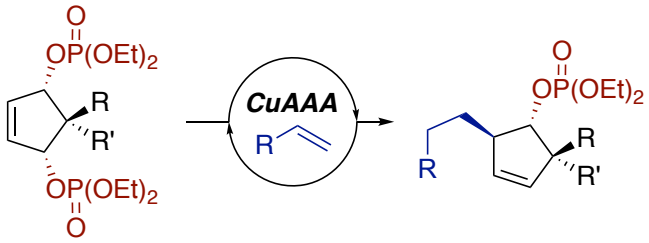
Scheme 2.6. CuAAA of racemic cyclic allylic chlorides using alkylzirconium nucleophiles by the Fletcher group.

2.3 Project Aims

As discussed in chapter 1, desymmetrizations of *meso*-compounds bearing an all-carbon quaternary stereocenters are extremely limited, with the majority of substrates being prochiral. In addition, none of those desymmetrizations use AAA as a method, despite its obvious success in asymmetric catalysis. Even the more mature field of Pd-catalysed AAA has no examples of this type of desymmetrization.

Thus far desymmetrizations via CuAAA have only been applied to simple substrates giving carbocyclic products with tertiary stereocenters. In some cases selectivities were modest and additions were limited to highly reactive organometallic reagents using cryogenic temperatures.

This project aims to use CuAAA with alkylzirconium nucleophiles to desymmetrize *meso*-bisphosphates with high enantioselectivity (Scheme 2.7). By exploiting the *meso*-symmetry of these compounds we aim to resolve pro-quaternary centers on the bisphosphate, which would represent a significant advance in AAA. Heterocyclic substrates which are often neglected in asymmetric copper catalysis will also be examined.

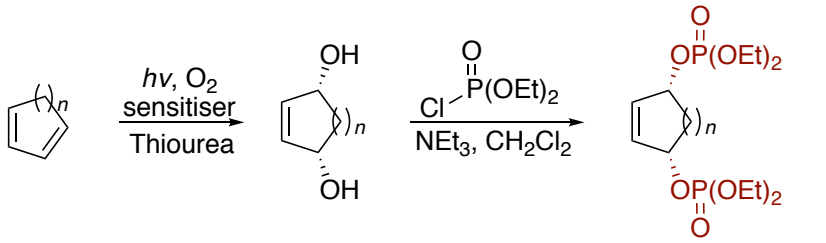


Scheme 2.7. Desymmetrization of *meso*-bisphosphates bearing an all-carbon quaternary center using CuAAA and alkylzirconium nucleophiles.

2.4 Results and Discussion

2.4.1 Reaction Optimisation

In order to probe the desymmetrization of *meso*-bisphosphates with alkylzirconium reagents the starting materials were prepared. The bisphosphates could be made via phosphorylation of the corresponding cyclic diol, which in turn were accessed by a [4 + 2] cycloaddition of an appropriate cyclic diene with singlet oxygen (Scheme 2.8).[147,148] Diethyl phosphates were selected as leaving groups as diethyl chlorophosphate was available commercially in large quantities. 5, 6 and 7 membered ring bisphosphates were prepared easily on multi-gram scale.

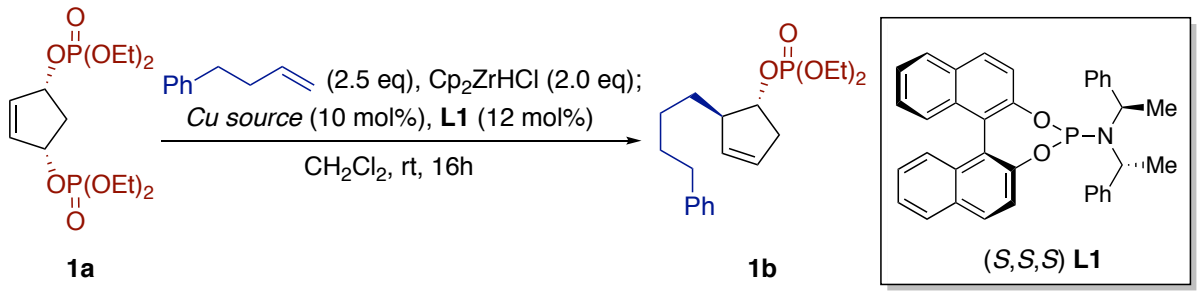


Scheme 2.8. Synthesis of unsubstituted *meso*-bisphosphates.

We selected the 5 membered ring bisphosphate **1a** for initial optimisation as other related desymmetrizations showed this ring size to generally give lower enantioselectivities.[127,130] The first experiments applied previously known conditions in the Fletcher group for CuAAA using alkylzirconium nucleophiles,[145] and were conducted by myself and Hengzhi You. 4-phenyl-1-butene was selected as a model alkene for optimisation as reactions optimised with 4-phenyl-1-butene often show better functional group tolerance and provide UV active products to speed up chiral HPLC/SFC analysis. Using CuI and the Feringa phosphoramidite ligand **L1** gave good conversion to product **1b**, albeit as a racemate (Table 2.1, entry 1). The relative stereochemistry of **1b** suggests that the nucleophile added via an *anti*-S_N2' pathway giving

almost exclusively the *trans* isomer. No S_N2 product was observed during any point of the optimisation. The previous CuAAA reaction developed in the group used allyl chlorides as substrates, and it was found that CuI was important to racemise the starting material in a DYKAT process. As this reaction was a desymmetrization there was no need for a racemisation process, hence a wide range of Cu^I sources were examined (entries 2-9). More Lewis acidic copper salts provided moderate levels of enantioselectivity. These copper salts are air sensitive and were generated in situ via a salt metathesis reaction with the appropriate bench-stable silver salt and CuCl, precipitating out AgCl. In situ generated $CuNTf_2$ in particular gave the highest levels of conversion and ee when using **L1** (entry 9).

Table 2.1. Optimisation of copper source – with Hengzhi You

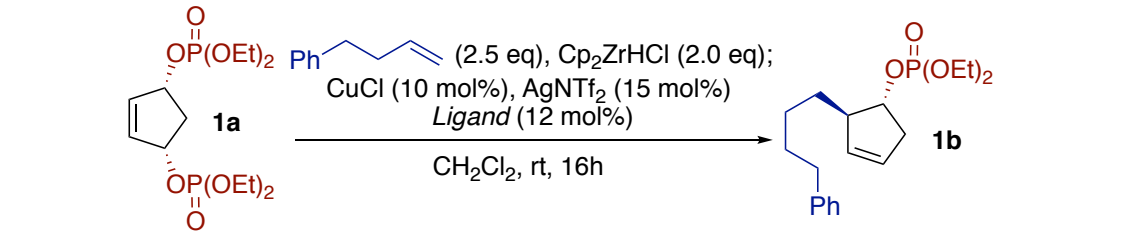


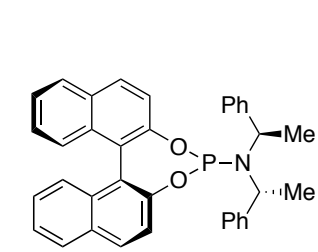
1a **1b**

Entry	Cu Source	Ag Salt (15 mol%)	Conversion (%)[a]	*trans*:*cis*	ee (%)[b]
1	CuI	-	71	20:1	0
2	CuBr•SMe_2	-	89	20:1	0
3	Cu(OAc)	-	22	20:1	9
4	CuTC	-	78	20:1	0
5	$Cu(OTf)_2$	-	39	20:1	69
6	CuCl	AgOTf	57	>20:1	70
7	CuCl	AgOMs	0	>20:1	21
8	CuCl	$AgClO_4$	52	>20:1	66
9	CuCl	$AgNTf_2$	83	>20:1	70

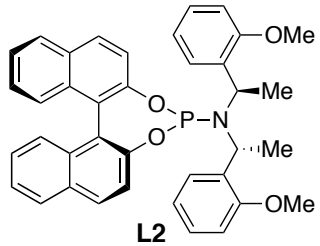
Conditions: Reactions carried out on 0.4 mmol scale of **1a**. 0.2M. [a]Conversion determined by ^1H NMR. [b]ee determined by chiral HPLC of crude reaction mixture.

Examination of BINOL-derived phosphoramidite ligands revealed that ligands with an indane moiety on nitrogen performed well, with enantioselectivity roughly correlating with the size of the remaining alkyl group (**L6**-**L12** Scheme 2.9). **L12**, developed in Fletcher group and highly selective in copper-catalysed ACA reactions,[142] gave 70% yield and 86% ee, approaching desired levels of enantioselectivity. It was noted that **L9** gave the highest yield of 76%.

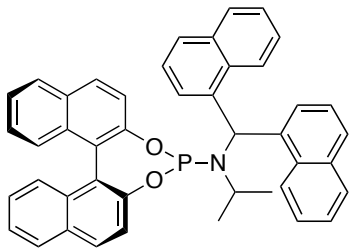




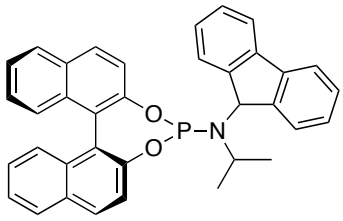
L1
Yield 66%, ee 70%



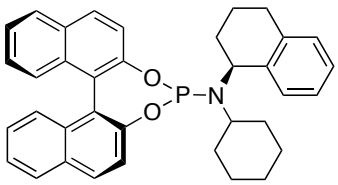
L2
Yield 32%, ee 51%



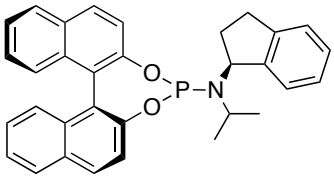
L3
Yield 61%, ee 67%



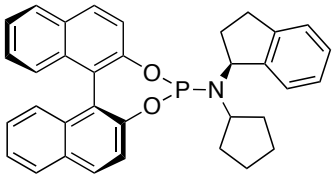
L4
Yield 58%, ee 60%



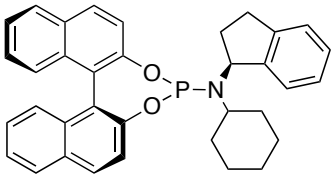
L5
Yield 33%, ee 55%



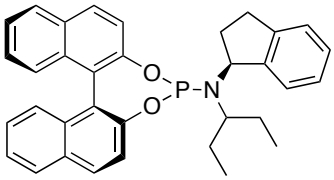
L6
Yield 61%, ee 65%



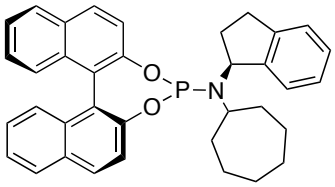
L7
Yield 61%, ee 75%



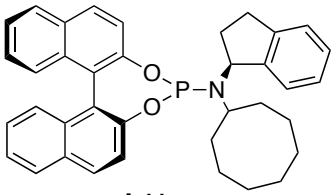
L8
Yield 74%, ee 81%



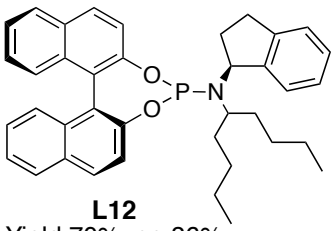
L9
Yield 76%, ee 84%



L10
Yield 67%, ee 83%



L11
Yield 66%, ee 80%

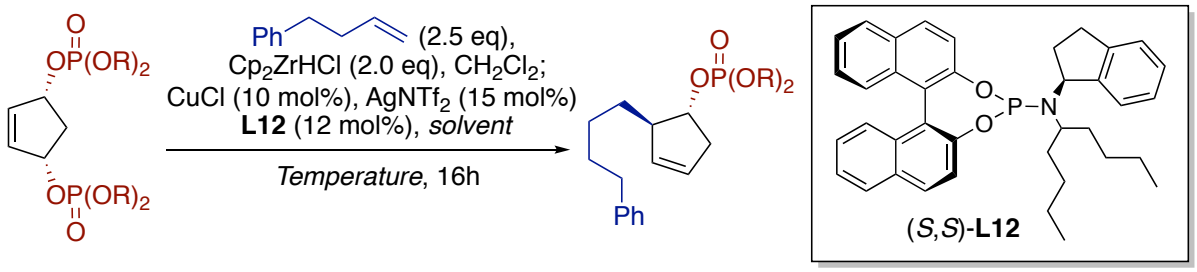


L12
Yield 70%, ee 86%

Scheme 2.9. Ligand screen. Isolated yields quoted.

Other parameters were screened in an attempt to improve the ee to ≥90%. The dialkyl substituents of the phosphate leaving group were examined, with a hypothesis that a bulkier group such as *i*Pr may improve enantioselectivity (Table 2.2). The alkyl substituent on the phosphate group appeared to have little effect on the reaction; while selectivities were similar for Me and Et phosphates (entries 1-6), lower yields were observed for the *i*Pr phosphate (entry 7). When substituted with Ph groups both starting material and product were acid sensitive and partially hydrolysed on silica, likely due to more stable phenolic leaving groups (entry 8). Diethylphosphate groups were maintained as the aforementioned availability of starting materials allowed large scale preparation of the bisphosphate. Reducing the temperature to 0 ºC pleasingly increased the ee to 90% whilst maintaining yield (entry 2), however further reductions to –10 ºC caused the reaction to slow significantly (entry 3), hence 0 ºC was retained. Finally, solvents were screened. In CuAAA reactions developed by the Fletcher group the catalyst and hydrozirconated alkene are prepared in separate flasks, before transferring the catalyst to the nucleophile via syringe. When using Schwartz' reagent CH_2Cl_2 is the only reliable solvent for successful and complete hydrozirconation of alkenes, so only the catalyst solution is tolerant of solvent changes. It appeared solvents had only a negligible effect on enantioselectivity, with some variation in yield (entries 9-14). In addition, changes to concentration negatively affected the reaction (entries 15-16). As a result, the conditions described in entry 2 were deemed to be optimal, using $CuNTf_2$ and **L12** in CH_2Cl_2 at 0 ºC.

Table 2.2. Optimisation of leaving group, solvent, temperature and concentration.

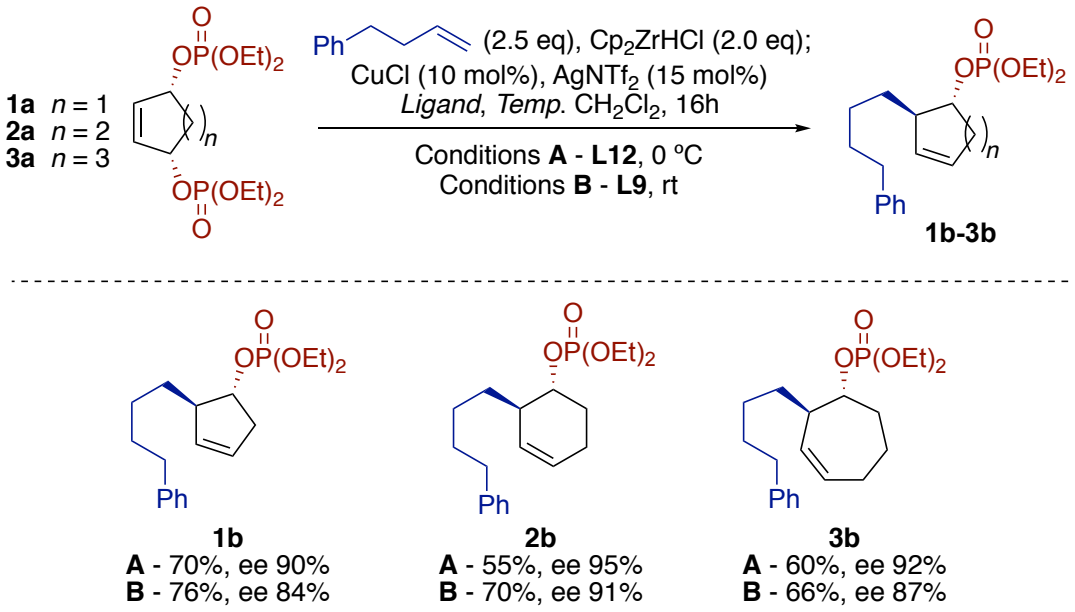


Entry	R	Solvent	Conc. (M)	T / ºC	Yield (%)	ee (%)[b]
1	Et	CH_2Cl_2	0.2	rt	70	86
2	Et	CH_2Cl_2	0.2	0	70	90
3	Et	CH_2Cl_2	0.2	–10	27	92
4	Me	CH_2Cl_2	0.2	rt	69	86
5	Me	CH_2Cl_2	0.2	0	55	88
6	Me	CH_2Cl_2	0.2	–10	49	91
7	*i*Pr	CH_2Cl_2	0.2	rt	45	84
8	Ph	CH_2Cl_2	0.2	rt	20	70
9	Et	$CHCl_3$[a]	0.2	rt	65	85
10	Et	Et_2O[a]	0.2	rt	41	85
11	Et	THF[a]	0.2	rt	40	82
12	Et	DME[a]	0.2	rt	42	86
13	Et	TBME[a]	0.2	rt	47	84
14	Et	PhMe[a]	0.2	rt	55	85
15	Et	CH_2Cl_2	0.1	rt	62	86
16	Et	CH_2Cl_2	0.5	rt	38	86

Conditions: Reactions carried out on 0.4 mmol scale of **1a**. [a]Hydrozirconation mixture in 0.4 mL CH_2Cl_2, catalyst mixture in 1.6 mL of stated solvent. [b]ee determined by chiral HPLC.

2.4.2 Ring Size and Alkene Scope

With suitable desymmetrization conditions in hand the effect on ring size was investigated (Scheme 2.10). The 6 and 7- membered ring variants of the *meso*-bisphosphate were synthesised and desymmetrized using 4-phenyl-1-butene and the optimal conditions for substrate **1a** (Table 2.2, entry 2). The 6-membered ring bisphosphate **2a** gave an excellent ee of 95%, but the reaction yield was 55% owing to poor conversion. Switching to **L9** at room temperature improved the yield to 70% whilst still maintaining a respectable enantioselectivity of 91%. The 7-membered ring bisphosphate **3a** gave 60% yield and 92% ee using **L12** at 0 ºC which was deemed satisfactory. Using **L9** at room temperature gave 66% yield but reduced the ee to 87%. Hence substrates **1a** and **3a** were desymmetrized using **L12** at 0 ºC and **2a** used **L9** at room temperature.



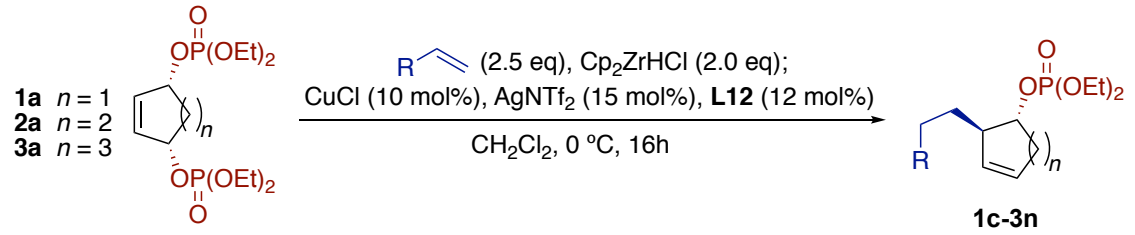
Scheme 2.10. Effect of ring size on desymmetrization.

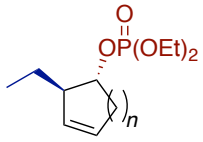
We next investigated the alkene pro-nucleophile scope to test if the desymmetrization was general and achieved the aim of providing better functional group tolerance than other organometallic methods (Scheme 2.11). The reaction was shown to be tolerant of a range of all

carbon nucleophiles, allowing the addition of sterically hindered alkenes as shown by **1f**-**2g**. The addition of ethene could also be carried out on 4 mmol scale with **1a** in 67% yield and 90% ee. Alkyl chlorides were compatible with the reaction with **2i** giving 67% yield and 95% ee. When alkyl bromides were used the coupling products were still obtained but in yields of <40%, which is likely due to reduction by Schwartz' reagent competing with hydrozirconation. Silyl protecting groups were tolerated (**1k**-**3k**) as well as substituted styrenes (**1l**-**2m**) which would likely not be compatible with other organometallic species. These functional groups can also serve as handles for further manipulation if desired. Interestingly when an alkene with a tertiary amine substituent was used mixed results were obtained dependent upon the electrophile ring size. Using the 5- or 7- membered ring systems gave low enantioselectivities, but high yields for **1a**. However, using **2a** gave 83% yield and 86% ee. These results were reproduced consistently and were not dependent on the use of **L9** or **L12**. If the alkylzirconium species undergoes transmetallation with the catalyst it is possible that the nitrogen atom could chelate to copper, but it is unknown why the ring size of the electrophile would have an impact on these results. As a general rule the highest yields and enantioselectivities are obtained with substrate **2a**, whilst they are the lowest for **1a**. It is known that 5-membered rings can often give poorer results in a range of asymmetric catalytic reactions, possibly down to the flatter nature of the ring which makes discrimination between enantiotopic faces more difficult.[7,89,149]

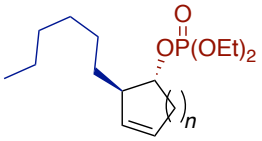
Some alkenes were not tolerated by the reaction (Scheme 2.12). 1,4-Pentadiene resulted in partially hydrogenated product via hydrozirconation. Interestingly allyl chloride resulted in the low yielding addition of a propyl group as a racemate, presumably via a π-allyl species. Allyltrimethylsilane which is effective in other CuAAA reactions developed in the Fletcher group gives no product in the desymmetrization. It may be that the electron rich nucleophile can undergo additions at the phosphorus center. Other functional groups which are reduced by Schwartz' reagent such as acetals, alkynes and amides were also unsuccessful.

Scheme 2.11. Alkene scope

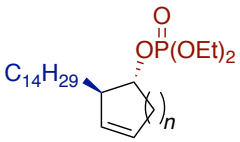




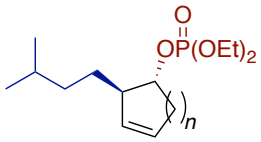
1c *n* = 1, 82%, ee 90%
2c *n* = 2, 79%, ee 97%[a]



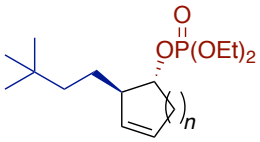
1d *n* = 1, 64%, ee 90%
2d *n* = 2, 87%, ee 96%[a]



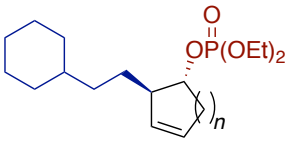
1e *n* = 1, 55%, ee 90%
2e *n* = 2, 74%, ee 96%[a]



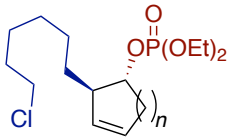
1f *n* = 1, 60%, ee 90%
2f *n* = 2, 78%, ee 96%[a]



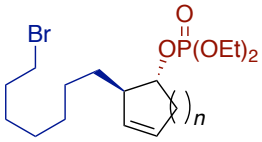
1g *n* = 1, 48%, ee 91%
2g *n* = 2, 63%, ee 95%[a]



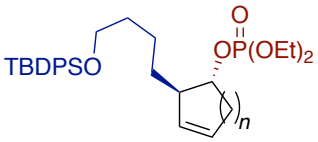
1h *n* = 1, 56%, ee 91%
2h *n* = 2, 68%, ee 95%[a]



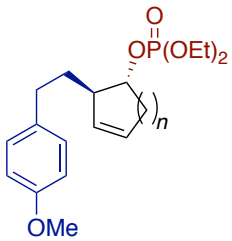
1i *n* = 1, 45%, ee 91%
2i *n* = 2, 67%, ee 95%[a]



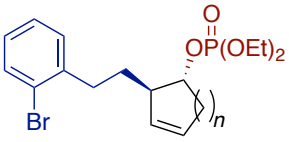
1j *n* = 1, Yield 28%, ee 88%
2j *n* = 2, Yield 36%, ee 90%[a]



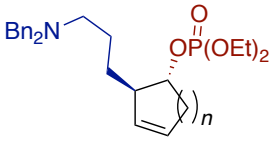
1k *n* = 1, 51%, ee 89%
2k *n* = 2, 64%, ee 92%[a]
3k *n* = 3, 60%, ee 91%



1l *n* = 1, 70%, ee 91%
2l *n* = 2, 70%, ee 99%[a]
3l *n* = 3, 52%, ee 94%



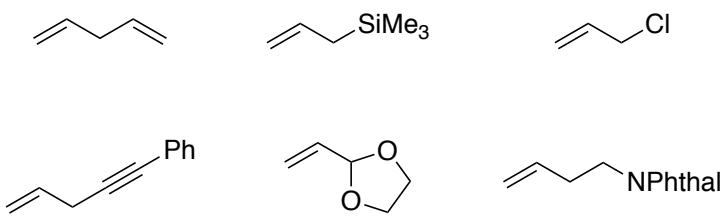
1m *n* = 1, 53%, ee 83%
2m *n* = 2, 61%, ee 91%[a]



1n *n* = 1, Yield 92%, ee 37%
2n *n* = 2, Yield 83%, ee 86%
3n *n* = 3, Yield 19%, ee 67%

[a]**L9** used at room temperature

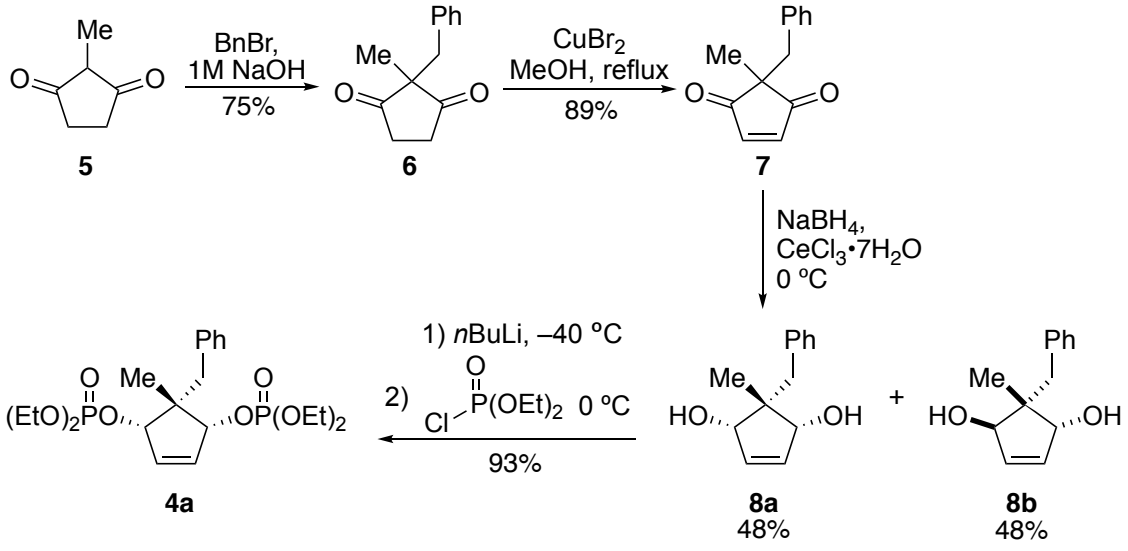
Scheme 2.12. Unsuccessful alkenes.



2.4.3 Quaternary Centers

The desymmetrization of simple cyclic *meso*-bisphosphates was shown to be successful with a range of alkylzirconium nucleophiles. In order to expand upon this work, we decided to investigate substitution at the 2-position of the bisphosphate electrophile. This would present an opportunity to develop a desymmetrization of a *meso*-compound bearing a pro-quaternary center using CuAAA. As previously discussed these desymmetrizations are rare and there are no examples using AAA.

To investigate this, we synthesised a cyclic 5-membered *meso*-bisphosphate with a methyl and benzyl group at the 2 position (**4a**) (Scheme 2.13). Synthesis began with the benzylation of 2-methyl-1,3-cyclopentanedione (**5**) under biphasic conditions to give dione **6**. A formal oxidation via bromination/elimination formed dienone **7**. Luche reduction afforded the diol as a 1:1 mixture of *cis*:*trans* diastereomers. However, the *cis* diol **8a** was obtained pure via column chromatography and NOESY experiments showed that the methyl group was *anti* to the alcohol and the benzyl group was *syn*. Subsequent phosphorylation via double deprotonation with *n*BuLi afforded the desired *meso*-bisphosphate **4a**.

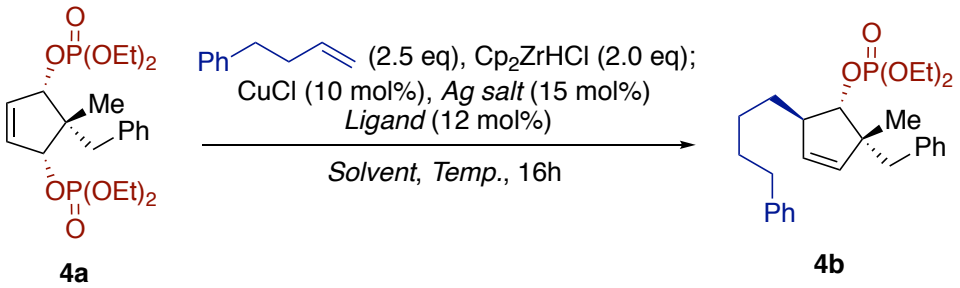


Scheme 2.13. Synthesis of 2-substituted *meso*-bisphosphate **4a**.

Examples of Luche reductions in the literature show a preference for formation of the *cis* diol when the substituents in the 2-position are equivalent.[150,151] In our case obtaining a 1:1 mixture there are 2 possibilities to explain the observed stereochemistry. It is possible that the first reduction is selective, with the hydride delivered *anti* to the larger benzyl group and that the second reduction is non-selective due to a change in conformation or chelation to the newly formed alcohol which could direct the subsequent reduction. Conversely it is possible that the first reduction is non-selective, thus giving a 1:1 mixture of hydroxyketones, with the second reduction always occurring *anti* to the benzyl group, giving the observed 1:1 mixture.

With a scalable synthesis for **4a** developed, a small screen of desymmetrization conditions was examined to determine if any other copper/ligand/solvent combinations may be more optimal for the 2-substituted substrate (Table 2.3). Applying the conditions used for substrate **1a** using **L12** at 0 ºC pleasingly gave *anti*-S_N2' product **4b** as a single diastereomer in 56% yield and 93% ee (entry 1). Switching to the conditions used for **2a** using **L9** at room temperature improved the results to 70% yield and 94% ee (entry 2). Other indane based ligands gave lower yields (entries 3-4). Switching the copper counter-ion to OTf gave 96% ee, albeit in low yield (entry 5). A brief solvent screen showed no further improvement, with $CHCl_3$ giving significantly lower ee (entries 6-8). Finally increasing the concentration to 0.5M also showed no further improvement (entry 9). The conditions in entry 2 were deemed to be optimal and it was apparent that the enantioselectivity of the desymmetrization of **4a** was greater than that of **1a** under several conditions. It may be possible that the substitution at the 2 position aids enantiotopic discrimination upon co-ordination of the chiral catalyst.

Table 2.3. Optimisation of desymmetrization conditions for **4a**.



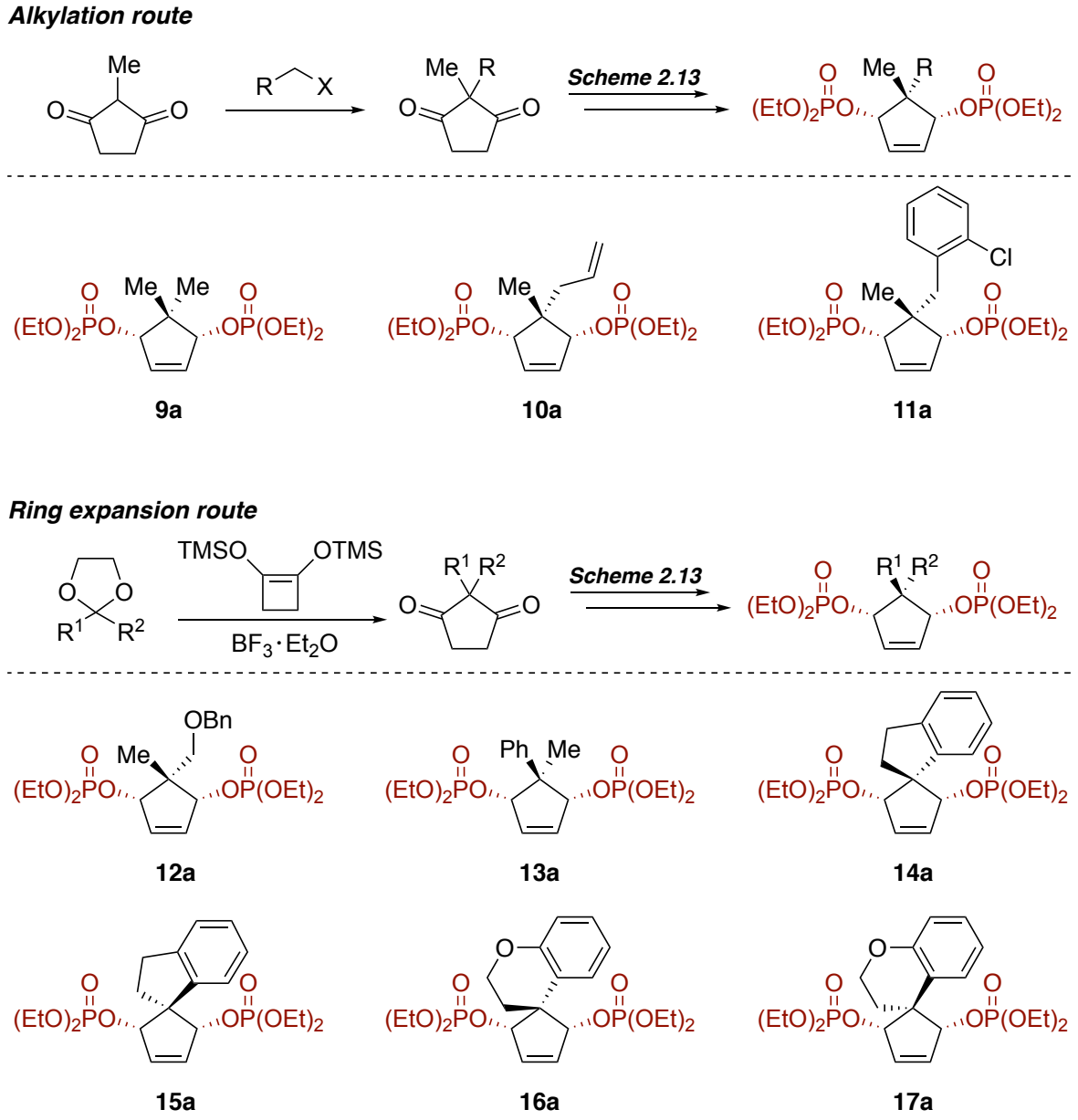
4a **4b**

Entry	Ag Salt	Ligand	Solvent	T / ºC	Yield (%)	ee (%)[a]
1	$AgNTf_2$	L12	CH_2Cl_2	0	56	93
2	$AgNTf_2$	L9	CH_2Cl_2	rt	70	94
3	$AgNTf_2$	L10	CH_2Cl_2	rt	47	93
4	$AgNTf_2$	L11	CH_2Cl_2	rt	47	90
5	AgOTf	L9	CH_2Cl_2	rt	24	96
6	$AgNTf_2$	L9	$CHCl_3$[b]	rt	63	78
7	$AgNTf_2$	L9	Et_2O[b]	rt	50	93
8	$AgNTf_2$	L9	PhMe[b]	rt	58	94
9[c]	$AgNTf_2$	L9	CH_2Cl_2	rt	55	92

Conditions: Reactions carried out on 0.4 mmol scale of **4a** at 0.2M. [a]ee determined by chiral HPLC. [b]Hydrozirconation mixture in 0.4 mL CH_2Cl_2, catalyst mixture in 1.6 mL of stated solvent. [c]Concentration 0.5M.

Further substrates were required to assess if the desymmetrization of *meso*-bisphosphates with pro-quaternary centers was general (Scheme 2.14). Using the method to synthesise **4a** allowed access to a range of bisphosphates with a methyl group and another substituent amenable to alkylation. This method was used to synthesise *gem*-dimethyl substrate **9a**, allyl substituted **10a** and 2-chlorobenzyl substituted **11a**. In order to access other substrates a route using a Lewis-acid catalysed ring expansion of 1,2-bis(trimethylsiloxy)cyclobutene with ketones was used.[152,153] This allowed preparation of substrates which were not accessible by alkylation chemistry such as the ones bearing a benzyl protected alcohol (**12a**), a phenyl ring (**13a**) and spirocyclic analogues such as indanes **14a** and **15a**, as well as chromanes **16a** and **17a**.

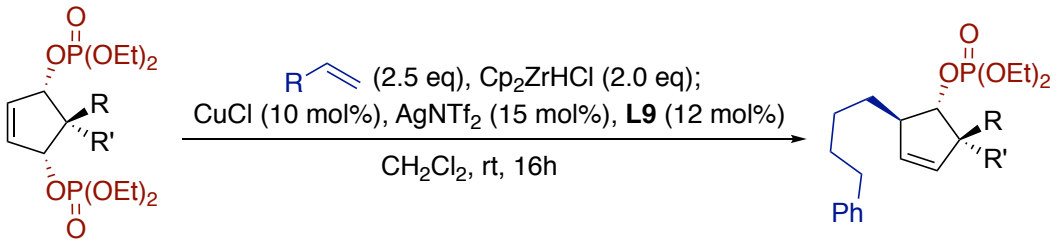
Interestingly **13a** was isolated with different stereochemistry to other methyl substituted substrates, with the methyl group *syn* to the phosphate substitutents. This may be due to a planar phenyl ring being less sterically demanding than a methyl group with a freely rotating bond during the reduction step. Also, the spirocyclic compounds were isolated as 1:1:1 mixtures of both *cis* diastereomers and the *trans* diastereomer, which were all separable by column chromatography.



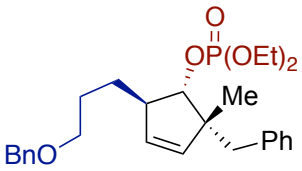
Scheme 2.14. Synthesis of 2-substituted *meso*-bisphosphates.

Using the optimised conditions above (Table 2.3, entry 2) **4a** was desymmetrized with functionalised alkenes to show that the reaction was tolerant of useful functional groups (Scheme 2.15). Benzyl protected alcohol (**4c**) was synthesised in good yield with 89% ee. An alkyl bromide nucleophile which gave low yields in previous examples reacted with **4a** in 44% yield and 90% ee (**4d**). 2-Bromo-5-fluorostyrene, an alkene with 2 orthogonal handles for further functionalisation, was added in 53% yield and 86% ee (**4e**). An alkene with a benzyl protected amine moiety was also added with 63% yield and 86% ee (**4f**). In this case the alkene nucleophile was one carbon chain longer than in the case of **1n**-**3n** which may have prevented chelation of the nitrogen atom to copper. The 2-substituted *meso*-bisphosphates **9a**-**17a** were desymmetrized with 4-phenyl-1-butene to examine the effect of substitution pattern in the 2-position on the reaction. The substrates obtained via the alkylation route all were all desymmetrized successfully, giving good yields and >90% ee as single diastereoisomers in all cases (**9b**-**11b**). The substrate with a benzyl protected alcohol substituent was similarly effective (**12b**). Spirocyclic substrates were also desymmetrized successfully. When the smaller methylene substitutents were *anti* to the phosphates (**14a** and **16a**) good yields and ees were obtained. This represents a useful method for the synthesis of enantioenriched spirocycles which can be difficult to prepare with diastereo- and enantiocontrol.[154–158] However when the opposite diastereomers **15a** and **17a** were used low yields were obtained, and in the case of **17b** only 13% ee. In these cases, the large aromatic units of the spirocycles were *anti* with respect to the phosphate groups. When a phenyl ring was *anti* to the phosphates as is the case in **13a** the desymmetrization is also ineffective, giving just 29% yield and 20% ee. Based on these results it seemed larger substituents present *anti* to the phosphate groups were not well tolerated, which may result from hindering the interaction between the catalyst and substrate which will be discussed later.

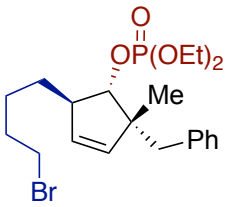
Scheme 2.15. Bisphosphate scope.



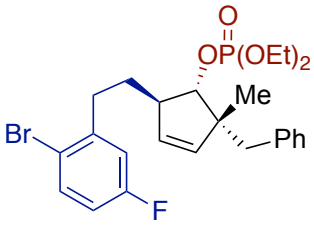
4a, **9a-17a** **4c-4f**, **9b-17b**



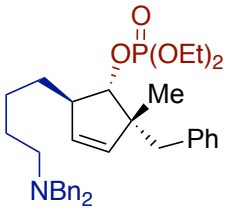
4c, 67%, ee 89%



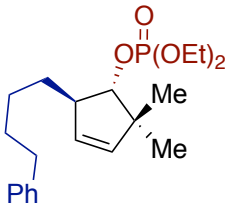
4d, 44%, ee 90%



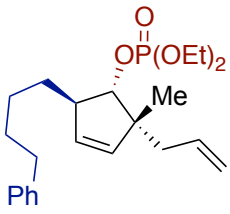
4e, 53%, ee 86%



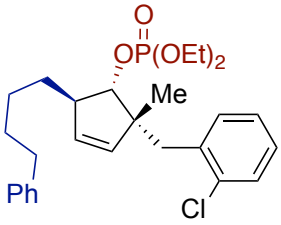
4f, 63%, 86% ee



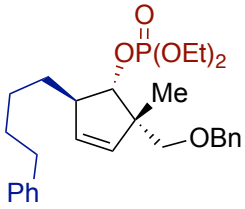
9b, 74%, ee 91%



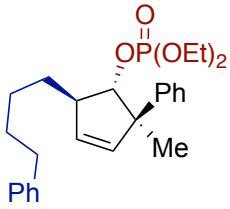
10b, 88%, ee 94%



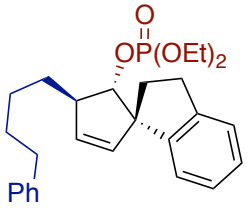
11b, 79%, ee 94%



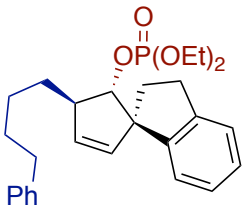
12b, 66%, ee 90%



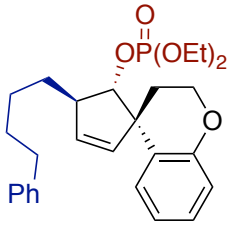
13b, 29%, ee 20%



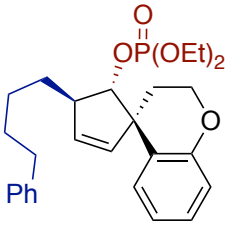
14b, 61%, ee 90%



15b, 19%, ee 91%



16b, 57%, ee 91%

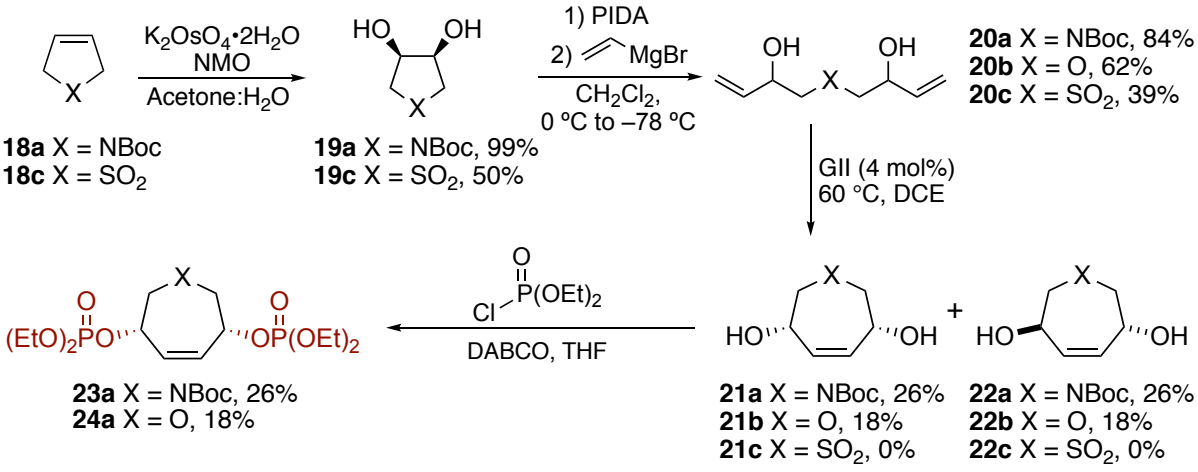


17b, 4%, ee 13%

2.4.4 Other Substrates

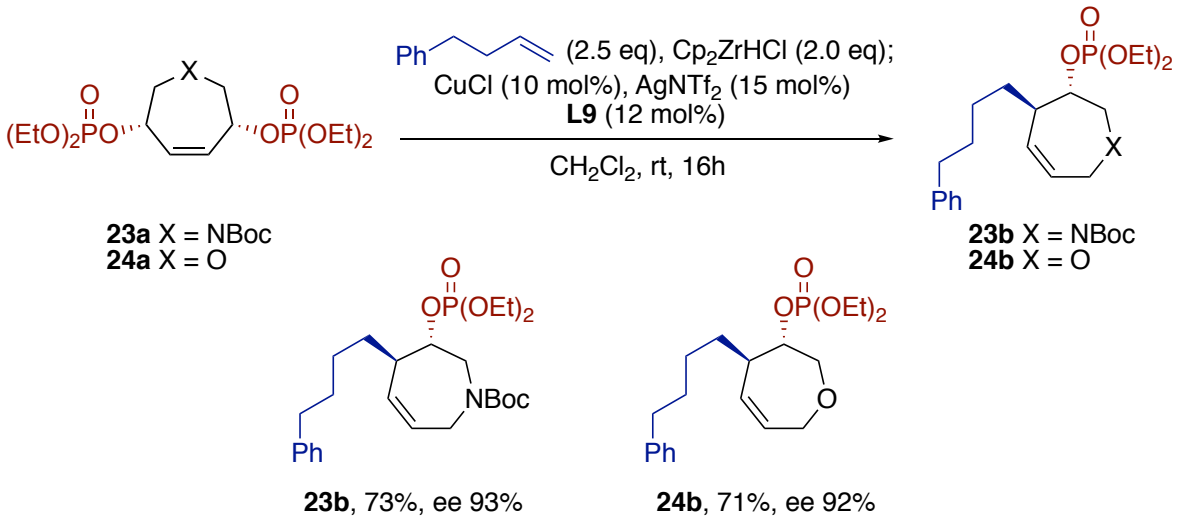
Previous desymmetrizations using CuAAA have used carbocyclic substrates exclusively as the use of heteroatoms in asymmetric copper-catalysis can greatly affect results.[159] Despite this we envisaged that medicinally relevant 7-membered ring heterocycles could be accessed via the desymmetrization, allowing synthesis of substituted oxepenes and azapenes.[160,161] Asymmetric transformations of these ring systems also appeared to be unexplored in the literature.

An *N*-Boc protected azepene and oxepene *meso*-bisphosphates were targeted to investigate if heterocycles could be desymmetrized via CuAAA (Scheme 2.16). Synthesis of the nitrogen analogue began with dihydroxylation of *N*-Boc-2,5-dihydropyrrole (**18a**) to give diol **19a**. Oxidative cleavage with PIDA and subsequent trapping of the dialdehyde with vinylmagnesium bromide gave the bis-allylic alcohol **20a**. Ring-closing metathesis with Grubbs II catalyst yielded the desired diol **21a** as a separable mixture of *cis*:*trans* diastereomers. Phosphorylation afforded the desired bisphosphate **23a**. The oxepene analogue could be synthesised in a similar fashion beginning from the diol intermediate which is commercially available to give bisphosphate **24a**. Attempts at making a sulfone derivative were also made, however the ring-closing metathesis step gave no product (**18c**-**20c**).



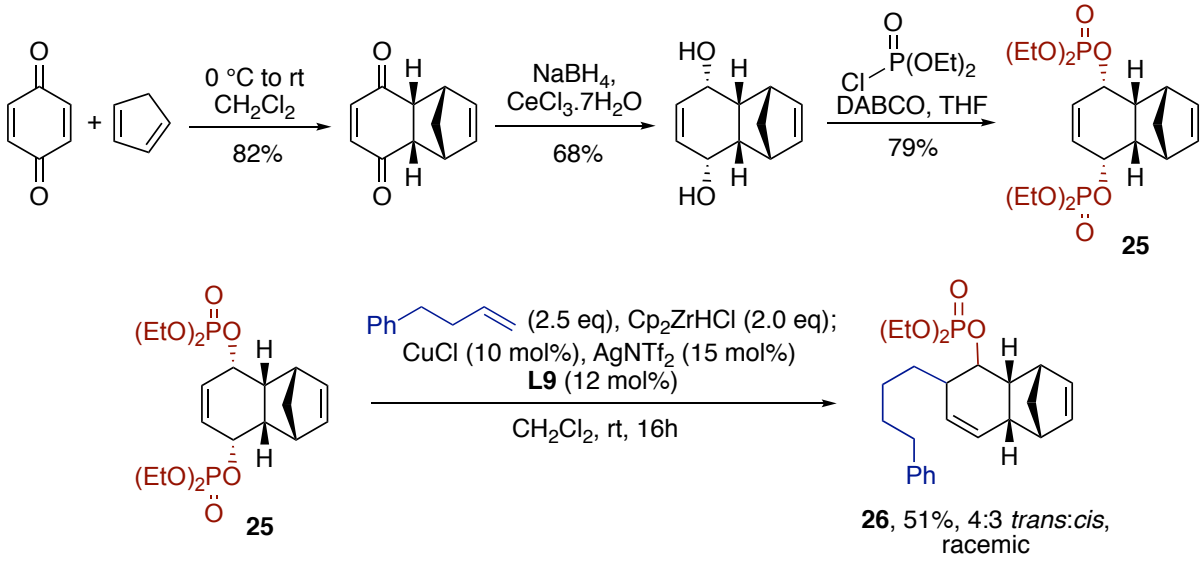
Scheme 2.16. Synthesis of heterocyclic bisphosphates.

The heterocycles **23a** and **24b** were subjected to the desymmetrization conditions used for **4a** and to our delight both underwent addition with 4-phenyl-1-butene in good yields and high enantioselectivities (Scheme 2.17). It is not known why the heterocyclic bisphosphates outperform the carbocyclic analogue **3a**.



Scheme 2.17. Desymmetrization of heterocyclic bisphosphates.

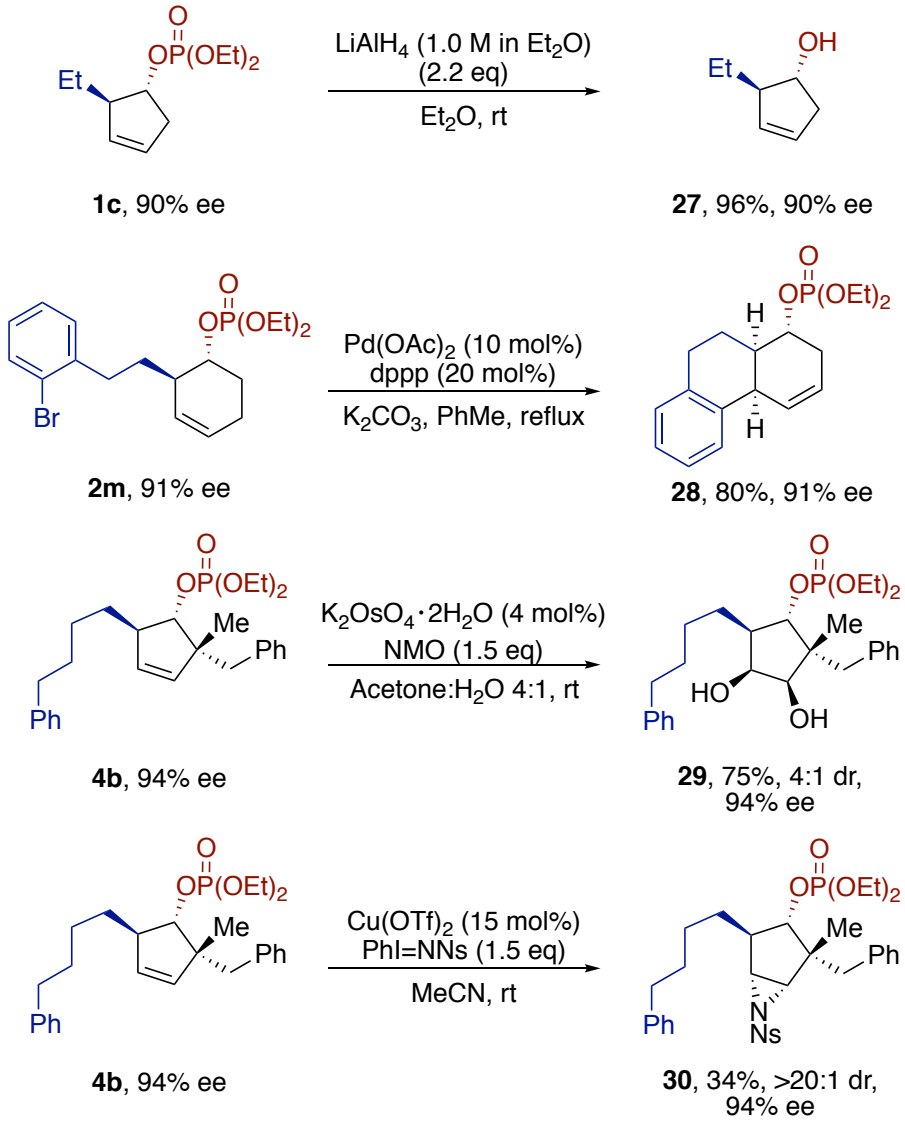
A bicyclic bisphosphate derived from the *p*-benzoquinone/cyclopentadiene Diels-Alder adduct (**25**) was also synthesised and subjected to the desymmetrization conditions (Scheme 2.18). However, the product **26** was obtained as a racemate and gave *trans*:*cis* diastereomers in a 4:3 ratio in 51% yield. It is unknown why this substrate performed so poorly.



Scheme 2.18. Attempted desymmetrization of bicyclic bisphosphate **25**.

2.4.5 Product Derivatisations

The downstream reactivity of the desymmetrization products was investigated to highlight their potential application in synthesis (Scheme 2.19). The phosphate group in product **1c** could be deprotected with $LiAlH_4$ in to give alcohol **27** in excellent yield. The product of CuAAA with 2-bromostyrene as the coupling partner could undergo an intramolecular Heck reaction to give a tricyclic product as illustrated by the conversion of **2m** to **28**. Dihydroxylation of 2-substituted product **4a** furnished diol **29** in 75% yield with 4:1 dr, creating a cyclopentane with 5 contiguous stereocenters, which is otherwise difficult to achieve with such a degree of control. Finally the double bond of **4b** underwent a Cu-catalysed aziridination using a nitrene source to yield **30**.[162,163] Optimisation of this procedure only reached 34% yield, likely due to steric crowding in the substrate. However, the procedure was highly diastereoselective and interestingly gave different stereochemistry to the dihydroxylation. It is possible that the phosphate could direct the aziridination reaction.

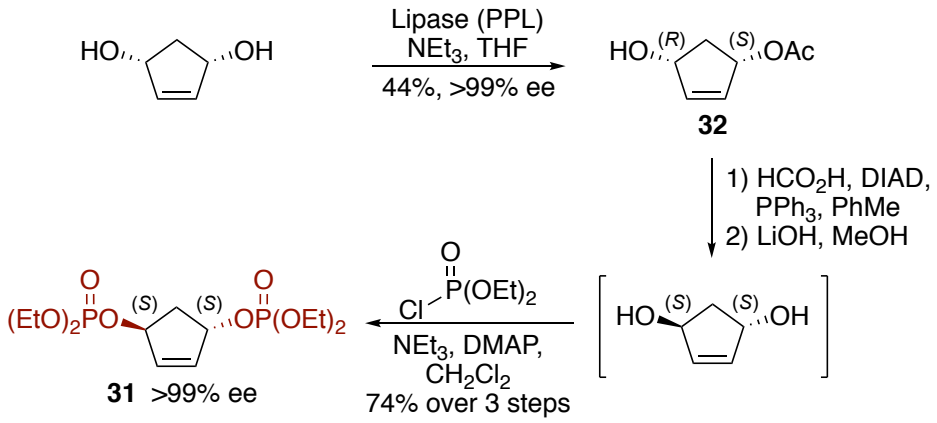


Scheme 2.19. Further functionalisation of products.

2.4.6 Kinetic Resolution of Cyclic Bisphosphates

Throughout the reaction optimisation and examination of the scope we only observed *anti*-S_N2' addition of the alkylzirconium species. This is consistent with generally accepted mechanisms of CuAAA, particularly where the copper species is electron deficient, as is the case with $CuNTf_2$.[91,99] In order to obtain the *syn* diastereomer it was clear that modification of the catalyst and conditions would not give the desired result. However, if an *anti*-S_N2' addition of a copper species was the stereodetermining step then using the opposite diastereomer of bisphosphate would give the *syn* product.

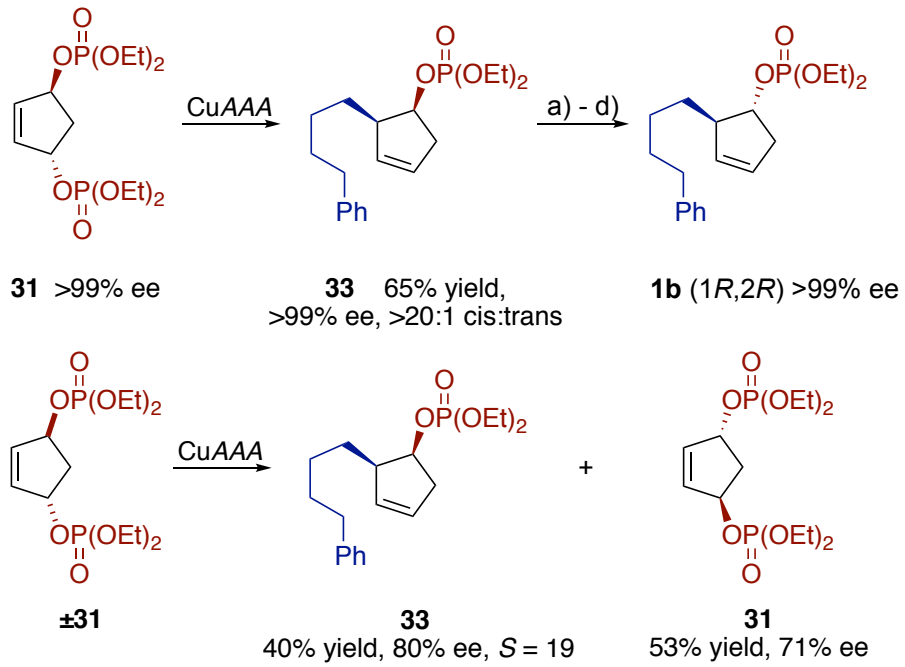
To investigate this a *trans*-bisphosphate would need to be synthesised. This molecule would no longer be a *meso*-compound and would exist as a mixture of enantiomers. Hence, the desired *trans*-bisphosphate was synthesised both in an enantiopure form (**31**) and as a racemate (**±31**) (Scheme 2.20). The enantiopure bisphosphate was made via an enzymatic mono-acetylation of *cis*-4-cyclopentene-1,3-diol to give enantiopure alcohol **32**.[164] Inversion of the alcohol using Mitsonobu conditions followed by ester hydrolysis gave the *trans*-diol which was phosphorylated in a telescoped procedure to give **31** in >99% ee. The racemic synthesis was completed in an analogous fashion, except the acetylation step used acetic anhydride with no catalyst. The absolute stereochemistry of **31** was assigned to be (*S*,*S*) based on the known absolute stereochemistry of **32**.



Scheme 2.20. Synthesis of enantiopure *trans*-bisphosphate **31**.

Desymmetrization of **31** using the conditions applied to the *cis* analogue **1a** did indeed give the *syn* diastereomer **33** in an enantiospecific fashion. Using the opposite absolute stereochemistry of **L12** also gave the same product, albeit in a slightly lower yield (Scheme 2.21). We hypothesised that the use of racemic **±31** would give a kinetic resolution. Cu-catalysed kinetic resolutions of racemic starting material are rare[165,166] and to the best of our knowledge there are no reports of Cu-catalysed additions to *trans*-diol derivatives. Pleasingly **±31** did undergo kinetic resolution giving **33** in 40% yield and 80% ee, with **31** recovered in 53% yield and 71% ee; a selectivity factor *S* of 19. To assign the absolute stereochemistry of the previous

desymmetrization products, **33** (with known absolute stereochemistry from **32**) was converted to the *anti*-diastereomer via a multistep procedure. Cleavage of the phosphate followed by Mitsonobu inversion and phosphorylation gave (1*R*,2*R*)**1b** with the same sign of optical rotation as the other desymmetrization products.

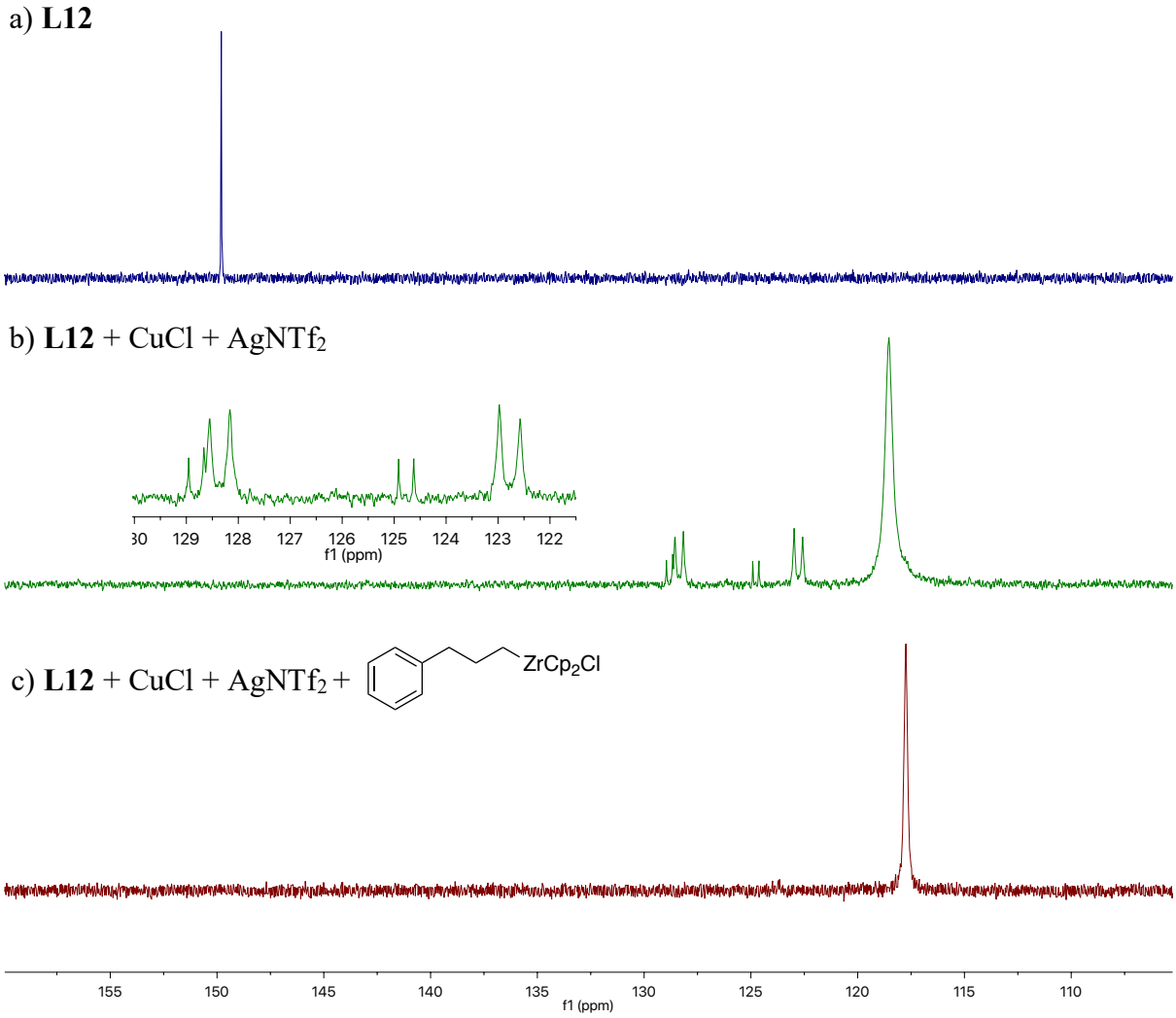


Scheme 2.21. CuAAA with *trans*-bisphosphates. Reaction conditions: CuAAA see Table 2.2, entry 2. **a)** $LiAlH_4$ (2.2 eq), Et_2O, rt; **b)** HCO_2H (2.05 eq), DIAD (2.0 eq), PPh_3 (2.0 eq), Toluene 0 °C; **c)** NEt_3 (0.05 eq), MeOH, rt; **d)** $(EtO)_2P(O)Cl$ (2.0 eq), NEt_3 (2.0 eq), DMAP (0.33 eq), CH_2Cl_2, rt. Selectivity factor S calculated using $S = \ln[1 - c(1 + ee)]/\ln[1 - c(1 - ee)]$.

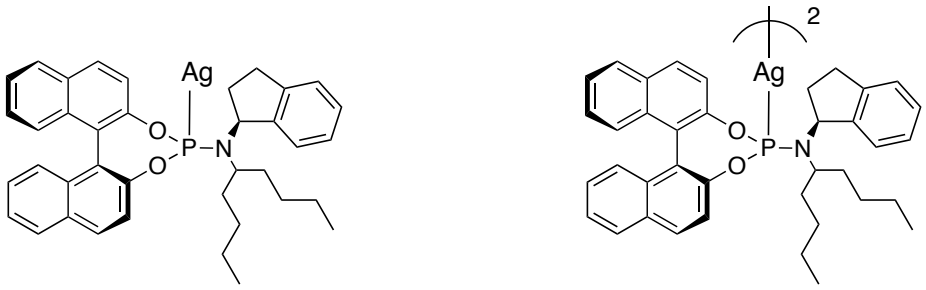
2.4.7 Postulated Mechanism

Additions to *trans*-bisphosphate **33** reaffirmed our belief that the *anti*-S_N2' addition of a copper species was the stereodetermining step in the desymmetrization reaction. Further details regarding the mechanism were investigated by NMR. In situ analysis of the copper-ligand mixture by ^{31}P NMR showed complexation of **L12** to the copper catalyst forming a broad peak at 118.5 ppm, a common observation for copper-phosphoramidite complexes (Scheme 2.2 b).[146] In addition, there were 2 sets of what appeared to be doublet of doublets present. These were Ag^I-phosphoramidite complexes and were in fact doublets. ^{31}P can couple to both ^{107}Ag (52% natural abundance) and ^{109}Ag (48% natural abundance), both of which are spin ½ nuclei, giving 2 sets of coupling constants. ^{109}Ag also has a larger γ value (gyromagnetic ratio) than ^{107}Ag. The result of this is that $J(^{31}P–^{109}Ag)$ coupling gives larger values than $J(^{31}P–^{107}Ag)$ coupling by approximately a factor of 1.15. This combined with the natural abundances means that ^{31}P coupled to silver often appears as a roofing doublet of doublets.[167,168] The larger doublet at 125.6 ppm showed a $J(^{31}P–^{107}Ag)$ value of 1053.1 Hz, which is indicative of a monodentate Ag-ligand complex, which can only be observed at room temperature with bulky ligand such as the phosphoramidite **L12**. The smaller doublet signal at 126.8 ppm showed a $J(^{31}P–^{107}Ag)$ value of 760.4 Hz, which suggested a multidentate Ag-ligand complex, likely bidentate considering the bulky nature of **L12** (Scheme 2.2 d).[169] Previous work in the Fletcher group showed Ag-phosphoramidite complexes present from counterion exchange to decrease enantioselectivity in CuACA reactions, however after addition of the alkylzirconium reagent the peaks corresponding to Ag-phosphoramidite complexes disappear, leaving just the Cu-phosphoramidite signal (Scheme 2.2 c). It is possible that the chloride present in the alkylzirconium complex sequesters the remaining silver in the reaction mixture, leaving just the Cu-ligand complex. No other significant observations were made using in situ NMR experiments except for conversion of starting material to product via no identifiable

intermediates. Diffusion-ordered spectroscopy (DOSY) was used in an attempt to detect a transmellated copper species[170] but no useful results were obtained.

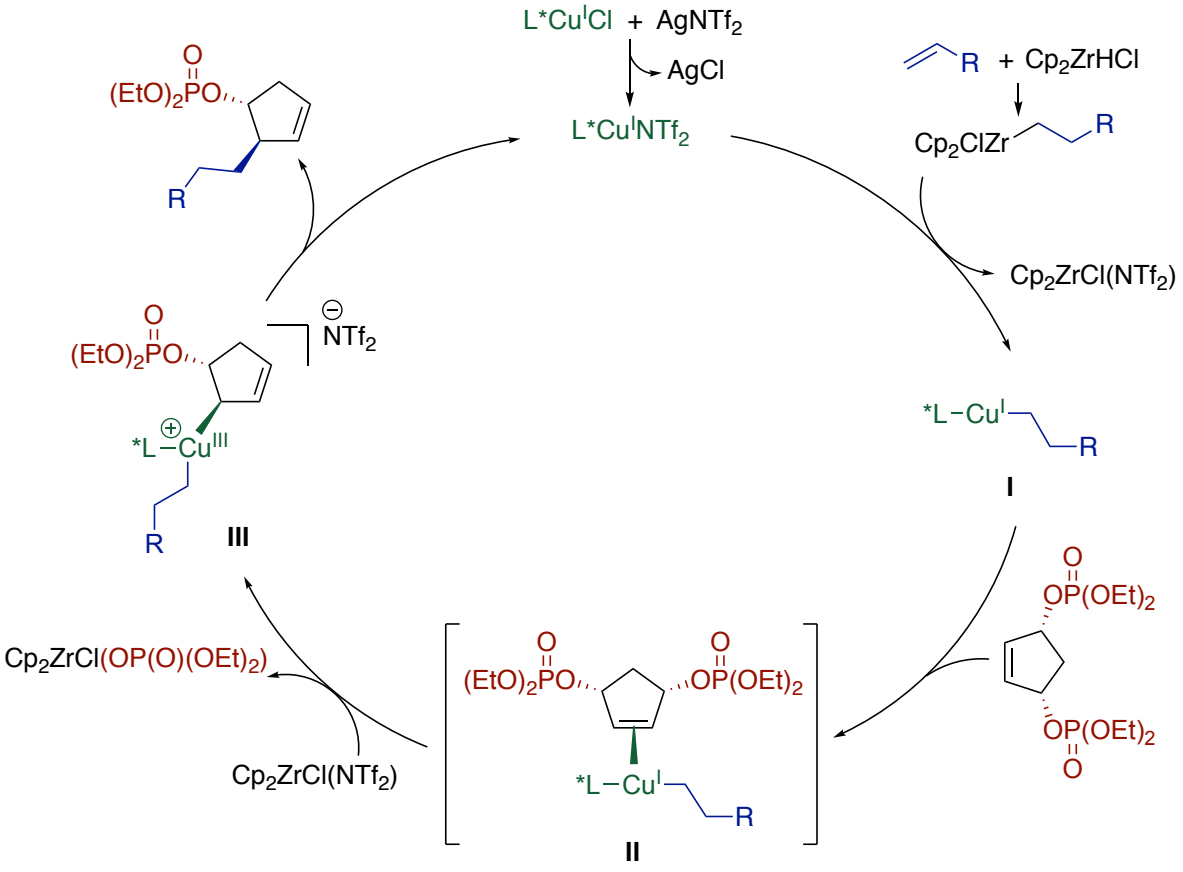


d)



Scheme 2.22. In situ ^{31}P NMR studies of the catalyst. All recorded in $CDCl_3$. **a)** ^{31}P NMR of free ligand **L12**. **b)** ^{31}P NMR of **L12** and catalyst solution. **c)** ^{31}P NMR of **L12**, catalyst solution and hydrozirconated 4-phenyl-1-butene. **d)** Possible Ag-phosphoramidite complexes detected in b).

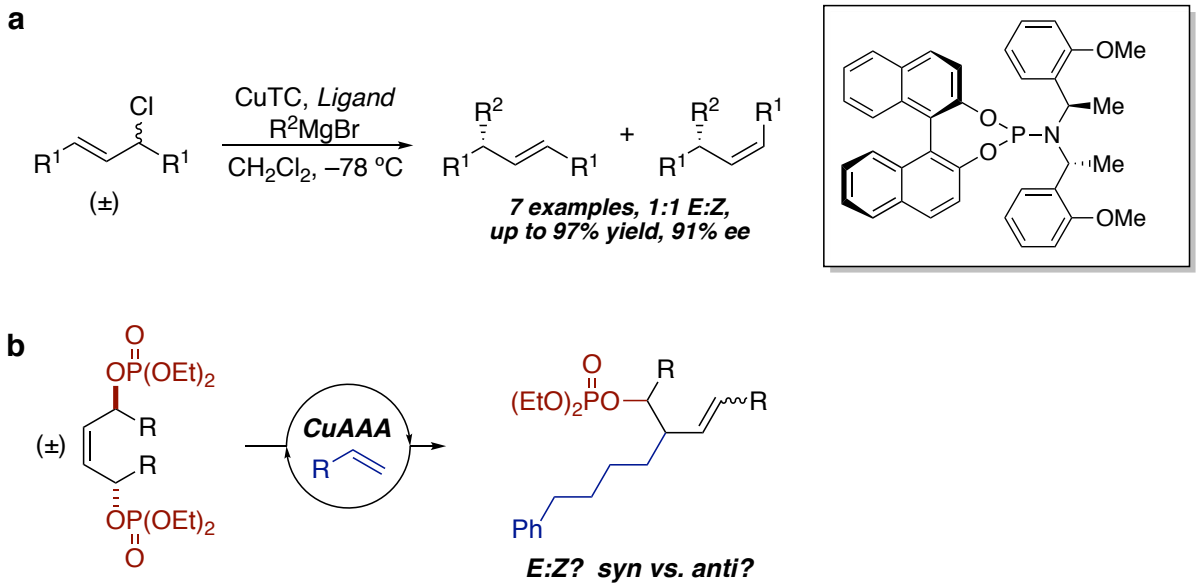
Mechanistically, we postulate that a Cu-phosphoramidite complex undergoes transmetallation with the hydrozirconated alkene to give alkyl-copper species **I**, which can co-ordinate to the bisphosphate and form an alkene donor complex (**II**) (Scheme 2.23). This may explain why large substituents *anti* to the phosphate groups are not well tolerated in the reaction, as exemplified by **13a**, **15a** and **17a**. Although in situ NMR studies showed no evidence of transmetallation it is possible that **I** reacts faster than it can be observed. **II** may react to form Cu^{III} σ-allyl species **III**, where the copper displaces the phosphate in a stereodetermining *anti*-S_N2' process. Reductive elimination of intermediate **III** would then give the product and regenerate the Cu-phosphoramidite catalyst.



Scheme 2.23. Postulated mechanism of desymmetrization of *meso*-bisphosphates via CuAAA.

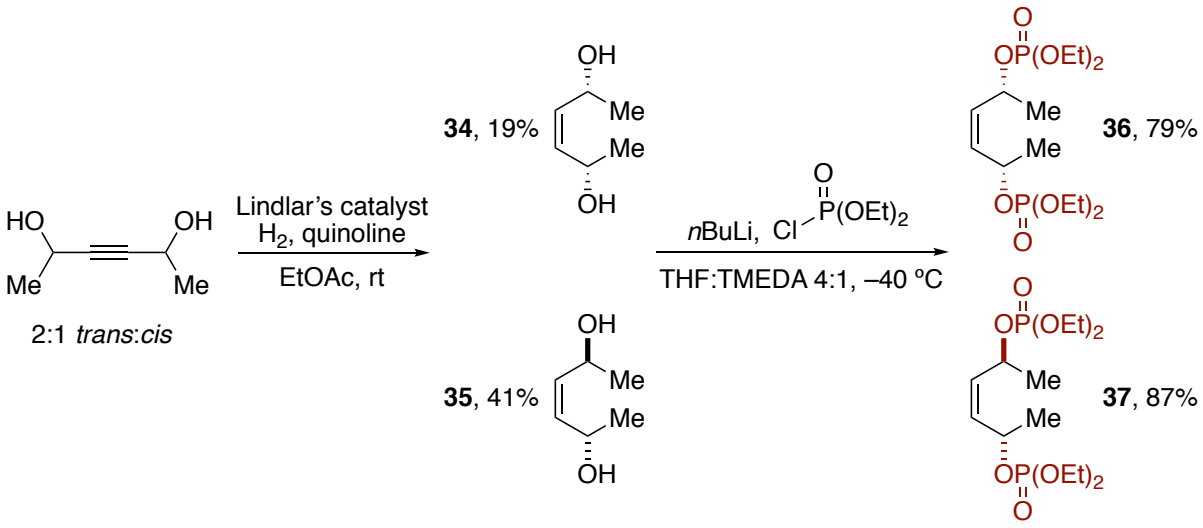
2.4.8 Kinetic Resolution of Linear Bisphosphates

Based on our successful kinetic resolution of cyclic *trans*-bisphosphates we wanted to apply our CuAAA method with alkylzirconium nucleophiles to linear *trans*-bisphosphates. Linear systems are often difficult substrates for asymmetric catalysis as they are conformationally more flexible than their cyclic counterparts.[8,9,171] We were encouraged by the parallel kinetic resolution reported by Alexakis and co-workers, which applied CuAAA with Grignard reagents to racemic linear allyl chlorides (Scheme 2.24 a).[172] The S_N2' products were obtained as roughly a 1:1 mixture of *E*:*Z* isomers, both in high ee. It was hypothesised that each enantiomer of the starting material reacted with the catalyst to give two different diastereotopic intermediates which led to the different products. Parallel kinetic resolutions and other enantiodivergent reactions are valuable processes to obtain enantiopure compounds from racemic mixtures, with efficiencies often higher than simple kinetic resolutions of starting material.[173–175] Our strategy was to apply CuAAA to racemic linear bisphosphates in the hope of observing an enantiodivergent process, either obtaining *E*:*Z* isomers, or perhaps *anti-syn* diastereomers (Scheme 2.24 b).



Scheme 2.24. **a)** Parallel kinetic resolution of linear allylic chlorides via CuAAA by Alexakis and co-workers. **b)** Our planned parallel kinetic resolution using linear *trans*-bisphosphates.

A linear bisphosphate with 2 methyl groups adjacent to the phosphate was selected as a model substrate as it closely resembled the cyclic analogue **1a**. Synthesis of the starting material was easily achieved from the *cis*-selective reduction of 3-hexyn-2,5-diol (purchased as a *cis*:*trans* mixture) to give diols **34** and **35** which could be separated and phosphorylated. (Scheme 2.25).

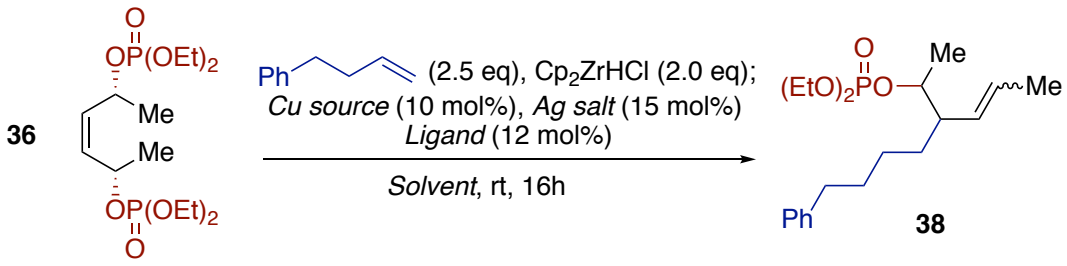


Scheme 2.25. Synthesis of *cis*-bisphosphate **36** and *trans*-bisphosphate **37**.

Our initial optimisation was carried out on the linear *cis*-bisphosphate **36**, as the analysis would be simpler than using the racemic *trans* form. Conditions found to be optimal here would then be used to investigate the *trans*-bisphosphate (Table 2.4). Applying CuAAA conditions using $CuNTf_2$ and **L9** to add 4-phenyl-1-butene gave product **38** in 18% yield as a single S_N2' regioisomer, but as a 3:1 *anti*:*syn* mixture and a 4.5:1 mixture of *E*:*Z* isomers (entry 1). The diastereomers were separated by column chromatography and the *anti*-diastereomer was shown to have an ee of 55% and the *syn* 53%. Separation of the *E*:*Z* isomers was not possible by SFC or HPLC so ee values were determined as combination of both geometrical isomers. A small counter-ion screen showed NTf_2 was still ideal in this case (entries 2-8). Ligands were next investigated, with **L13** giving the highest ee value of 83%, but only moderate control over dr and *E*:*Z* ratio (entry 13). Ligand **L14**, which is often used as a bidentate phosphoramidite in Rh and Ir-catalysis pioneered by the Carreira group,[176] gave 27% yield and good control of dr

(11:1) and the *E*:*Z* ratio (17:1) (entry 14). As a result **L15** and **L16** which are analogues of **L14** were screened but showed no further improvement of results (entries 15-16). Increasing the catalyst loading to 20 mol% with **L14** gave almost a single geometric isomer but the yield only improved to 32% (entry 17). Cooling the reaction to 0 ºC slightly improved selectivities but gave just 20% yield (entry 18) and heating to 40 ºC also failed to improve the yield whilst reducing selectivities (entry 19). A solvent screen using **L14** showed that $CHCl_3$ (entry 20) and PhMe (entry 24) gave improved yields of 47% but with reduced selectivities. Ethereal solvents gave impressive selectivities but yields were still >20% (entries 22-23). Overall these results were disappointing, with low conversion of the bisphosphate an issue. The liner substrate also gave poorer selectivities compared to cyclic systems, which was to be expected in a more flexible system.

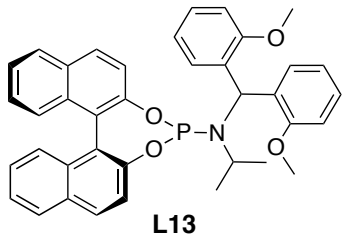
Table 2.4. Desymmetrization of linear *cis*-bisphosphate **34**.



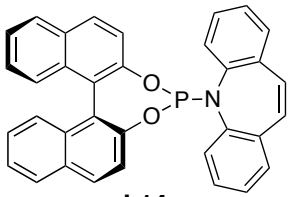
Entry	Cu Source	Ag Salt	Ligand	Solvent	Yield (%)	*anti*:*syn*	*E*:*Z*	ee (%)[d]
1	CuCl	$AgNTf_2$	L9	CH_2Cl_2	18	3:1	4.5:1	55
2	CuI	-	L9	CH_2Cl_2	Traces	-	-	-
3	CuTC	-	L9	CH_2Cl_2	-	-	-	-
4	CuCl	AgOTf	L9	CH_2Cl_2	Traces	-	-	-
5	CuCl	$AgClO_4$	L9	CH_2Cl_2	7	2:1	4:1	52
6	CuCl	$AgBF_4$	L9	CH_2Cl_2	5	2:1	3:1	18
7	CuCl	$AgPF_6$	L9	CH_2Cl_2	7	1.4:1	5:1	52

8	CuCl	$AgSbF_6$	L9	CH_2Cl_2	8	2:1	4:1	18
9	CuCl	$AgNTf_2$	L1	CH_2Cl_2	12	3.4:1	5:1	12
10	CuCl	$AgNTf_2$	L2	CH_2Cl_2	7	2:1	4:1	32
11	CuCl	$AgNTf_2$	L3	CH_2Cl_2	18	2:1	3:1	37
12	CuCl	$AgNTf_2$	L12	CH_2Cl_2	24	2.5:1	4:1	53
13	CuCl	$AgNTf_2$	L13	CH_2Cl_2	20	3.3:1	6:1	83
14	CuCl	$AgNTf_2$	L14	CH_2Cl_2	27	11:1	17:1	78
15	CuCl	$AgNTf_2$	L15	CH_2Cl_2	10	2:1	4:1	59
16	CuCl	$AgNTf_2$	L16	CH_2Cl_2	25	12:1	17:1	73
17[a]	CuCl	$AgNTf_2$	L14	CH_2Cl_2	32	20:1	20:1	76
18[b]	CuCl	$AgNTf_2$	L14	CH_2Cl_2	20	20:1	>20:1	76
19[c]	CuCl	$AgNTf_2$	L14	CH_2Cl_2	22	4.7:1	10:1	70
20	CuCl	$AgNTf_2$	L14	$CHCl_3$	47	1.5:1	2.5:1	61
21	CuCl	$AgNTf_2$	L14	DCE	28	8:3:1	14:1	74
22	CuCl	$AgNTf_2$	L14	Et_2O	18	11:1	>20:1	76
23	CuCl	$AgNTf_2$	L14	TBME	27	11:1	>20:1	79
24	CuCl	$AgNTf_2$	L14	PhMe	47	2.4:1	4:1	78

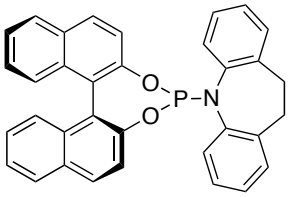
Conditions: Reactions carried out on 0.4 mmol scale of **1a**. 0.2M. [a]20 mol% CuCl, 24 mol% L14, 30 mol% $AgNTF_2$. [b]Reaction carried out at 0 ºC. [c]Reaction carried out at 40 ºC. [d]ee values of *anti*-diastereomer, mixture of inseparable *E*:*Z* isomers. Determined by SFC of purified product.



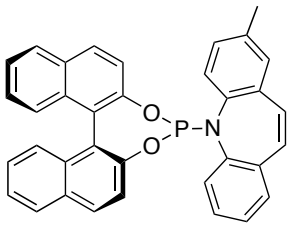
L13



L14

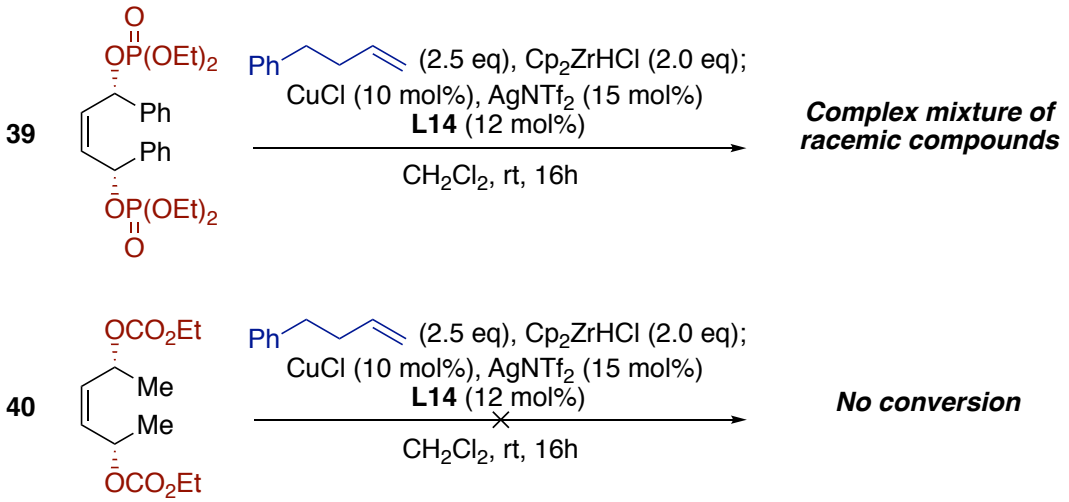


L15



L16

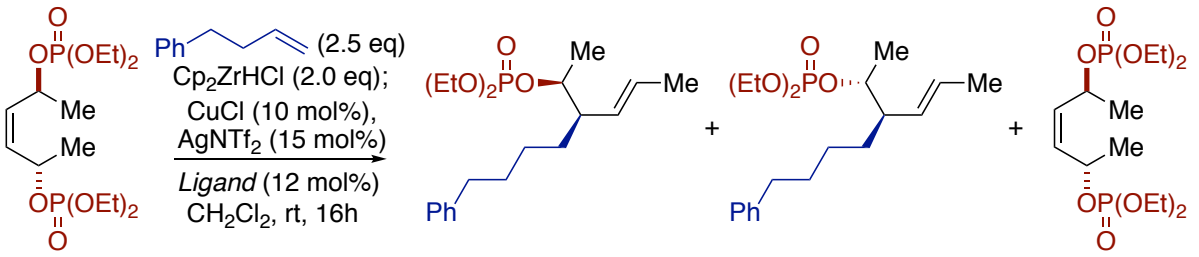
In an attempt to boost the reactivity of linear bisphosphate the methyl groups were switched out for phenyl rings, as it was thought this would stabilise any positive charge built up in the transition state of the allylic alkylation. Linear *cis*-bisphosphate **39** was synthesised in a similar fashion to **36** and **37**. Despite undergoing some hydrolysis during column chromatography **39** was obtained pure and subjected to the conditions shown in Table 2.4, entry 4, using **L14** (Scheme 2.26). Disappointingly, a complex mixture of regio-, diastereo- and *E*:*Z* isomers were observed by NMR analysis of the crude reaction mixture, and decomposition of the products occurred during an attempted purification. Chiral SFC analysis also showed a multitude of racemic peaks. Finally a biscarbonate derived from *cis*-diol **34** was synthesised but failed to react under CuAAA conditions.



Scheme 2.26. Attempted desymmetrizations of phenyl-substituted linear bisphosphate **39** and methyl substituted linear biscarbonate **40**.

Despite this, we decided to examine the racemic *trans*-bisphosphate **37** using **L13** and **L14** which provided the highest enantioselectivities for the desymmetrization of **36** (Scheme 2.27). Using **L13** gave 28% yield of **38** in a 2.5:1 dr favouring the *syn* diastereomer with 20:1 *E*:*Z* ratio, which replicates the reversal of selectivity shown by the cyclic bisphosphates. A 34% ee was obtained for the major *syn* product and 27% ee for the *anti*-product. The remaining starting material was recovered in 55% yield and 14% ee. Using **L14** gave 25% yield of **38** with the same dr and *E*:*Z* ratio, but 74% ee. The *anti*-diastereomer was obtained in 69% ee. Starting

material was recovered in 57% yield and 30% ee, an *S* factor of 9, in comparison with an *S* factor of 19 obtained for the cyclic system. What appearing to be occurring was a regular kinetic resolution of starting materials, with the selectivity of the reaction governed by the preference of an *anti*-S_N2' addition of the alkylzirconium reagent. Unlike the method described by Alexakis and co-workers[172] there was a significant preference to form the *E* isomer in the alkene product. It appeared there was no likelihood of this system producing an enantiodivergent reaction and no further experiments were conducted.



(±)-37		*syn*-38	*anti*-38	37
	L13	20%, 34% ee	8%, 29% ee	55%, 14% ee
	L14	18%, 74% ee	7%, 69% ee	57%, 30% ee

Scheme 2.27. Kinetic resolutions of linear *trans*-bisphosphate **37** using **L13** and **L14**.

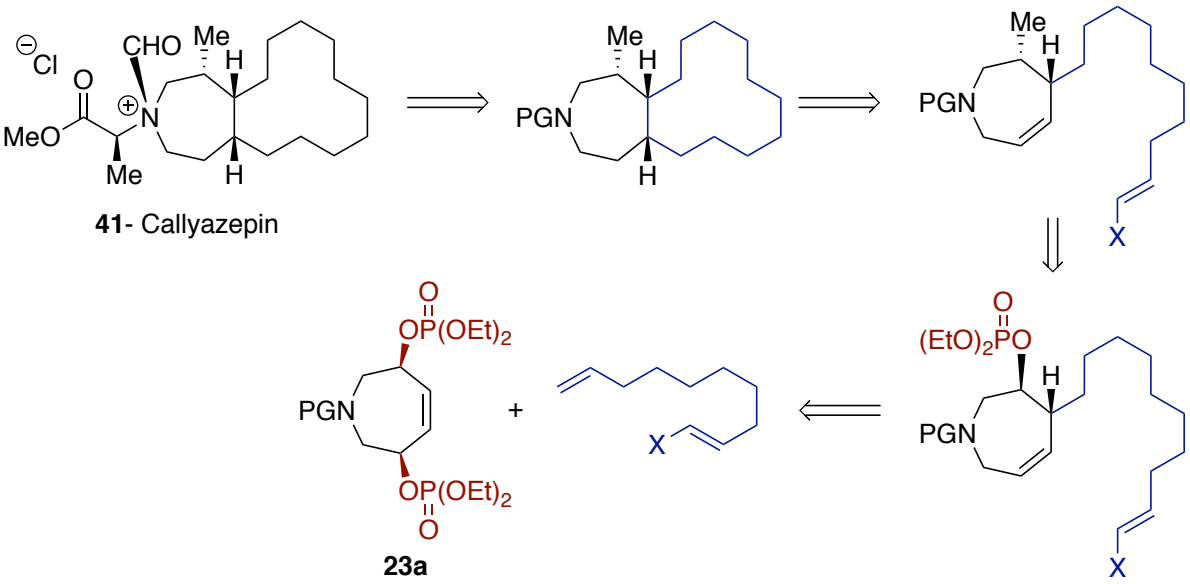
2.5 Conclusions and Future Work

A highly regio-, diastereo- and enantioselective Cu-catalysed desymmetrization of cyclic *meso*-bisphosphates using alkylzirconium reagents was developed. The reaction was also applicable to complex *meso*-starting materials bearing all-carbon pro-quaternary centers, allowing access to functionalised products with up to 3 contiguous stereocenters. 7-membered heterocycles could also be desymmetrized to access pharmaceutically relevant products.

The protocol could also be extended to the kinetic resolution of racemic, C_2-symmetric bisphosphates to provide the *cis*-diastereomer unattainable from the desymmetrization of the *meso* compounds. These experiments also re-enforced our mechanistic understanding by confirming an *anti*-S_N2' addition was likely to be the key stereodetermining step of the reaction.

Further work to extend the reaction scope to linear systems was ultimately unsuccessful, with low yields severely hampering progress in both desymmetrization of linear *meso*-bisphosphates and the kinetic resolution of linear racemic bisphosphates. In addition the racemic systems did not show enantiodivergent reactivity as hoped.

Future work may focus on the development of a small chemical library which may have applications in medicinal chemistry, particularly with heterocyclic substrates **23a** and **24a**. The desymmetrization protocol could also be showcased in natural product synthesis. Marine natural product Callyazepin (**41**), which has shown activity against cancer cell lines, as shown below would be a suitable target which could possibly be accessed via the desymmetrization of **23a** (Scheme 2.28).[177] After the desymmetrization step the remaining phosphate group could undergo S_N2 substitution with a methyl nucleophile, followed by a macrocyclisation step to give the Callyazepin core.



Scheme 2.28. Possible retrosynthesis of Callyazepin (**41**) to **23a**.

3 Desymmetrization of *Meso*-Bisphosphates via Rh-Catalysed Asymmetric Allylic Arylation

Sections of this chapter are published in *Tetrahedron*.[178]

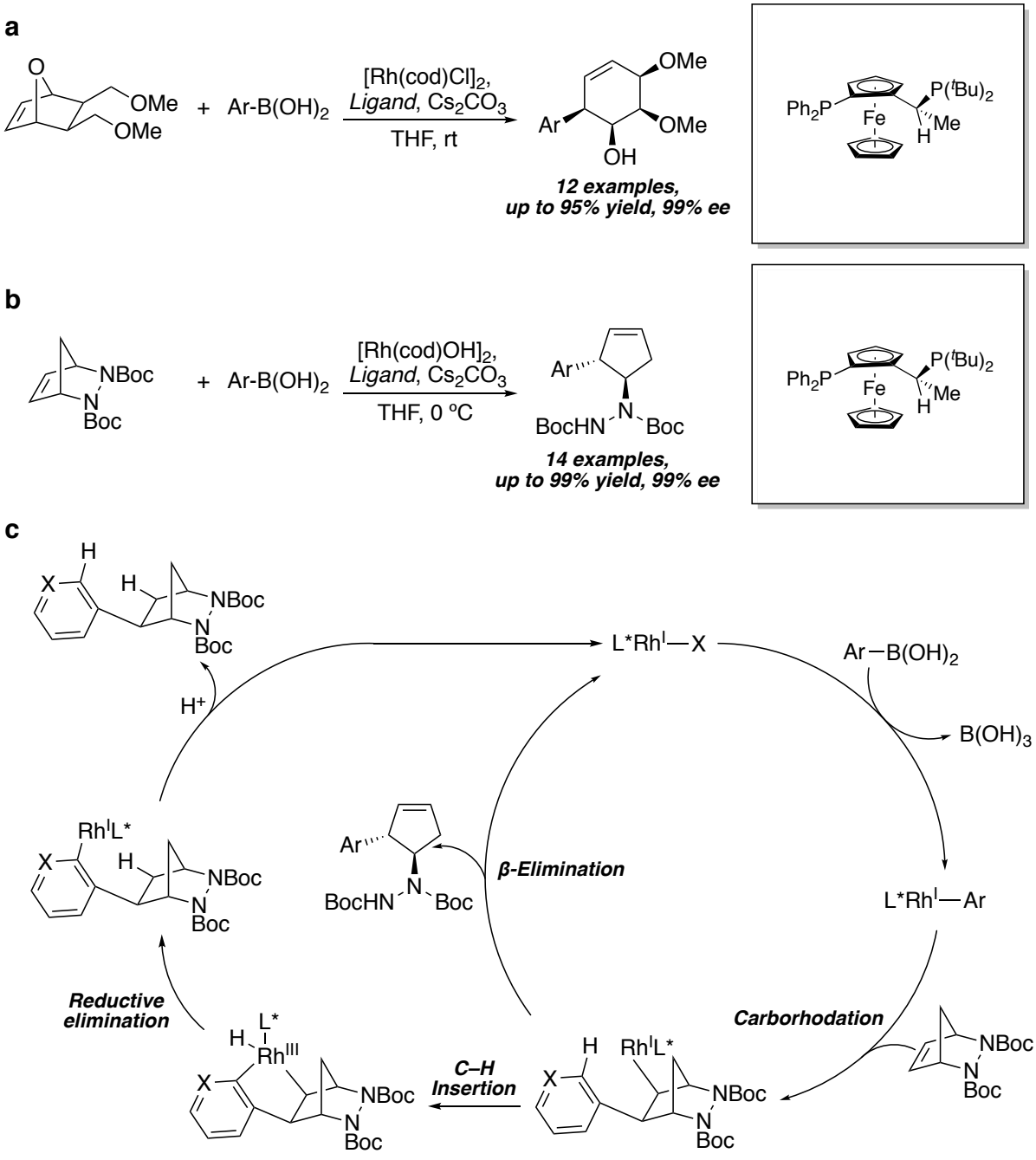
Work in Scheme 3.7 carried out by Alex Hell.

3.1 Rh-Catalysed Asymmetric Allylic Arylation

The last 20 years has seen the emergence of Rhodium-catalysis as a powerful method for the enantioselective formation of carbon-carbon bonds.[179] Boronic acids have been shown to be useful nucleophiles in Rh^I catalysis and have been extensively applied in asymmetric 1,4-additions[180] and allylic substitutions[181] to form arylated products. These formal Csp^2-Csp^3 couplings allow access to enantiopure heterocyclic scaffolds which are valuable motifs in drug discovery.[159,182,183]

Rh-catalysed asymmetric allylic arylation (AAAr) has also been successfully applied to desymmetrization reactions. The first example was the desymmetric ring-opening of strained oxabicycles by Lautens and co-workers (Scheme 3.1 a). Use of $[Rh(cod)Cl]_2$ and a Josiphos type ligand allowed addition of a range of arylboronic acids in excellent ee.[184] The Lautens group have used the oxabicyclic scaffold in a range of Rh-catalysed additions to form various C-C and C-X bonds.[185–192] Azabicycles have also been opened with a similar catalytic system (Scheme 3.1 b).[193,194] This reaction was shown to proceed via a hydroarylation mechanism followed by a C-H insertion process for activated aryl species (Scheme 3.1 c). Interestingly

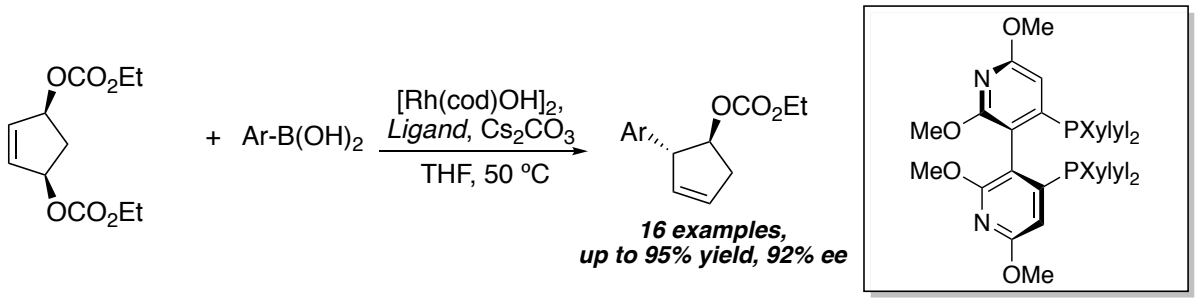
with certain boronic acids the hydroarylation product could be isolated before ring opening occurred. This in addition to deuterium labelling experiments confirmed the reaction mechanism.



Scheme 3.1. Desymmetric Rh-catalysed allylic arylations using boronic acids by Lautens and co-workers. **a)** Ring-opening of oxabicycles. **b)** Ring-opening of azabicycles. **c)** Proposed mechanism for ring-opening/hydroarylation of azabicycles.

Meso-biscarbonates have also been targeted using this chemistry (Scheme 3.2). *Anti*-S_N2' addition of arylboronic acids was achieved using Xylyl-P-Phos with $[Rh(cod)OH]_2$.[195] Some

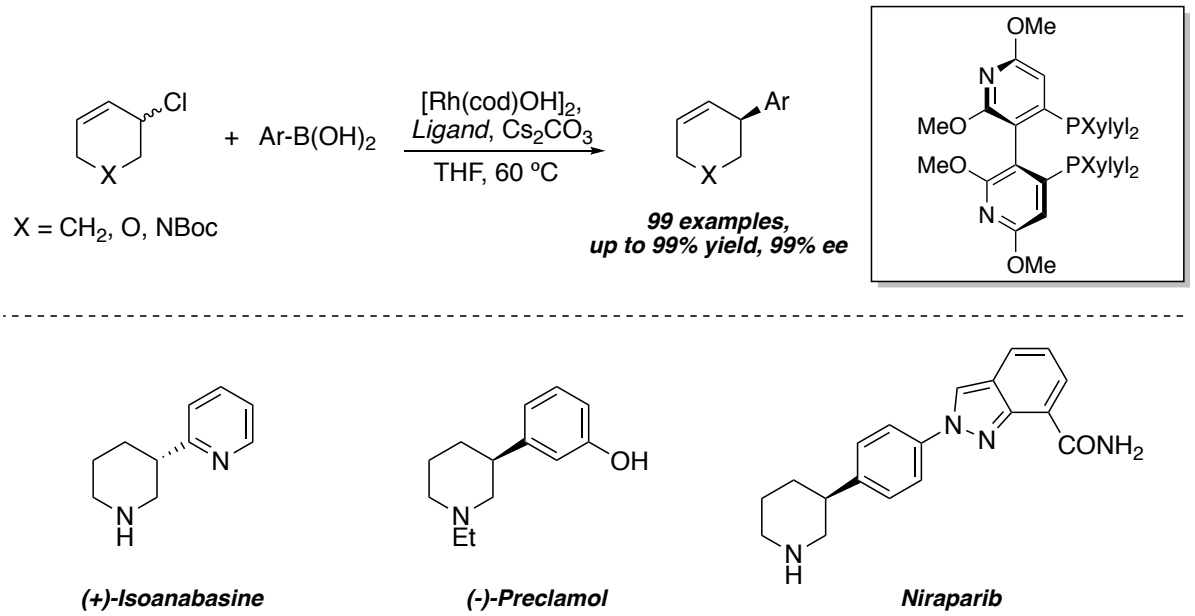
boronic acids gave poor regioselectivity with 1:1 S_N2'/S_N2 ratios obtained in some cases. Altering the conditions with phenylboronic acid allowed the S_N2 product to be obtained in up to a 2:1 ratio.[196]



Scheme 3.2. Desymmetrization of *meso*-biscarbonates by Lautens and co-workers.

The desymmetrization of compounds bearing a pro-quaternary center using Rh-catalysed AAAr was demonstrated by Marek and co-workers using a prochiral cyclopropene as discussed in chapter 1 (Scheme 1.11 a).[53] However, no *meso*-compounds with pro-quaternary centers have been desymmetrized using Rh-AAAr.

The Fletcher group have expertise in Rh-catalysed AAAr, particularly when applied to asymmetric Suzuki-Miyaura couplings (Scheme 3.3). The group initially demonstrated the addition of arylboronic acids to racemic allyl chlorides using $[Rh(cod)OH]_2$ with Xylyl-P-Phos.[197] The reaction proceeded via a DYKAT mechanism and has since been applied to heterocyclic allylic chlorides[198,199] and bicyclic scaffolds[200], which has allowed access to a range of drug candidates.

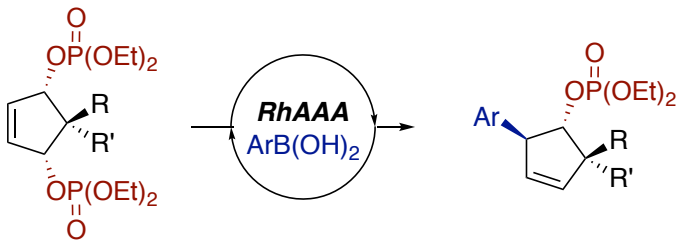


Scheme 3.3. Rh-AAAr of racemic allyl chlorides by the Fletcher group.

3.2 Project Aims

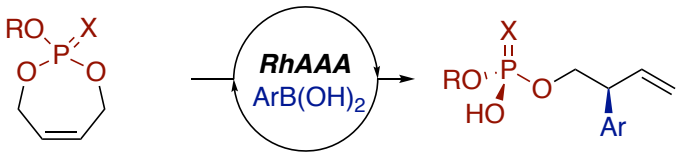
Despite successful application in desymmetrization reactions Rh-AAAr has only been applied to a prochiral substrate bearing a pro-quaternary center in one case.[53] Furthermore, addition to *meso*-compounds is limited to simple substrates with up to 2 stereocenters.

The success of the Cu-AAA of complex *meso*-compounds as discussed in chapter 2, combined with the experience the Fletcher group has in Rh-AAAr, suggested that a Rh-catalysed enantioselective addition of boronic acids to substituted *meso*-bisphosphates could be achievable (Scheme 3.3). This would represent a Csp^2-Csp^3 coupling which could form compounds with up to 3 contiguous stereocenters.



Scheme 3.3. Proposed Rh-AAAr of complex *meso*-bisphosphates.

It was hypothesised that symmetrical cyclic allylic phosphates could also act as substrates in AAAr (Scheme 3.4). These substrates would be 7-membered rings and a ring-opening AAAr process occurring at the allylic position may be able to control the stereochemistry at phosphorus, something which remains a challenge in synthetic chemistry.[201,202]



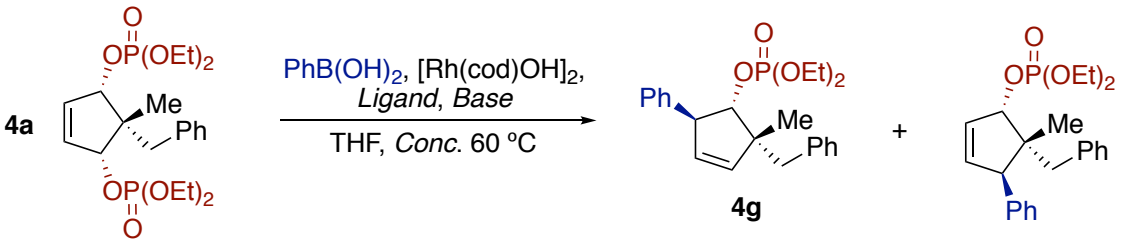
Scheme 3.4. Rh-AAAr of allylic cyclic phosphates to control stereochemistry at phosphorus.

3.3 Results and Discussion

3.3.1 Reaction Optimisation

As the Lautens group had already demonstrated the desymmetrization of simple *meso*-diol derivatives by Rh-AAAr we decided to develop the system with 2-substituted bisphosphate **4a**, in the hope the final reaction conditions would be more suited towards complex substrates (Table 3.1). Initial conditions used a $[Rh(cod)OH]_2$ and (*S*)-BINAP catalyst with Cs_2CO_3 in THF at 60 ºC to add phenylboronic acid, similar conditions to reported Suzuki-Miyaura couplings with allyl chlorides.[197] A 3:1 mixture of separable S_N2':S_N2 regioisomers was obtained with 10% conversion, however the desired S_N2' regioisomer **4g** was obtained as a single *anti*-diastereomer in a promising 48% ee (entry 1). A diethylcarbonate analogue of **4a** was examined under these conditions but failed to react. A mixture of regioisomers were also obtained in Lautens' desymmetrization with *meso*-biscarbonates, further highlighting the challenge of regiocontrol. Switching base to a 50% aqueous solution of CsOH improved the conversion to 40% and to our delight gave >99% ee of **4g** (entry 2). It is possible that the extra water content helped solubilise the boronic acid, form an active boronate species,[203] or regenerate the catalyst, improving conversion. Increasing the temperature to 80 ºC did not improve results further (entry 3). A ligand screen (Figure 3.1) revealed that (*S*)-P-Phos gave 60% conversion as almost a single regioisomer (15:1 rr) (entry 5). (*S*)-DM-SEGPHOS however gave full conversion of starting material with a rr of 8.7:1 in >99% ee (entry 8). Disappointingly as this reaction was scaled up from 0.2 to 0.4 mmol to investigate isolated yields the conversion stalled at 89%, giving an 80% isolated yield (entry 11). It was hypothesised that solvent may have evaporated on a smaller scale and increasing the concentration to 0.2M improved the isolated yield of **4g** to 86% (entry 13). Replication of entry 8 could not be achieved for reasons unknown, but the conditions in entry 13 were deemed satisfactory.

Table 3.1. Optimisation of Rh-AAAr conditions.



Entry	Ligand	Base	Conc. (M)	Conv. (%)[a]	rr	ee (%)[b]
1	(*S*)-BINAP	Cs_2CO_3	0.1	10	3:1	48
2	(*S*)-BINAP	CsOH	0.1	40	4.3:1	>99
3[c]	(*S*)-BINAP	CsOH	0.1	36	4:1	>99
4	(*R*)-TOL-BINAP	CsOH	0.1	51	3.3:1	–>99
5	(*S*)-P-Phos	CsOH	0.1	60	15.5:1	>99
6	(*S*)-Xylyl-P-Phos	CsOH	0.1	55	9.1:1	>99
7	(*S*)-SEGPHOS	CsOH	0.1	79	7.6:1	>99
8*	(*S*)-DM-SEGPHOS	CsOH	0.1	100	8.7:1	>99
9	(*S*)-DTBM-SEGPHOS	CsOH	0.1	2	4:1	N/A
10	(*S*)-Cl-MeO-BIPHEP	CsOH	0.1	70	2.7:1	>99
11[d]	(*S*)-DM-SEGPHOS	CsOH	0.1	80[e]	8.1:1	>99
12[d]	(*S*)-DM-SEGPHOS	CsOH	0.15	73[e]	9.1:1	>99
13[d]	(*S*)-DM-SEGPHOS	CsOH	0.2	86[e]	8.9:1	>99
14[d]	(*S*)-DM-SEGPHOS	CsOH	0.3	82[e]	8.8:1	>99

Conditions: Reactions carried out on 0.2 mmol scale of **4a** at 60 ºC. [a]Conversion determined by ^{1}H NMR. [b]ee of **4g** determined by chiral HPLC. [c]80 ºC. [d]0.4 mmol scale. [e]Isolated yield of **4g**. *Result could not be replicated.

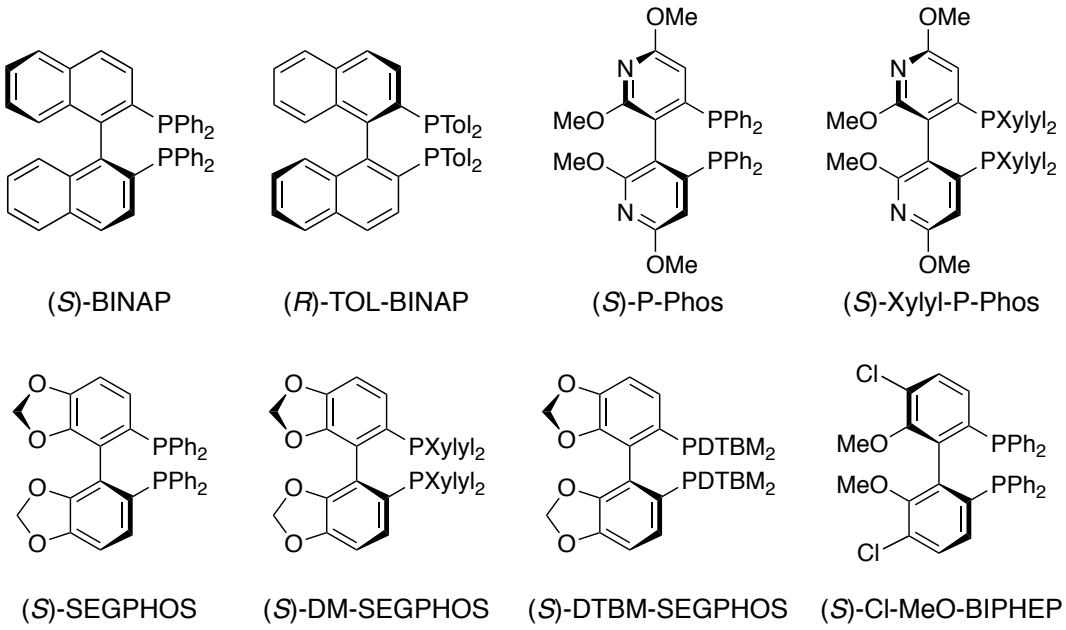
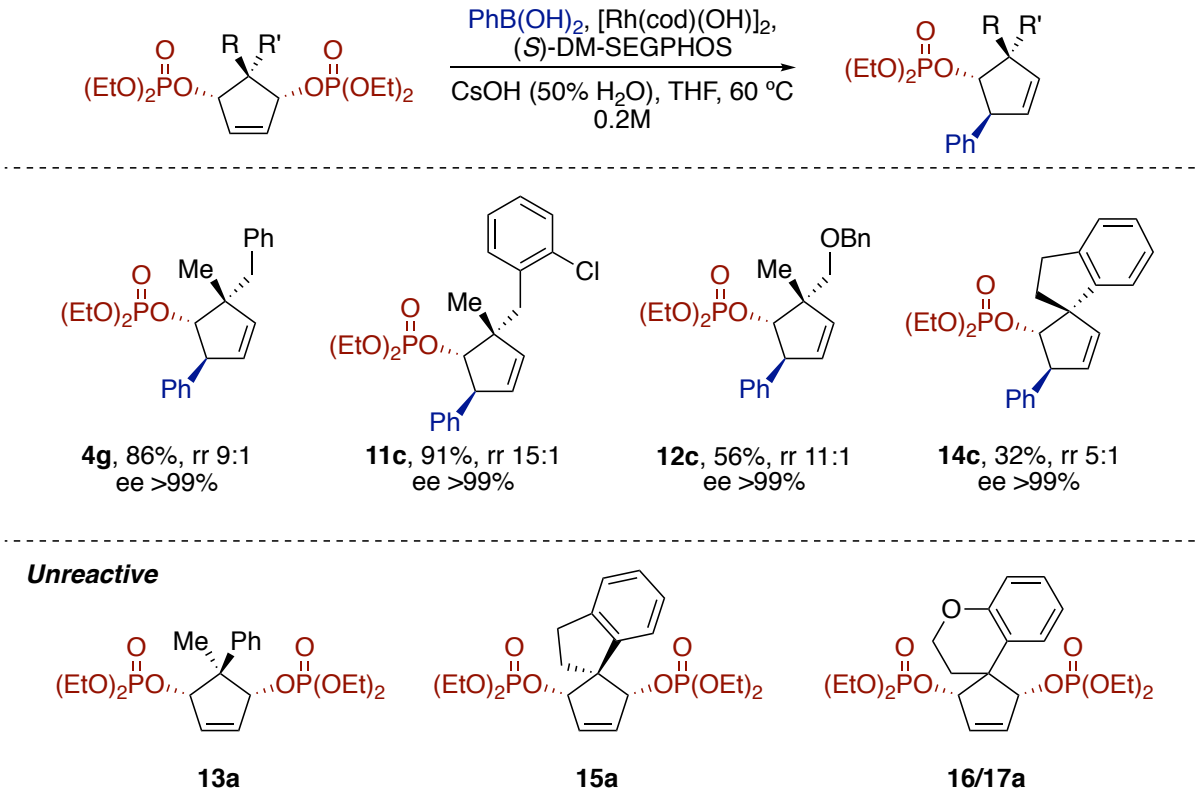


Figure 3.1. Ligands used in Table 3.1.

3.3.2 Electrophile Scope

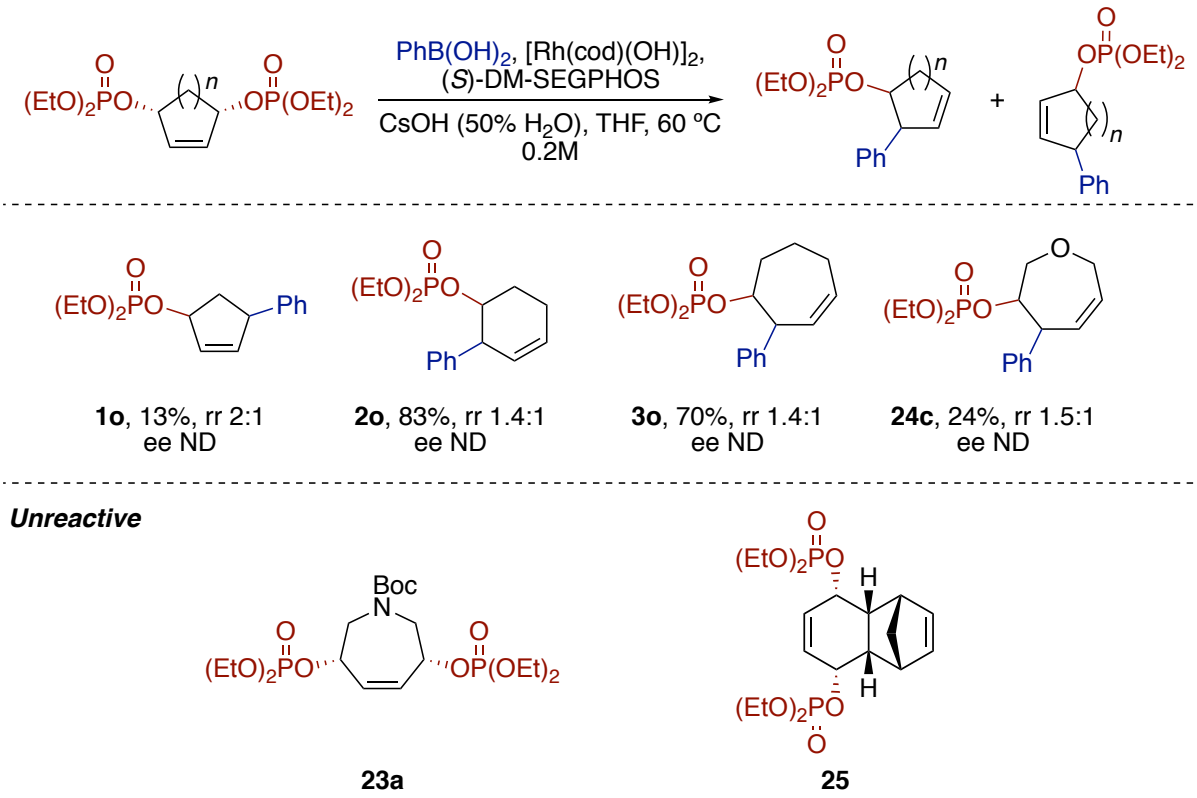
With suitable conditions in hand for the desymmetrization, a range of bisphosphates were examined. 2-Substituted bisphosphates in general performed well (Scheme 3.5), tolerating a 2-chlorobenzyl group (**11c**), a benzyl protected alcohol (**12c**) and an indane diastereomer (**14c**) where the aromatic ring was *syn* to the phosphates. In all of these cases the *anti*-S_N2' product is favoured, with up to 15:1 regioselectivity in the case of **12c**, and enantioselectivity is >99%. In contrast to **14a**, the other indane diastereomer (**15a**) failed to give any conversion in the desymmetrization. In addition, both diastereomers of the chromane bisphosphate **16a** and **17a** failed to react, as well as *anti*-phenyl substituted **13a**. These results correlate well to related Cu-AAA reactions, where large groups *anti* to the phosphates were not tolerated, suggesting the Rh-catalyst may approach the substrate in a similar fashion.



Scheme 3.5. 2-Substituted bisphosphate scope for desymmetrization via Rh-AAAr.

Unsubstituted bisphosphates were investigated next (Scheme 3.6). Under desymmetrization conditions with phenylboronic acid **1a** gave a 2:1 mixture of S_N2/S_N2' regioisomers, the first time the S_N2 product had been favoured. However, the yield was only 13% and both products were obtained as an inseparable mixture of *syn*/*anti* diastereomers. This also meant the enantioselectivity of the reaction could not be determined with any confidence as separation of the regio- and diastereomers was not possible by chiral SFC or HPLC. 6-Membered **2a** and 7-membered **3a** favoured the S_N2' regioisomer in a 1.4:1 ratio with higher yields as a diastereomeric mixture. Oxepene **24a** gave a similar result whilst azepene **23a** did not react at all. Finally, the bicyclic bisphosphate **25** was examined but also failed to react. The results were disappointing and the mixtures of regio- and diastereomers made analysis difficult. Attempts to improve the S_N2 ratio with substrate **1a** were attempted but 2:1 was not improved upon. It is not known why the ring size affected the rr, or why the NBoc protected substrate failed to react. As Lautens had already published suitable conditions for a diethylcarbonate

analogue of **1a**[195] it was decided that no further work would be carried out to optimise the Rh-AAAr with unsubstituted bisphosphates.

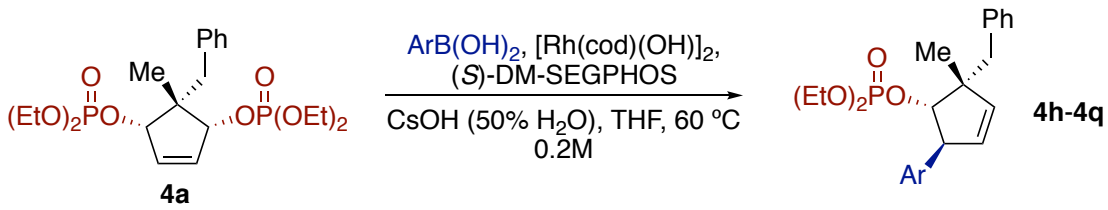


Scheme 3.6. Unsubstituted bisphosphate scope for desymmetrization via Rh-AAAr.

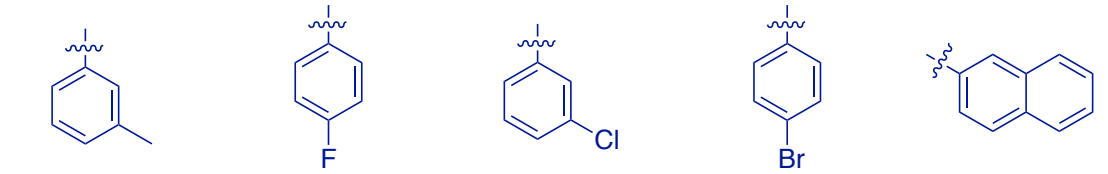
3.3.3 Nucleophile Scope

During these studies Alex Hell compared the reactivity of a range of boronic acids with 2-substituted bisphosphate **4a** (Scheme 3.7). A *meta*-methyl substituent (**4h**) resulted in a yield of 77% and a rr of 8:1 in favour of the S_N2' regioisomer. *Para*-fluoro substitution (**4i**) was similarly well tolerated, giving a yield of 61%, as were other halogen functionalities such as chloride (**4j**) and bromide (**4k**), giving 64% and 59% yield respectively. A naphthalene substituent could also be added 66% yield (**4l**). *Para*-methoxy substitution (**4m**) resulted in a yield of 63%, while (4-(trifluoro-methyl)phenyl)boronic acid gave the corresponding product (**4n**) in a yield of 55%, thus demonstrating that both strongly electron donating and withdrawing groups are tolerated. Enantioselectivity was >99% ee in all cases. More

challenging heterocyclic boronic acids, which can be prone to proto-deborylation, were also examined. This system tolerated the oxygen containing benzofuran-2-ylboronic acid, giving the corresponding product (**4o**) in 42% yield, with a moderate rr of 3:1. A benzofuran moiety could also be incorporated in 42% yield (**4p**), with an rr of 3:1. In the case of thiophen-3-ylboronic acid only a 12% yield was obtained (**4q**) with an rr of 4.5:1. A diverse range of heteroaryl boronic acids kindly provided from the inventory of Vertex Pharmaceuticals were examined, but showed no reactivity. In general the reaction appears to be sensitive to *ortho*-substitution due to steric reasons. Heteroaryl boronic acids perform poorly overall which may be due to co-ordination of heteroatoms to the catalyst or rapid proto-deborylation outcompeting AAAr.



4a



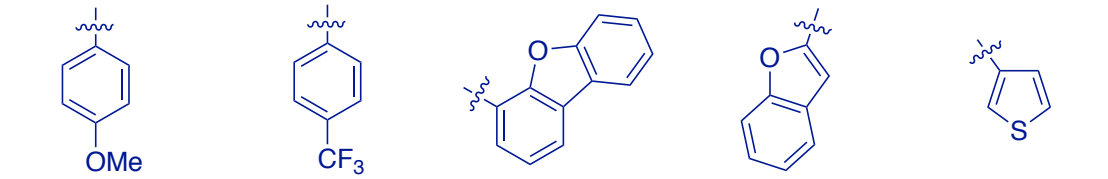
4h, 77%, 8:1 rr
>99% ee

4i, 61%, 7:1 r.r
>99% ee

4j, 64%, 7:1 rr
>99%ee

4k, 59%, 7:1 r.r
>99% ee

4l, 66%, 8:1 rr
>99% ee



4m, 63%, 7:1 rr
>99% ee

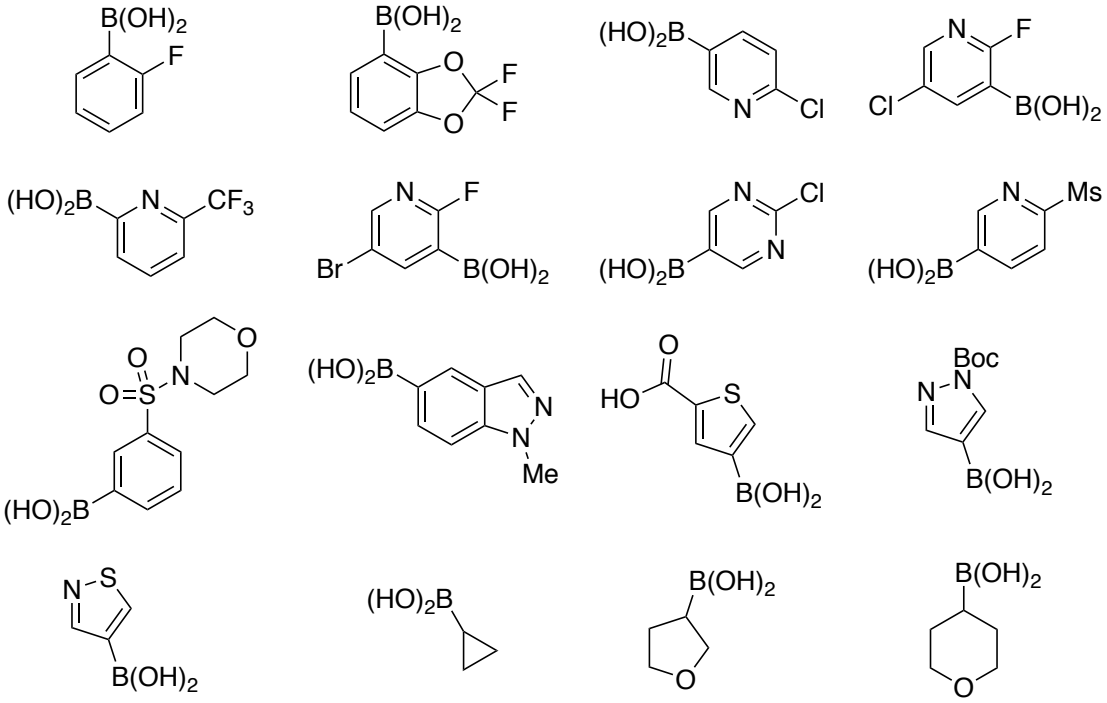
4n, 55%, 8:1 rr
>99% ee

4o, 29%, 8:1 rr
94% ee

4p, 42%, 3:1 rr
>99% ee

4q, 12%, 4.5:1 rr
>99%ee

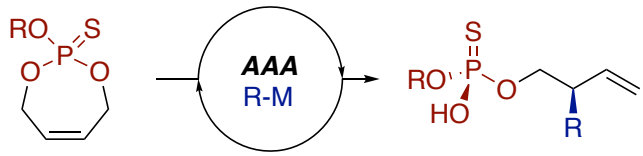
Unreactive



Scheme 3.7. Rh-AAAr boronic acid scope with **4a**. Work carried out by Alex Hell.

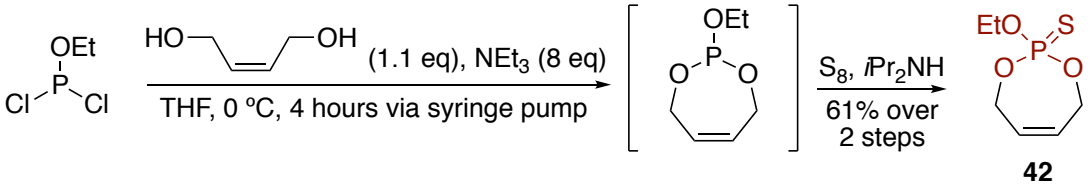
3.3.4 Desymmetrization of Cyclic Phosphates

Based on our success with both Cu-AAA and Rh-AAAr with *meso*-bisphosphates we reasoned that a symmetrical cyclic phosphate could undergo a ring-opening AAAr reaction which could set the stereochemistry at the phosphorus center (Scheme 3.8). This idea would in theory allow access to enantiopure thiophosphates which are important in oligonucleotide synthesis, improving cellular uptake, metabolic stability and efficacy.[204–206] Current medical applications of thiophosphate oligonucleotides do not control stereochemistry at the phosphorus center due to synthetic complexity, despite an efficacy boost for doing so.[207] This has led to the development of strategies relying on chiral auxiliaries,[208–210] but so far no catalytic asymmetric method of synthesising thiophosphates exists, highlighting the difficulty of the challenge. Potential issues include the use of a sulphur atom in the substrate which can act as a catalyst poison, shutting down any reactivity. The ring opening product would also be anionic,[211] possibly forming a salt with the catalyst and preventing further turnovers.



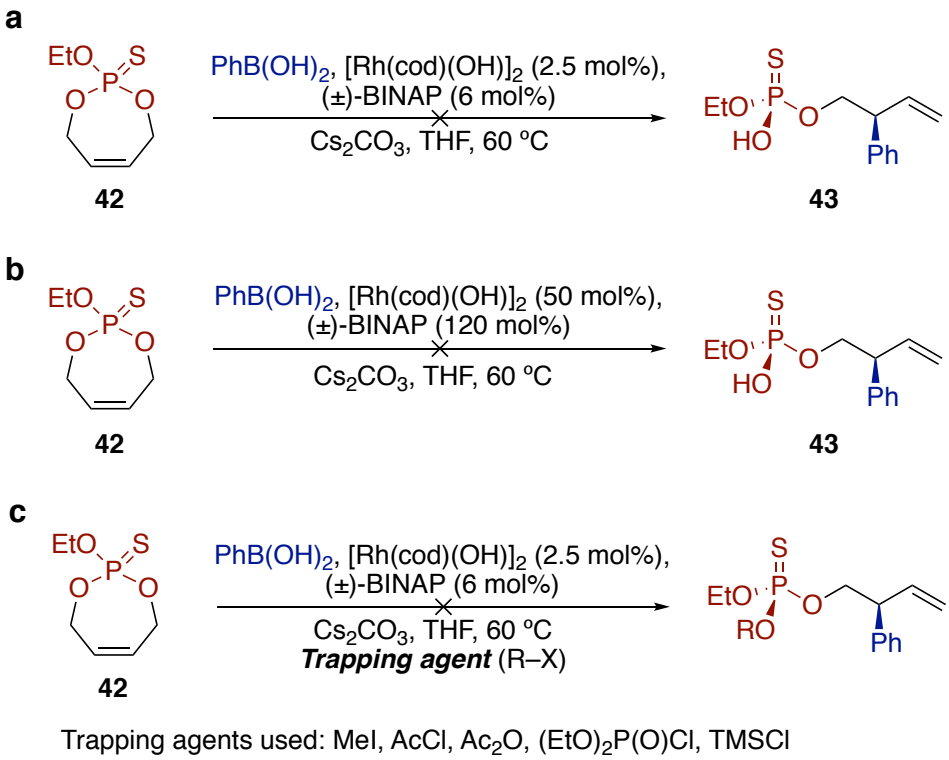
Scheme 3.8. Proposed desymmetrization of cyclic thiophosphates via ring-opening AAAr.

The first proposed substrate was a 7-membered cyclic thiophosphate with an ethyl group (**42**) which had performed well in other previous AAAr reactions. Slow addition of cis-buten-1,4-diol to ethyl dichlorophosphite at high dilution gave the phosphite ester which could be oxidised with elemental sulphur to give thiophosphate **42** in 61% yield over both steps.



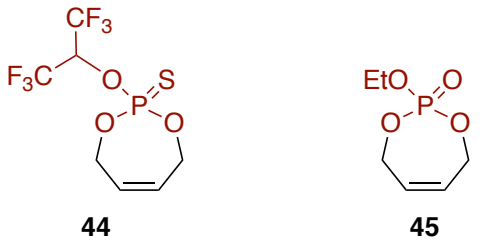
Scheme 3.9. Synthesis of cyclic thiophosphate **42**.

The cyclic thiophosphate **42** was subjected to Rh-AAAr conditions using racemic BINAP as a ligand in the hope of obtaining ring opening product **43** (Scheme 3.10). The stability of **43** was confirmed by an alternative synthesis. Disappointingly, no conversion of starting material was observed by NMR (Scheme 3.10 a). Further examination of ligands and general reaction conditions, including heating up to 120 ºC in 1,4-dioxane, showed no conversion. It was possible that the catalyst was unable to turnover, so an experiment using the Rh-catalyst in stoichiometric quantities was undertaken (Scheme 3.10 b). Crude analysis by ^{1}H NMR showed full conversion of starting material but only broad peaks were observed. The reaction mixture was divided into different aliquots and quenched with different aqueous media including H_2O, 1M HCl, 1M NH_4Cl, saturated $NaHCO_3$ and 1M NaOH. Analysis of all these workups showed no sign of a product-like species. It became clear at this point that **42** behaved differently to other electrophiles examined in Rh-AAAr by the Fletcher group and another strategy would be needed to develop a catalytic ring opening reaction. In an attempt to achieve turnover the reaction was carried out with a range of electrophiles present in the mixture, in the hope that any anionic product would be neutralised allowing catalyst turnover (Scheme 3.10 c). Use of methyl iodide, acetyl chloride, acetic anhydride, diethylchlorophosphate and trimethylsilyl chloride had no positive effect on the reaction.



Scheme 3.10. Attempts to desymmetrize thiophosphate **42** using Rh-AAAr. **a)** Example of catalytic conditions. **b)** Stoichiometric conditions. **c)** Attempts to trap product with an electrophile.

It was reasoned that switching the ethyl group on the substrate for a hexafluoroisopropyl group (**44**) would improve the reactivity of substrate, however this also failed to react (Scheme 3.11). A cyclic phosphate with no sulphur atom (**45**) was also examined but showed no reactivity.

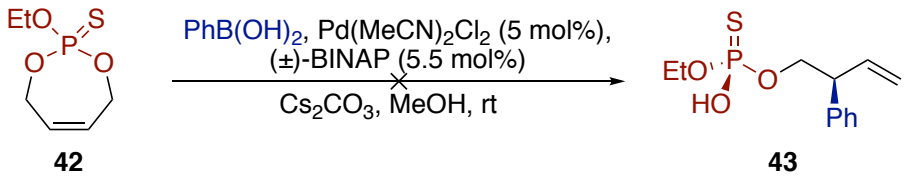


44 **45**

Scheme 3.11. Alternative substrates: electron deficient **44** and phosphate **45**.

Having had no success with Rh-AAAr an examination of the literature revealved that Pd^{II} can be used in the asymmetric ring opening of oxa- and azabicycles with arylboronic acids as an alternative to Rh^{I}, and is more successful in some cases.[212] However, attempts using a range of

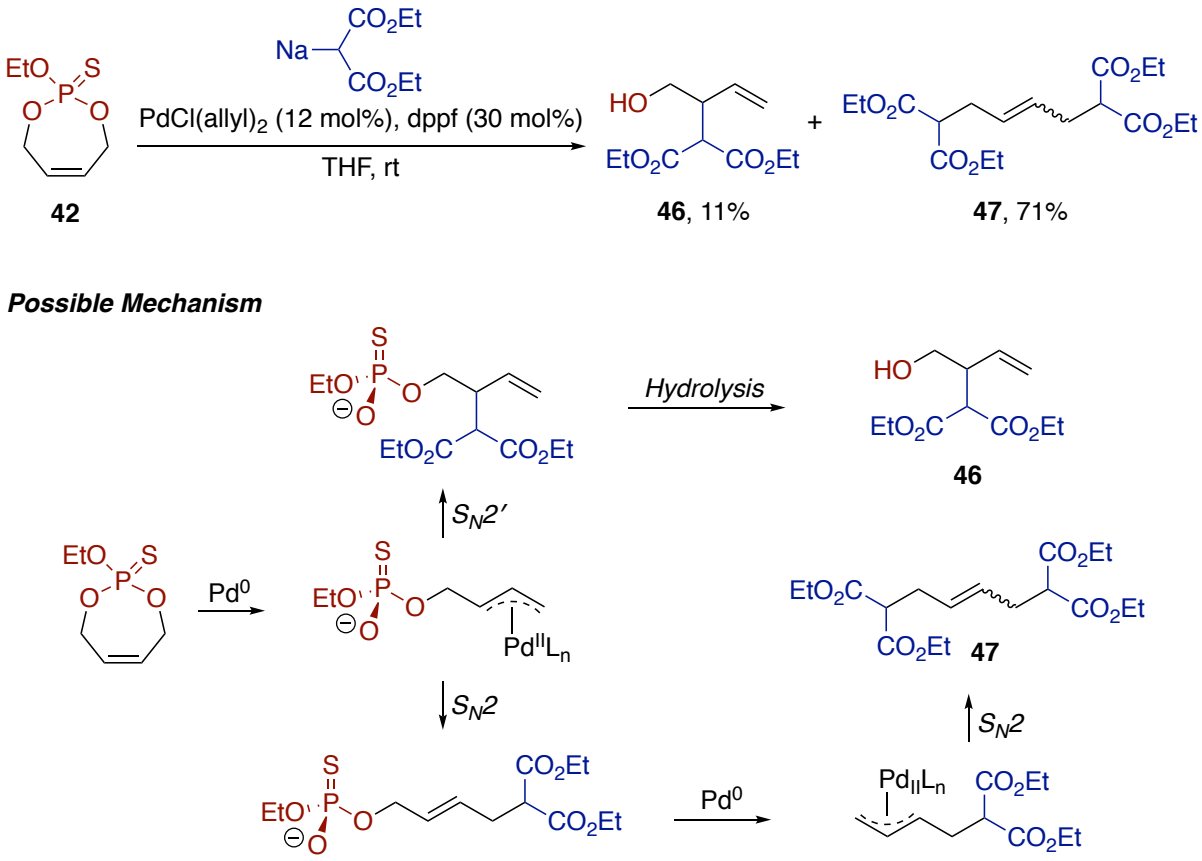
Pd^{II} catalysts with bisphosphine ligands under various conditions with thiophosphate **42** showed no reactivity (Scheme 3.12).



42 **43**

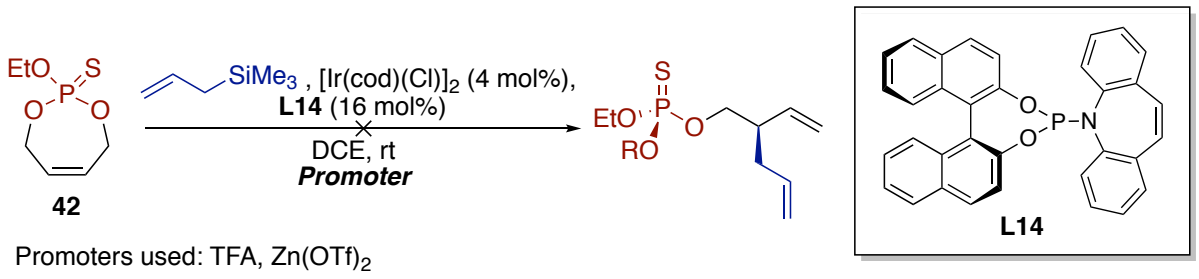
Scheme 3.12. Example of a desymmetrization attempt with Pd^{II}-catalysis.

The ring opening of **42** was then attempted using Tsuji-Trost conditions, as Pd^0 catalysts are known to form π-allyl species with allylic electrophiles (Scheme 3.13). Using known Tsuji-Trost conditions with a malonate nucleophile[213] showed full conversion of the starting material **42** after 1 hour at room temperature. A mixture of products was formed, however none contained a phosphate group. After quenching with 1M HCl 2 products were isolated by column chromatography, homoallylic alcohol **46** and alkene **47**. The homoallylic alcohol appears to arise from an overall S_N2' addition of malonate followed by hydrolysis of the thiophosphate. It is unknown why the hydrolysis occurred as **43** was shown to be stable in 1M HCl over a period of 3 hours. **46** was also present in the crude mixture, showing that the hydrolysis of the phosphate was occurring in the reaction media. **47** was likely made via an overall S_N2 addition of malonate to give an intermediate which can undergo π-allyl formation again, followed by another S_N2 addition of malonate to give **47** as a mixture of *E*:*Z* isomers. In contrast to attempts with Rh^I and Pd^{II}, Pd^0 appeared to be too active a system leading to overreaction and phosphate removal.



Scheme 3.13. Tsuji-Trost ring opening of **42**.

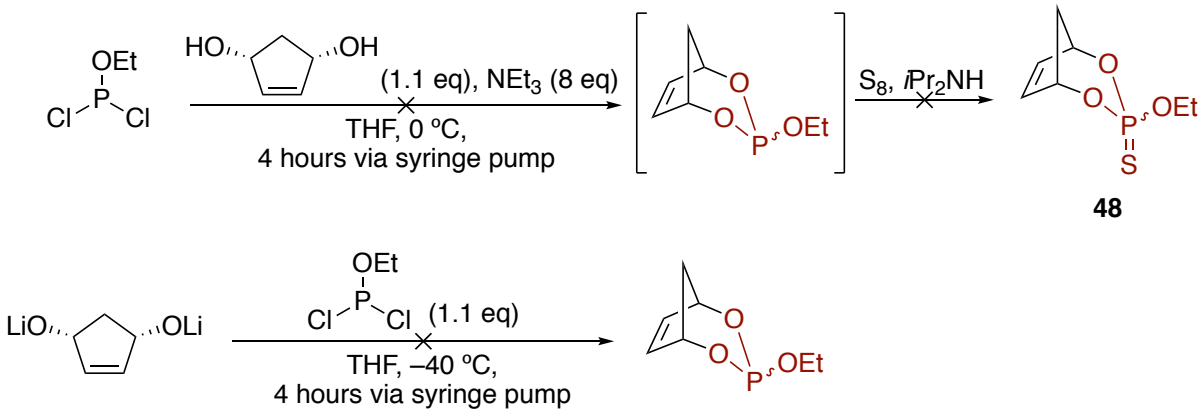
Attempts were made to open **42** with Iridium catalysis (Scheme 3.14). The Carreira group have used Ir^{I} catalysis in allylic substitutions using allylic alcohols as substrates.[214,215] An allylation was tested using allyltrimethyl silane as a nucleophile with $[Ir(cod)Cl]_2$ and bidentate phosphoramidite ligand **L14**.[216] Lewis and Brønsted acids were shown to act as promoters in this chemistry so TFA and $Zn(OTf)_2$ were used in the attempted ring opening of **42**. To our disappointment no conversion of starting material was observed.



Scheme 3.14. Attempted Ir-catalysed ring opening of **42**.

Finally Cu-AAA was explored using conditions developed for the addition of alkylzirconium reagents to *meso*-bisphosphates discussed in chapter 2. Attempts using **42**, **44** and **45** as electrophiles were all unsuccessful with no conversion of the starting materials. The reactions also formed white precipitates which is a signal of catalyst deactivation in Cu-AAA reactions with alkylzirconium reagents.

Despite exploring a large range of catalytic systems no AAAr conditions were found for the ring opening of 7-membered ring cyclic phosphates. Other successful systems developed by Lautens were hypothesised to go through a hydroarylation mechanism, not a π-allyl species.[184] As a 7-membered ring has less ring strain than the bicyclic scaffolds used by Lautens it may be that hydroarylation is not possible as there is no relief of ring strain to act as the driving force of the reaction. Pd^0 which is known to form π-allyl intermediates was able to open the ring without the requirement of ring strain, but poor regioselectivity led to unwanted side-products. Therefore, in order to obtain reactivity in a Rh^I or Pd^{II}-catalysed addition of a boronic acid more ring strain would be required in the substrate. Bicyclic thiophosphate **48** was thought to be reactive enough to undergo Rh-AAAr with arylboronic acids. It was noted that **48** may exist as a mixture of diastereomers which could behave differently in any AAAr reactions. Attempts to synthesise **48** from cis-4-cyclopentene-1,3-diol were unsuccessful, with intermediates showing decomposition via both TLC and NMR (Scheme 3.15). Due to time constraints no further attempts were made to make **48** or any other suitable substrates.



Scheme 3.15. Attempts to synthesise bicyclic thiophosphate **48**.

3.4 Conclusions and Future Work

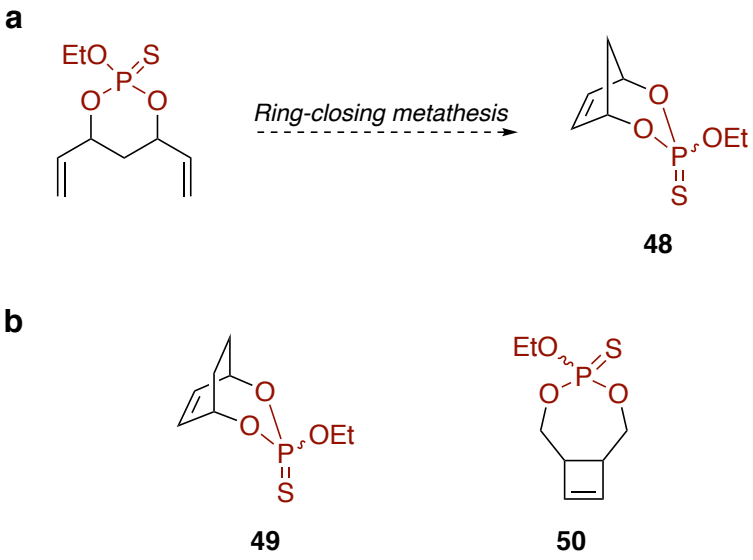
A highly diastereo- and enantioselective desymmetrization of *meso*-bisphosphates using Rh-catalysis with arylboronic acid nucleophiles was developed. The reaction could incorporate a range of boronic acid nucleophiles, including some heteroarylboronic acids, and allowed the synthesis of complex 5-membered ring compounds with up to 3 contiguous stereocenters, including an all carbon quaternary center.

Compared to the Cu-AAA of *meso*-bisphosphates with alkylzirconium nucleophiles the Rh-AAAr with arylboronic acids appeared to be much more sensitive to changes in either electrophile or nucleophile structure. Regioselectivity was much lower in the case of Rh-AAAr for a range of electrophiles, highlighting the remarkable regiocontrol offered by copper catalysis. Complex heterocyclic boronic acids were generally not tolerated by the desymmetrization, highlighting the need to develop transition metal-catalysed reactions which are not sensitive to heteroatoms.

Following on from this the desymmetrization of 7-membered cyclic thiophosphates was attempted, with hope of controlling stereochemistry at the phosphorus center. Using a large range of catalysts including Rh^{I}, Pd^{II}, Pd^{0}, Ir^{I} and Cu^{I}, no desired ring opening product was observed. It is clear that a more reactive substrate with ring strain is required to develop this chemistry further.

Although a few attempts were made to synthesise a bicyclic electrophile **48**, there are still more alternative routes that could be considered, including using ring-closing metathesis. Other alternative substrates could be synthesised and examined. A 6-membered bridged bicyclic thiophosphate (**49**) may be a suitable desymmetrization substrate. A fused cyclobutene (**50**)

would represent a different overall strategy, using hydroarylation of the cyclobutene as a remote functionalisation rather than AAAr.



Scheme 3.16. Future work to desymmetrize thiophosphates. **a)** Possible ring-closing metathesis route to **48**. **b)** Alternative bicyclic substrates **49** and **50**.

4 Experimental Information

4.1 General Information

Procedures using oxygen and/or moisture-sensitive materials were performed with anhydrous solvents under an atmosphere of anhydrous argon in flame-dried flasks, using standard Schlenk techniques. Analytical thin-layer chromatography was performed on precoated glass-backed plates (Silica Gel 60 F254; Merck), and visualized using a combination of UV light (254 nm) and anisaldehyde solution or aqueous basic potassium permanganate stain. Flash column chromatography was carried out using Apollo Scientific silica gel 60 (0.040 – 0.063 nm), Merck 60 Å silica gel, VWR (40-63 μm) silica gel and Sigma Aldrich silica gel. Pressure was applied at the column head via hand bellows or a flow of nitrogen with the solvent system used in parentheses.

Reactions at 0 ˚C were performed using an ice-water bath, covered with cotton wool and aluminium foil if overnight stirring is needed. Other temperatures were obtained using a Julabo FT902 immersion cooler or the heating plate of the stirrer.

Unless stated otherwise, solution NMR spectra were recorded at room temperature; ^{1}H, ^{31}P and ^{13}C NMR experiments were carried out using Bruker AVIII HD 400 (400/101/162 MHz) or AVIII HD 500 (500/126/202 MHz) spectrometers. Chemical shifts are reported in ppm from the residual solvent peak. Chemical shifts (δ) are given in ppm and coupling constants (*J*) are

quoted in hertz (Hz). Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Assignments were made with the assistance of COSY, HSQC, HMBC or NOESY NMR spectra.

Chiral HPLC separations were achieved using an Agilent 1230 Infinity series normal phase HPLC unit and HP Chemstation software. Chiralpak® columns (250 × 4.6 mm), fitted with matching Chiralpak® Guard Cartridges (10 × 4 mm), were used as specified in the text. Solvents used were of HPLC grade (Fisher Scientific, Sigma Alrich or Rathburn); all eluent systems were isocratic.

Chiral SFC (supercritical fluid chromatography) separations were conducted on a Waters Acquity UPC2 system using Waters Empower software. Chiralpak® columns (150 × 3 mm, particle size 3 μm) were used as specified in the text. Solvents used were of HPLC grade (Fisher Scientific, Sigma Aldrich or Rathburn). Compounds **4e**, **4f, 23b** and **29** used specific instruments and conditions detailed later in the text.

Chiral GC measurements were conducted on an Agilent 7820A GC (He as a vector gas) with the stated column in the characterisation. Temperature programs are described as follows: initial temperature (°C) – initial time (min) – temperature gradient (°C/min) – final temperature (°C) – holding time (min). Flow rate is given in mL/min. Retention times (R_T) are given in min.

Low-resolution mass spectra were recorded using a Walters LCT premier XE. High-resolution mass spectra (EI and ESI) were recorded using a Bruker MicroTOF spectrometer by the internal service at the University of Oxford. Infrared measurements (neat, thin film) were carried out using a Bruker Tensor 27 FT-IR with internal calibration in the range 600-4000 cm^{-}

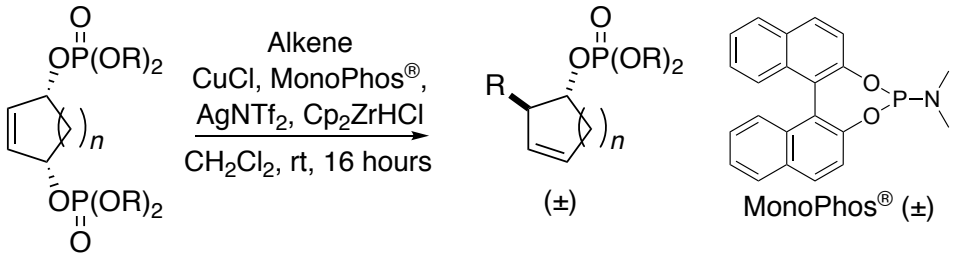
[1]. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter at 25°C in a 10 cm cell in the stated solvent; $[\alpha]_D$ values are given in 10^{-1} deg.cm^2 g^{-1} (concentration c given as g/100 mL).

4.2 Chemicals

Dry THF, CH_2Cl_2, $CHCl_3$, Et_2O and Toluene were collected fresh from an mBraun SPS-5 solvent purification system having been passed through anhydrous alumina columns. All other dry solvents used were dried over 3 Å molecular sieves and stored under argon. All other solvents were used as purchased from Sigma Aldrich, Honeywell or Fisher Scientific. Unless stated otherwise, commercially available reagents were purchased from Sigma-Aldrich, Fisher Scientific, Apollo Scientific, Acros Organics, Strem Chemicals, Fluorochem, Alfa Aesar or TCI UK and were used without purification. Petroleum ether refers to light petroleum boiling in the range 40-60 °C. Deuterated solvents were purchased from Sigma-Aldrich ($CDCl_3$). PPL refers to Lipase from porcine pancreas, Type II, 100-500 units/mg of protein, purchased from Sigma-Aldrich (Cat no. L3126). Schwartz reagent was prepared according to the literature procedure[217] from Cp_2ZrCl_2 purchased from Acros or Strem Chemicals.

4.3 General Procedures

4.3.1 General Procedure 1a: Racemic CuAAA Products



Note: All manipulations are carried out under an Ar atmosphere and in the absence of light where possible. Additional details on the procedure are described here: *Nature Protoc.* **2014**, 9, 104-111. Procedures can be carried out without flame drying, instead using oven dried glassware and N_2 purging without detriment to yield or ee.

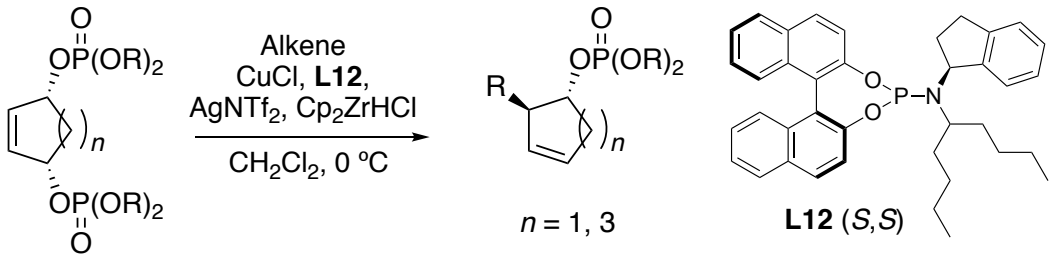
Flask **A**: A flame-dried 5 mL round bottomed flask was charged with CuCl (4 mg, 0.04 mmol, 0.1 eq) and racemic (3,5-dioxo-4-phosphacyclohepta[2,1-a:3,4-a']dinaphthalen-4-yl)dimethylamine (MonoPhos®) (17.2 mg, 0.048 mmol, 0.12 eq). Dry CH_2Cl_2 (1.5 mL) was added to the mixture which was left to stir at room temperature for 1 hour. $AgNTf_2$ (23 mg, 0.06 mmol, 0.15 eq) was then added to the flask and left to stir at room temperature for 15 mins. A pale brown suspension was formed.

Flask **B**: Meanwhile a separate flame-dried round bottomed flask was charged with Cp_2ZrHCl (206 mg, 0.8 mmol, 2.0 eq) and suspended in dry CH_2Cl_2 (0.8 mL). Alkene (1.0 mmol, 2.5 eq) was added to the mixture which was left to stir at room temperature in the absence of light, until the mixture became a homogenous yellow solution (approx. 30 mins, varies with alkene). Note: The alkylzirconium species can be left for up to 2-3 hours without issue.

The contents of flask **A** were transferred into flask **B** using a syringe equipped with a Camlab PTFE syringe filter (13 mm size, pore diameter 0.22 μm) to remove excess AgCl. The combined flask contents formed a black mixture which was left to stir at room temperature in the absence of light for 10 mins. *Meso*-cyclic bisphosphate (0.4 mmol) was added to the mixture which was left to stir at room temperature in the absence of light for 16 hours.

The mixture was quenched with 1M aq. NH_4Cl (1 mL) and left to stir for 10 mins. The organic layer was separated, filtered through a plug of Celite and evaporated *in vacuo* to give an off-white mixture of solid and oil. The crude product was purified on silica (eluent specified below) to give a yellow oil.

4.3.2 General Procedure 1b: 5 and 7-Membered CuAAA Products



Note: All manipulations are carried out under an Ar atmosphere and in the absence of light where possible. Additional details on the procedure are described here: *Nature Protoc.* **2014**, 9, 104-111. Procedure can be carried out without flame drying, instead using oven dried glassware and N_2 purging without detriment to yield or ee.

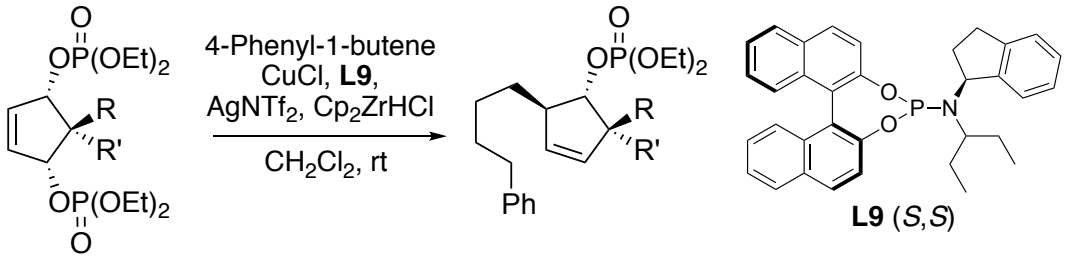
Flask **A**: A flame-dried 5 mL round bottomed flask was charged with CuCl (4 mg, 0.04 mmol, 0.1 eq) and phosphoramidite ligand **L12** (28 mg, 0.048 mmol, 0.12 eq). Dry CH_2Cl_2 (1.5 mL) was added to the mixture which was left to stir at room temperature for 1 hour. $AgNTf_2$ (23 mg, 0.06 mmol, 0.15 eq) was then added to the flask and left to stir at room temperature for 15 mins. A pale brown suspension was formed.

Flask **B**: Meanwhile a separate flame-dried round bottomed flask was charged with Cp_2ZrHCl (206 mg, 0.8 mmol, 2.0 eq) and suspended in dry CH_2Cl_2 (0.8 mL). Alkene (1.0 mmol, 2.5 eq) was added to the mixture which was left to stir at room temperature in the absence of light, until the mixture became a homogenous yellow solution (approx. 30 mins, varies with alkene). Note: The alkylzirconium species can be left for up to 2-3 hours without issue.

The contents of flask **A** were transferred into flask **B** using a syringe equipped with a Camlab PTFE syringe filter (13 mm size, pore diameter 0.22 μm) to remove excess AgCl. The combined flask contents formed a black mixture which was left to stir at 0 ˚C in the absence of light for 10 mins. *Meso*-cyclic bisphosphate (**2a**/**2c**) (0.4 mmol) was added to the mixture which was left to stir at 0 ˚C in the absence of light for 16 hours.

The mixture was quenched with 1M aq. NH_4Cl (1 mL) and left to stir for 10 mins. The organic layer was separated, filtered through a plug of Celite and evaporated *in vacuo* to give an off-white mixture of solid and oil. The crude residue was purified on silica (eluent specified below) to afford the product.

4.3.3 General Procedure 1c: 6-Membered Rings, Quaternary Centers and Heterocyclic CuAAA Products



Note: All manipulations are carried out under an Ar atmosphere and in the absence of light where possible. Additional details on the procedure are described here: *Nature Protoc.* **2014**,

9, 104-111. Procedure can be carried out without flame drying, instead using oven dried glassware and N_2 purging without detriment to yield or ee.

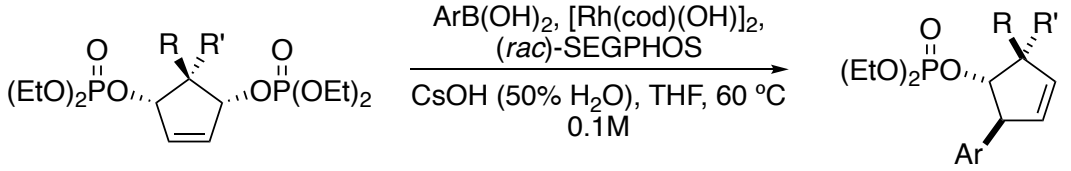
Flask **A**: A flame-dried 5 mL round bottomed flask was charged with CuCl (4 mg, 0.04 mmol, 0.1 eq) and phosphoramidite ligand **L9** (24.7 mg, 0.048 mmol, 0.12 eq). Dry CH_2Cl_2 (1.3 mL) was added to the mixture which was left to stir at room temperature for 1 hour. $AgNTf_2$ (23 mg, 0.06 mmol, 0.15 eq) was then added to the flask and left to stir at room temperature for 15 mins. A pale brown suspension was formed.

Flask **B**: Meanwhile a separate flame-dried round bottomed flask was charged with Cp_2ZrHCl (206 mg, 0.8 mmol, 2.0 eq) and suspended in dry CH_2Cl_2 (0.8 mL). Alkene (1.0 mmol, 2.5 eq) was added to the mixture which was left to stir at room temperature in the absence of light, until the mixture became a homogenous yellow solution (approx. 30 mins, varies with alkene). Note: The alkylzirconium species can be left for up to 2-3 hours without issue.

The contents of flask **A** were transferred into flask **B** using a syringe equipped with a Camlab PTFE syringe filter (13 mm size, pore diameter 0.22 μm) to remove excess AgCl. The combined flask contents formed a black mixture which was left to stir at room temperature in the absence of light for 10 mins. *Meso*-cyclic bisphosphate (**2b**, **4a-17a, 23a-24a**) (0.4 mmol) in CH_2Cl_2 (0.2 mL) was added to the mixture which was left to stir at room temperature in the absence of light for 16 hours.

The mixture was quenched with 1M aq. NH_4Cl (1 mL) and left to stir for 10 mins. The organic layer was separated, filtered through a plug of Celite and evaporated *in vacuo* to give an off-white mixture of solid and oil. The crude residue was purified on silica (eluent specified below) to afford the product.

4.3.4 General Procedure 2a: Racemic RhAAAr Products

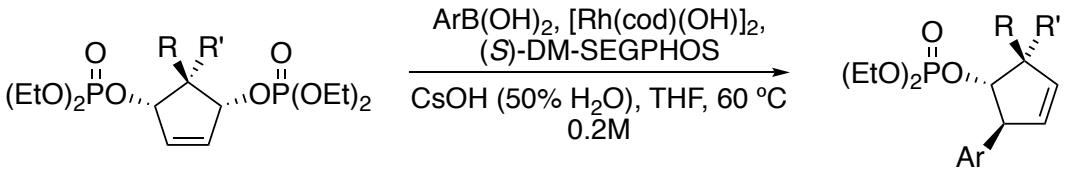


Flask **A**: A flame-dried 5 mL round-bottomed-flask was charged with (*rac*)-SEGPHOS (7.3 mg, 0.012 mmol, 0.06 eq) and $[Rh(cod)(OH)]_2$ (2.3 mg, 0.005 mmol, 0.025 eq) and the solids were dissolved in 1.0 mL dry THF. An aqueous solution (50 wt. % in H_2O) of CsOH (35 µL, 0.2 mmol, 1.0 eq) was added to this mixture which was subsequently stirred at 60 °C for 30 min.

Flask **B**: A flame-dried 5 mL round-bottomed-flask was charged with bisphosphate **4a**-**17a** (95.2 mg, 0.2 mmol, 1.0 eq) and a boronic acid (0.4 mmol, 2.0 eq). The mixture was stirred in 0.8 mL dry THF for 30 min at room temperature.

After both mixtures in Flask **A** and **B** were stirred for 30 min, the contents of flask **B** were transferred into flask **A** *via* syringe. Flask **B** was rinsed with 0.2 mL dry THF which was transferred into flask **A** in the same way. The reaction was stirred at 60 °C overnight and then allowed to cool down to room temperature. The solvent was evaporated under reduced pressure and the crude residue was purified on silica (eluent specified below) to afford the product.

4.3.5 General Procedure 2b: Asymmetric RhAAAr Products



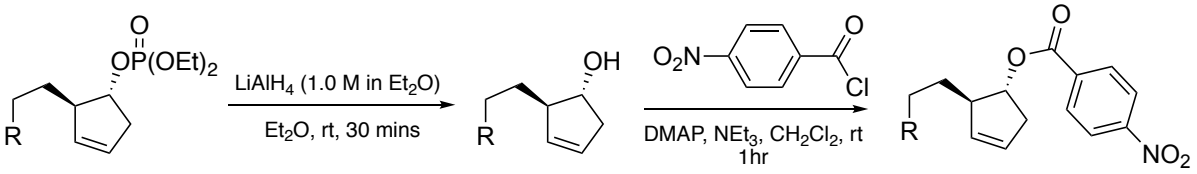
Flask **A**: A flame-dried 5 mL round-bottomed-flask was charged with (*S*)-DM-SEGPHOS (17.3 mg, 0.024 mmol, 0.06 eq) and $[Rh(cod)(OH)]_2$ (4.6 mg, 0.010 mmol, 0.025 eq) and the

solids were dissolved in 1.0 mL dry THF. An aqueous solution (50 wt. % in H_2O) of CsOH (70 µL, 0.4 mmol, 1.0 eq) was added to this mixture which was subsequently stirred at 60 °C for 30 min.

Flask **B**: A flame-dried 5 mL round-bottomed-flask was charged with bisphosphate **4a**-**17a** (190.4 mg, 0.4 mmol, 1.0 eq) and a boronic acid (0.8 mmol, 2.0 eq). The mixture was stirred in 0.8 mL dry THF for 30 min at room temperature.

After both mixtures in Flask **A** and **B** were stirred for 30 min, the contents of flask **B** were transferred into flask **A** *via* syringe. Flask **B** was rinsed with 0.2 mL dry THF which was transferred into flask **A** in the same way. The reaction was stirred at 60 °C for 4 hours and then allowed to cool down to room temperature. The solvent was evaporated under reduced pressure and the crude residue was purified on silica (eluent specified below) to afford the product.

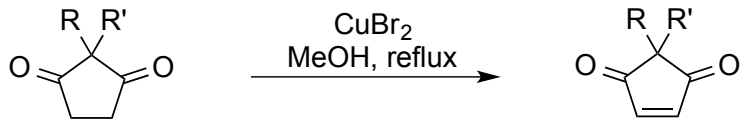
4.3.6 General Procedure 3: Phosphate Reduction/Esterification for HPLC Analysis



Phosphate (0.1 mmol, 1.0 eq) was dissolved in Et_2O (1.0 mL) and cooled to 0 ˚C before adding $LiAlH_4$ (1.0 M in Et_2O, 0.6 mL, 0.6 mmol, 6 eq) dropwise. The solution was warmed to room temperature and left to stir for 30 mins. The reaction mixture was quenched with H_2O dropwise until effervescence stopped. The residue was suspended in CH_2Cl_2 and filtered through celite, washing with CH_2Cl_2. The filtrate was evaporated *in vacuo* to give the crude alcohol.

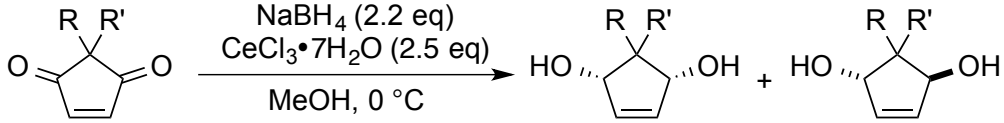
The crude alcohol (0.1 mmol) was dissolved in CH_2Cl_2 (2.0 mL) before adding NEt_3 (28 µL, 0.2 mmol, 2.0 eq), DMAP (5 mg, 0.04 mmol, 0.4 eq) and *p*-nitrobenzoyl chloride (37 mg, 0.2 mmol, 2.0 eq). The mixture was left to stir for 1 hour, and was then evaporated *in vacuo* to give a yellow residue. The residue was purified on silica (5% EtOAc in petroleum ether) to give a colourless oil.

4.3.7 General Procedure 4: Oxidation of Diones



Under an Ar atmosphere, dione (15 mmol, 1.0 eq) was dissolved in anhydrous MeOH (100 mL) before addition of $CuBr_2$ (7.37 g, 33.0 mmol, 2.2 eq). The mixture was heated to reflux and stirred for 1 hour. The resulting black mixture was cooled, quenched with dropwise addition of H_2O (25 ml) and 1M HCl (50 mL). The mixture was concentrated *in vacuo* to remove MeOH. The resulting mixture was extracted with EtOAc (3 x 75 mL) and the organic extracts were combined, washed with brine (2 x 50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified on silica (eluent specified below) to give the dienone product. **NOTE**: All examples give bright yellow products.

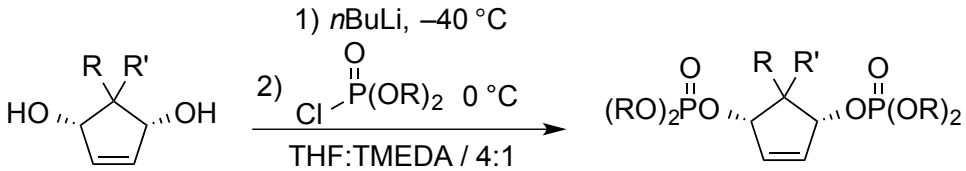
4.3.8 General Procedure 5: Luche Reduction of Dienones



Dienone (5.00 mmol, 1.0 eq) was dissolved in MeOH (60 mL, not dry) and stirred until dissolution. $CeCl_3 \cdot 7H_2O$ (4.66 g, 12.50 mmol, 2.5 eq) was added and stirred until dissolution.

The resulting solution was cooled to 0 ˚C before portionwise addition of $NaBH_4$ (416 mg, 11 mmol, 2.2 eq) over 10 minutes. The resulting suspension was left to stir at 0 ˚C for 2 hours before slow quenching with H_2O (5 ml) and 1M HCl (10 mL). The mixture was concentrated *in vacuo* to remove MeOH. The resulting mixture was extracted with EtOAc (3 x 30 mL) and the organic extracts were combined, washed with brine (2 x 30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified on silica (eluent specified below) to give the diol product. **NOTE**: The examples presented gave separable 1:1 *cis*/*trans* mixtures unless stated otherwise. The *cis* isomer was isolated and characterised in all cases.

4.3.9 General Procedure 6: Phosphorylation of Diols via an Dianion Approach



A solution of diol (10.0 mmol, 1.0 eq.) in THF (60 mL) and TMEDA (15 mL) was cooled to –40 ˚C using a MeCN/CO_2 bath before *n*BuLi (2.5 M in hexane, 8.80 mL, 22.0 mmol, 2.2 eq.) was added dropwise. The resulting solution was left to stir for 10 minutes at –40 ˚C before dialkyl chlorophosphate (25.0 mmol, 2.5 eq.) was added dropwise. The resulting mixture was left to stir at –40 ˚C for 2 hours and then warmed to 0 °C. Brine (10 mL) was added slowly to the mixture which was then poured over H_2O (80 mL) and extracted with CH_2Cl_2 (3 x 80 mL). The organic extracts were combined, washed with brine (100 mL), dried ($MgSO_4$) and evaporated *in vacuo.* The crude material was purified on silica (eluent specified below) to give the diphosphate product.

4.4 Experimental Procedures for Chapter 2

Cis-4-cyclopentene-1,3-diol



Chemical Formula: $C_5H_8O_2$
Molecular Weight: 100.1170

Cyclopentadiene (2.00 mL, 24.3 mmol, 1.0 eq.), thiourea (1.84g, 24.3 mmol, 1.0 eq.) and Rose Bengal (50 mg, 0.048 mmol, 0.002 eq.) were added to a round-bottomed flask containing methanol (400 mL). O_2 gas was bubbled through the resulting pink solution for 15 mins before being maintained under an atmosphere of O_2. The flask was partially submersed in an ice bath and irradiated with a 500 W halogen lamp with stirring for 8 hours (Figure 4.1). The lamp was turned off and the mixture was left to stir in the dark at room temperature for 16 hours. The mixture was evaporated *in vacuo* to give a viscous pink residue. The residue was dissolved in water (250 mL) and extracted with Et_2O (3 x 200 mL). The aqueous layer was evaporated *in vacuo* to give a pink residue, which was dissolved in methanol (50 mL) and loaded onto Chem Tube-Hydromatrix for purification on silica (1% MeOH in EtOAc) to give *cis*-4-cyclopentene-1,3-diol as a white solid (1.72 g, 71% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ_H/ppm: 5.75 (s, 2H), 4.84 (dd, 2H, J = 7.8, 2.0 Hz), 2.96-2.85 (m, 2H), 1.28-1.21 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 137.0, 75.7, 44.2. Consistent with data in the literature.[196]

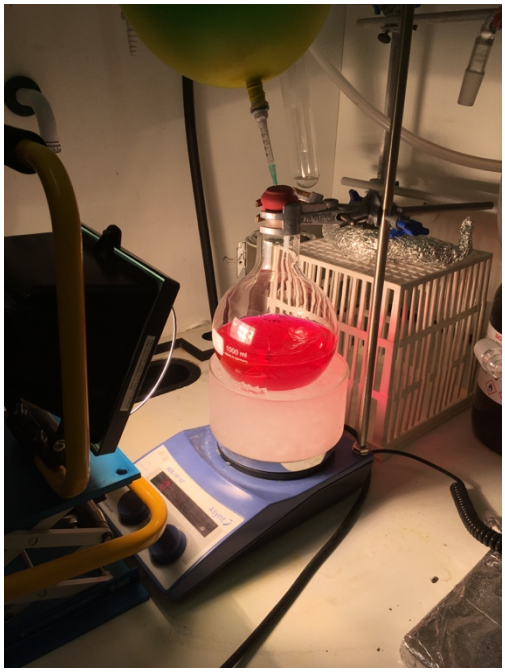


Figure 4.1. Setup of photo-oxidation, illustrating partial submersion of flask in an ice bath.

Cis-5-cyclohexene-1,4-diol



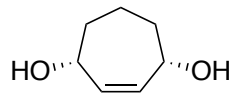
Chemical Formula: $C_6H_{10}O_2$
Molecular Weight: 114.1440

1,3-Cyclohexadiene (2.50 mL, 26.2 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (105 mL) before adding *meso*-tetraphenylporphyrin (56 mg, 0.09 mmol, 0.0035 eq.). O_2 gas was bubbled through the resulting purple solution for 15 mins before being maintained under an atmosphere of O_2. The flask was partially submersed in an ice bath and irradiated with a 500 W halogen lamp with stirring for 8 hours (Figure 4.1). The reaction mixture was then evaporated *in vacuo* to give a purple residue which was then dissolved in MeOH (105 mL) and thiourea (2.01 g, 26.5 mmol, 1.01 eq.) was added. The mixture was left to stir in the dark at room temperature for 16 hours. The mixture was then evaporated *in vacuo* to give a viscous, dark brown residue which was dissolved in methanol (50 mL) and loaded onto Chem Tube-Hydromatrix for

purification on silica (2% MeOH in Et_2O), to give *cis*-5-cyclohexene-1,4-diol as a white solid (2.28 g, 76% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ_H/ppm: 5.75 (s, 2H), 4.07 (br. s, 2H), 3.90 (br. s, 2H), 1.78-1.71 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 132.6, 64.1, 28.6. Consistent with data in the literature.[218]

Cis-6-cycloheptene-1,5-diol

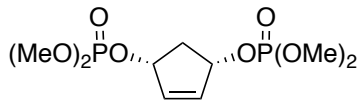


Chemical Formula: $C_7H_{12}O_2$
Molecular Weight: 128.1710

1,3-Cycloheptadiene (1.00 g, 210.6 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (80 mL) before adding *meso*-tetraphenylporphyrin (23 mg, 0.04 mmol, 0.0035 eq.). O_2 gas was bubbled through the resulting purple solution for 15 mins before being maintained under an atmosphere of O_2. The flask was partially submersed in an ice bath and irradiated with a 500 W halogen lamp with stirring for 8 hours (Figure 4.1). The reaction mixture was then evaporated *in vacuo* to give a purple residue which was then dissolved in MeOH (80 mL) and thiourea (816 mg, 10.7 mmol, 1.01 eq.) was added. The mixture was left to stir in the dark at room temperature for 16 hours. The mixture was then evaporated *in vacuo* to give a viscous, dark brown residue which was dissolved in methanol (50 mL) and loaded onto Chem Tube-Hydromatrix for purification on silica (2-3% MeOH in CH_2Cl_2), to give *cis*-6-cycloheptene-1,5-diol as a white solid (576 mg, 42% yield).

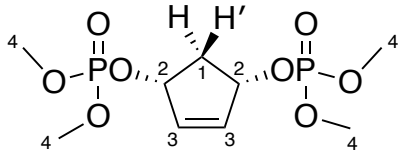
^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 5.76 (s, 2H), 4.30 (d, 2H, J = 8.0 Hz), 2.10-2.00 (m, 1H) 1.78-1.73 (m, 2H), 1.75 (br. s, 1H), 1.72-1.56 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 135.8, 71.4, 36.0, 23.1. Consistent with data in the literature.[219]

***Meso*-4-cyclopentene-1,3-bisdimethylphosphate**



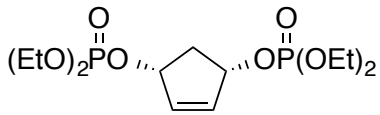
Chemical Formula: $C_9H_{18}O_8P_2$
Molecular Weight: 316.1825

Synthesised according to general procedure 6 using *cis*-4-cyclopentene-1,3-diol on 1.0 mmol scale. Purified by flash chromatography (4% MeOH in CH_2Cl_2) to give *meso*-4-cyclopentene-1,3-bisdimethylphosphate as a pale yellow oil (207 mg, 65% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 6.15 (s, 2H, 2CH-(3)), 5.27 – 5.18 (m, 2H, 2CH-(2)), 3.77 (d, J = 11.1 Hz, 12H, 4CH_3-(4)), 2.98 – 2.85 (m, 1H, C***H***H´-(1)), 2.10 – 1.99 (m, 1H, CH***H´***-(1)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 135.1 (C(3)), 79.4 (C(2)), 54.3 (C(4)), 39.5 (C1)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: 0.29; HRMS (ESI) *m/z* calcd for $C_9H_{18}O_8P_2Na$ $[M+Na]^+$: 339.0369, found: 339.0365; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2980.7 (w), 1461.7 (w), 1377.8 (w), 1266.4 (m), 1185.8 (w), 1037.9 (s), 991.8 (s), 934.3 (w), 849.5 (m), 751.8 (w).

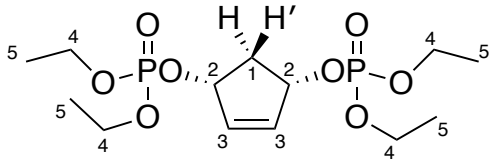
***Meso*-4-Cyclopentene-1,3-bisdiethylphosphate (1a)**



1a

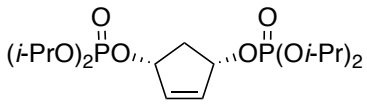
Chemical Formula: $C_{13}H_{26}O_8P_2$
Molecular Weight: 372.2905

To a solution of *cis*-4-cyclopentene-1,3-diol (3.15 g, 31.5 mmol, 1.0 eq) in CH_2Cl_2 (142 mL) was added NEt_3 (13.2 mL, 94.4 mmol, 3.0 eq) and DMAP (1.92 g, 15.8 mmol, 0.5 eq). The resulting solution was cooled to 0 °C before dropwise addition of diethylchlorophosphate (13.7 mL, 94.4 mmol, 3.0 eq). The resulting mixture was left to stir at room temperature for 16 hours. The mixture was then quenched with H_2O (100 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The organic extracts were combined, washed with brine (100 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. The yellow oil was purified by flash chromatography (3% MeOH in EtOAc) to give *meso*-4-cyclopentene-1,3-bisdiethylphosphate (**1a**) as a pale yellow oil (11.23g, 96% yield).



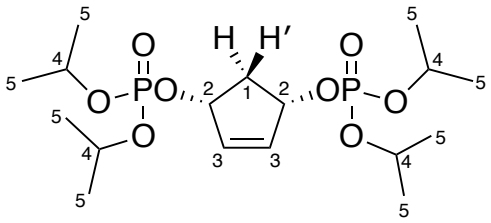
^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 6.12 (d, J = 0.8 Hz, 2H, 2CH-(3)), 5.21 (d, J = 4.4 Hz, 2H, 2CH-(2)), 4.10 (m, J = 8.3, 7.1, 1.3 Hz, 8H, 4CH_2-(4)), 2.91 (dt, J = 14.6, 7.3 Hz, 1H, C***H***H′-(1)), 2.03 (dt, J = 14.6, 4.3 Hz, 1H, CH***H′***-(1)), 1.33 (t, J = 7.1 Hz, 12H, 4CH_3-(5)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 135.2 (C(3)), 79.3 (C(2)), 64.0 (C(4)), 39.7 (C(1)), 16.3 (C(5)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.91; HRMS (ESI) *m/z* calcd for $C_{13}H_{26}O_8P_2Na$ $[M+Na]^+$: 395.0995, found: 395.0993; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2982.8 (w), 1373.3 (w), 1261.4 (m), 1165.5 (w), 1024.0 (s), 980.7 (s), 802.9 (w), 749.9 (w). Consistent with data in the literature.[127]

***Meso*-4-Cyclopentene-1,3-bisdiisopropylphosphate**



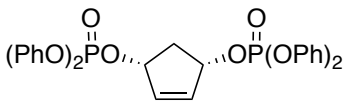
Chemical Formula: $C_{17}H_{34}O_8P_2$
Molecular Weight: 428.3985

Synthesised according to general procedure 6 using *cis*-4-cyclopentene-1,3-diol on 1.50 mmol scale. Purified by flash chromatography (3% MeOH in CH_2Cl_2) to give *meso*-4-cyclopentene-1,3-bisdiisopropylphosphate as a pale yellow oil (456 mg, 71% yield).



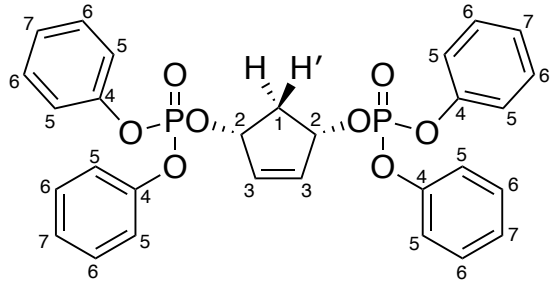
^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 6.09 (s, 2H, 2CH-(3)), 5.16 (q, J = 6.4 Hz, 2H, 2CH-(2)), 4.61 (m, J = 12.3, 6.7, 6.2 Hz, 4H, 4CH-(4)), 2.88 (dt, J = 14.6, 7.3 Hz, 1H, C***H***H´-(1)), 2.00 (dt, J = 14.5, 4.6 Hz, 1H, CH***H´***-(1)), 1.31 (d, J = 6.2 Hz, 24H, 8CH_3-(5)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 135.4 (C(3)), 79.5 (C(2)), 73.0 (C(4)), 40.2 (C(1)), 24.2 (C(5)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -3.50; HRMS (ESI) *m/z* calcd for $C_{17}H_{34}O_8P_2Na$ $[M+Na]^+$: 451.1621, found: 451.1618; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2981.0 (w), 1467.8 (w), 1376.3 (w), 1259.8 (m), 1179.3 (w), 1142.8 (w), 1108.6 (w), 979.5 (s), 928.5 (m), 779.3 (w), 729.3 (w).

***Meso*-4-Cyclopentene-1,3-bisdiphenylphosphate**



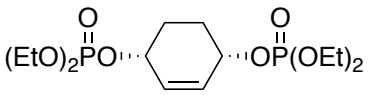
Chemical Formula: $C_{29}H_{26}O_8P_2$
Molecular Weight: 564.4665

Synthesised according to general procedure 6 using *cis*-4-cyclopentene-1,3-diol on 1.0 mmol scale. Purified by flash chromatography (EtOAc:Petroleum Ether, 1:1, using silica which was pre-washed with 2% NEt_3 in petroleum ether) to give *meso*-4-cyclopentene-1,3-bisdiphenylphosphate as a yellow oil (462 mg, 82% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.36 – 7.31 (m, 8H, ArH-(5)), 7.23 – 7.16 (m, 12H, ArH-(6,7)), 6.11 (s, 2H, 2CH-(3)), 5.46 – 5.42 (m, 2H, 2CH-(2)), 2.89 (dt, J = 14.7, 7.2 Hz, 1H, C***H***H′-(1)), 2.08 (dt, J = 14.9, 3.9 Hz, 1H, CH***H′***-(1)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 150.5 (C(4)), 135.3 (C(3)), 129.9 (C(6)), 125.6 (C(5)), 120.2 (C(7)), 80.9 (C(2)), 39.3 (C(1)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -12.74; HRMS (ESI) *m/z* calcd for $C_{29}H_{26}O_8P_2Na$ $[M+Na]^+$: 587.0995, found: 587.0988; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2980.6 (w), 1589.6 (w), 1486.9 (m), 1573.2 (w), 1284.1 (m), 1218.5 (w), 1186.1 (s), 1161.8 (m), 1071.3 (w), 990.1 (m), 942.4 (s), 754.8 (s), 687.8 (m), 616.7 (w).

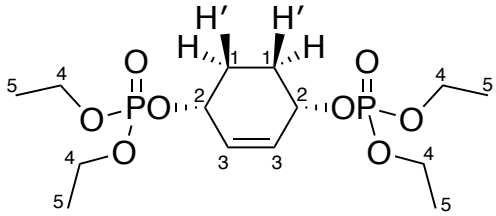
***Meso*-5-Cyclohexene-1,4-bisdiethylphosphate (2a)**



2a

Chemical Formula: $C_{14}H_{28}O_8P_2$
Molecular Weight: 386.3175

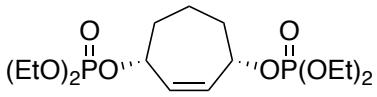
To a solution of *cis*-5-cyclohexene-1,4-diol (2.20 g, 19.3 mmol, 1.0 eq) in CH_2Cl_2 (87 mL) was added NEt_3 (8.06 mL, 57.8 mmol, 3.0 eq) and DMAP (1.18 g, 9.64 mmol, 0.5 eq). The resulting solution was cooled to 0 °C before dropwise addition of diethylchlorophosphate (8.36 mL, 57.8 mmol, 3.0 eq). The resulting mixture was left to stir at room temperature for 16 hours. The mixture was then quenched with H_2O (100 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The organic extracts were combined, washed with brine (100 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. The yellow oil was purified by flash chromatography (3% MeOH in EtOAc) to give *meso*-5-cyclohexene-1,4-bisdiethylphosphate (**2a**) as a yellow oil (6.56 g, 88% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 5.97 (d, J = 1.4 Hz, 2H, 2CH-(3)), 4.92 – 4.70 (m, 2H, 2CH-(2)), 4.10 (dq, J = 7.9, 7.0 Hz, 8H, 4CH_2-(4)), 2.07 – 1.99 (m, 2H, 2C***H***H′-(1)), 1.98 – 1.89 (m, 2H, 2CH***H′***-(1)), 1.34 (td, J = 7.0, 1.0 Hz, 12H, 4CH_3-(5)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm: 130.7 (C(3)), 70.9 (C(2)), 63.8 (C(4)), 26.1 (C(1)), 16.2 (C(5)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.38; HRMS (ESI) *m/z* calcd for $C_{14}H_{28}O_8P_2$ $[M+H]^+$: 387.1338, found: 387.1379; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2985.2 (w), 1644.4 (w), 1396.8 (w),

1261.4 (m), 1164.2 (w), 1027.0 (s), 989.3 (s), 817.6 (w). Consistent with data in the literature.[127]

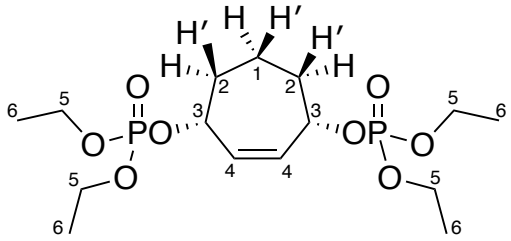
***Meso*-6-Cycloheptene-1,5-bisdiethylphosphate (3a)**



3a

Chemical Formula: $C_{15}H_{30}O_8P_2$
Molecular Weight: 400.3445

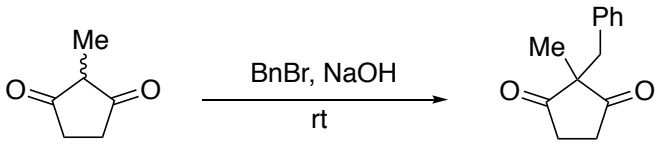
To a solution of *cis*-6-cycloheptene-1,5-diol (400 mg, 3.12 mmol, 1.0 eq) in CH_2Cl_2 (14 mL) was added NEt_3 (1.30 mL, 9.36 mmol, 3.0 eq) and DMAP (191 mg, 1.56 mmol, 0.5 eq). The resulting solution was cooled to 0 °C before dropwise addition of diethylchlorophosphate (1.35 mL, 9.36 mmol, 3.0 eq). The resulting mixture was left to stir at room temperature for 16 hours. The mixture was then quenched with H_2O (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The organic extracts were combined, washed with brine (50 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. The yellow oil was purified by flash chromatography (2% MeOH in CH_2Cl_2) to give *meso*-6-cycloheptene-1,5-bisdiethylphosphate (**3a**) as a yellow oil (1.10 g, 88% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 5.79 (s, 2H, 2CH-(4)), 5.06 – 4.71 (m, 2H, 2CH-(3)), 4.34 – 3.92 (m, 8H, 4CH_2-(5)), 2.12 – 1.94 (m, 3H, 3C***H***H′-(1, 2)), 1.74 – 1.59 (m, 3H, 3CH***H′***-

(1, 2)), 1.31 (tq, J = 7.1, 1.1 Hz, 12H, 2CH_3-(6)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C/pm: 133.07 (C(4)), 77.57 (C(3)), 63.86 (C(5)), 34.01 (C(2)), 22.64 (C(1)), 16.24 (C(6)); ^{31}P NMR (162 MHz,$CDCl_3$) δ_P/ppm: -1.68; HRMS (ESI) *m/z* calcd for $C_{15}H_{30}O_8P_2$ $[M+H]^+$: 400.1316, found: 400.1441; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2985.4 (w), 1646.2 (w), 1396.3 (w), 1263.5 (m), 1164.6 (w), 1027.5 (s), 988.9 (s), 804.1 (w) Consistent with data in the literature.[127]

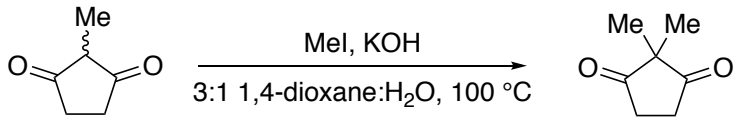
2-Benzyl-2-methylcyclopentane-1,3-dione (6)



2-Methyl-1,3-cyclopentanedione (1.50 g, 13.4 mmol, 1 eq) was dissolved in 1M aq. NaOH (15.0 mL) before addition of benzyl bromide (3.20 mL, 26.8 mmol, 2.0 eq). The resulting mixture was vigorously stirred (1000 rpm) at room temperature for 44 hours. The reaction mixture was extracted with EtOAc (3 x 20 mL). The organic extracts were combined, washed with brine (20 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. The yellow oil was purified by flash chromatography (5-10-15% EtOAc in petroleum ether) to give 2-benzyl-2-methylcyclopentane-1,3-dione (2.025 g, 75%) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.25 – 7.18 (m, 3H), 7.06 – 7.01 (m, 2H), 2.95 (s, 2H), 2.54 (dd, J = 19.2, 7.3 Hz, 2H), 2.05 (dd, J = 18.4, 6.2 Hz, 2H), 1.20 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 217.6, 135.9, 129.7, 128.7, 127.4, 58.4, 43.2, 35.6, 20.2. Consistent with data in the literature.[79]

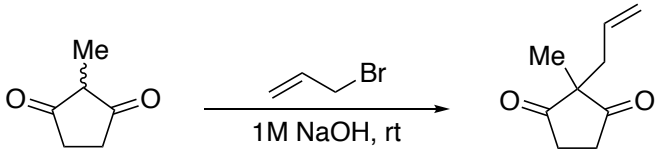
2,2-Dimethylcyclopentane-1,3-dione



2-Methyl-1,3-cyclopentanedione (2.50 g, 22.23 mmol, 1.0 eq) was dissolved in 1,4-dioxane (18.75 mL) and water (6.5 mL) before addition of KOH (1.31 g, 23.41 mmol, 1.05 eq) and methyl iodide (1.53 mL, 24.53 mmol, 1.1 eq). The resulting mixture was heated to reflux at left to stir for 12 hours. The reaction mixture was poured over water (50 mL) and extracted with EtOAc (3 x 50 mL). The organic extracts were combined, washed with brine (50 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. The yellow oil was purified by flash chromatography (10-20-30% EtOAc in petroleum ether) to give 2,2-dimethylcyclopentane-1,3-dione (1.765 g, 63%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 2.76 (s, 4H), 1.10 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 216.4, 52.7, 34.6, 20.3. Consistent with data in the literature.[220]

2-Allyl-2-methylcyclopentane-1,3-dione

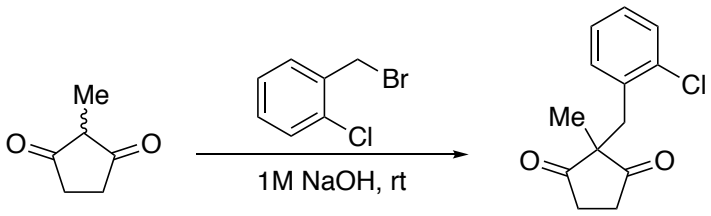


2-Methyl-1,3-cyclopentanedione (2.50 g, 22.30 mmol, 1 eq) was dissolved in 1M aq. NaOH (25.0 mL) before addition of allyl bromide (3.86 mL, 44.60 mmol, 2.0 eq). The resulting mixture was vigorously stirred (1000 rpm) at room temperature for 40 hours. The reaction mixture was extracted with EtOAc (3 x 20 mL). The organic extracts were combined, washed with brine (20 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. The yellow

oil was purified by flash chromatography (5-10% EtOAc in petroleum ether) to give 2-benzyl-2-methylcyclopentane-1,3-dione (2.555 g, 75%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 5.54 (ddt, J = 16.1, 10.9, 7.5 Hz, 1H), 5.05 – 5.03 (m, 1H), 5.02 – 4.98 (m, 1H), 2.77 – 2.59 (m, 4H), 2.30 (dt, J = 7.5, 1.1 Hz, 2H), 1.07 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 216.3, 131.6, 119.9, 56.8, 40.1, 35.5, 18.9. Consistent with data in the literature.[79]

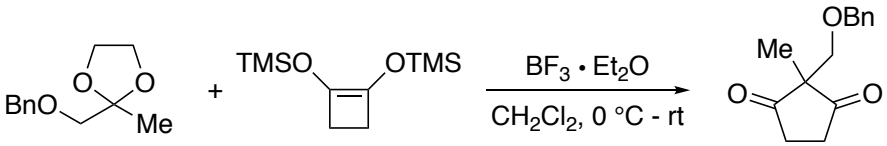
2-(2-Chlorobenzyl)-2-methylcyclopentane-1,3-dione



2-Methyl-1,3-cyclopentanedione (2.50 g, 22.30 mmol, 1 eq) was dissolved in 1M aq. NaOH (25.0 mL) before addition of 2-chlorobenzyl bromide (5.80 mL, 44.60 mmol, 2.0 eq). The resulting mixture was vigorously stirred (1000 rpm) at room temperature for 96 hours. The reaction mixture was extracted with EtOAc (3 x 20 mL). The organic extracts were combined, washed with brine (20 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. The yellow oil was purified by flash chromatography (5-10-20% EtOAc in petroleum ether) to give 2-benzyl-2-methylcyclopentane-1,3-dione (1.453 g, 28%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.35 – 7.30 (m, 1H), 7.19 – 7.14 (m, 2H), 7.12 – 7.08 (m, 1H), 3.10 (s, 2H), 2.67 – 2.48 (m, 4H), 1.18 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 215.8, 134.7, 133.4, 132.0, 130.0, 128.9, 126.9, 57.2, 39.1, 35.7, 18.6. Consistent with data in the literature.[79]

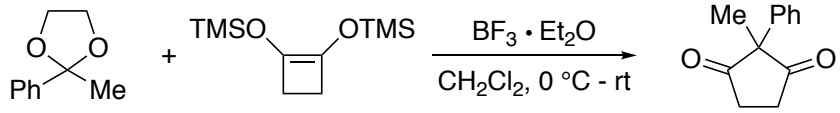
2-((Benzyloxy)methyl)-2-methylcyclopentane-1,3-dione



2-((Benzyloxy)methyl)-2-methyl-1,3-dioxolane (1.00 g, 4.81 mmol, 1.0 eq) and 1,2-bis(trimethylsiloxy)cyclobutene (1.85 mL, 7.21 mmol, 1.50 eq) were dissolved in CH_2Cl_2 (8.0 mL) and cooled to 0 °C before dropwise addition of boron trifluoride diethyl etherate (0.89 mL, 7.21 mmol, 1.50 eq). The resulting solution was left to stir at room temperature for 16 hours. The reaction mixture was poured over water (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The organic extracts were combined, washed with brine (50 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. The yellow oil was purified by flash chromatography (10-15% EtOAc in petroleum ether) to give 2-((benzyloxy)methyl)-2-methylcyclopentane-1,3-dione (188 mg, 17%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.36 – 7.25 (m, 3H), 7.21 – 7.17 (m, 2H), 4.39 (s, 2H), 3.61 (s, 2H), 2.86 – 2.67 (m, 4H), 1.00 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 216.8, 137.4, 128.5, 127.9, 127.5, 75.4, 73.7, 56.4, 36.4, 15.2. Consistent with data in the literature.[78]

2-Methyl-2-phenylcyclopentane-1,3-dione

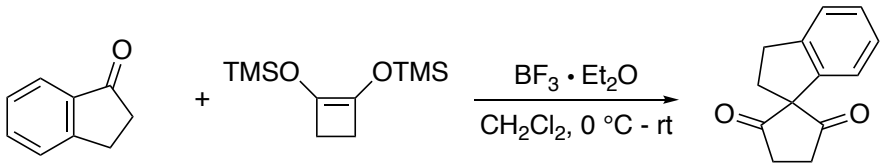


2-Methyl-2-phenyl-1,3-dioxolane (426 mg, 2.60 mmol, 1.0 eq) and 1,2-bis(trimethylsiloxy)cyclobutene (1.00 mL, 3.89 mmol, 1.50 eq) were dissolved in CH_2Cl_2 (4.5 mL) and cooled to 0 °C before dropwise addition of boron trifluoride diethyl etherate (0.48

mL, 3.89 mmol, 1.50 eq). The resulting solution was left to stir at room temperature for 16 hours. The reaction mixture was poured over water (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The organic extracts were combined, washed with brine (50 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. The yellow oil was purified by flash chromatography (5-10% EtOAc in petroleum ether) to give 2-methyl-2-phenylcyclopentane-1,3-dione (411 mg, 85%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.38 – 7.32 (m, 2H), 7.32 – 7.27 (m, 1H), 7.24 – 7.19 (m, 2H), 2.98 – 2.66 (m, 4H), 1.44 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 213.2, 137.1, 129.5, 129.4, 128.1, 126.5, 62.2, 35.4, 19.9. Consistent with data in the literature.[79]

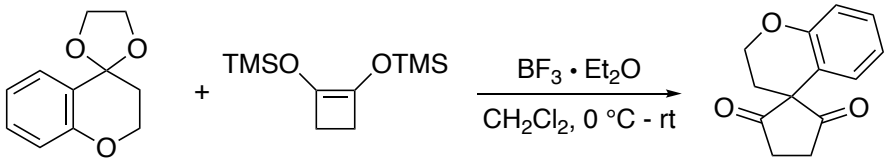
2',3'-Dihydrospiro[cyclopentane-1,1'-indene]-2,5-dione



1-Indanone (514 mg, 3.89 mmol, 1.0 eq) and 1,2-bis(trimethylsiloxy)cyclobutene (1.50 mL, 5.84 mmol, 1.50 eq) were dissolved in CH_2Cl_2 (7.0 mL) and cooled to 0 °C before dropwise addition of boron trifluoride diethyl etherate (0.72 mL, 5.84 mmol, 1.50 eq). The resulting solution was left to stir at room temperature for 24 hours. The reaction mixture was poured over water (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The organic extracts were combined, washed with brine (50 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. The yellow oil was purified by flash chromatography (10-20% EtOAc in petroleum ether) to give 2',3'-dihydrospiro[cyclopentane-1,1'-indene]-2,5-dione (454 mg, 58%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.31 – 7.27 (m, 1H), 7.23 (td, *J* = 7.5, 1.2 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 3.18 (t, *J* = 7.5 Hz, 2H), 3.11 – 2.83 (m, 4H), 2.40 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 213.3, 145.0, 140.8, 128.5, 127.1, 125.6, 122.6, 70.0, 35.7, 33.0, 31.8. Consistent with data in the literature.[153]

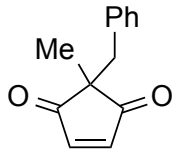
Spiro[chromane-4,1'-cyclopentane]-2',5'-dione



Spiro[chromane-4,2'-[1,3]dioxolane] (961 mg, 5.00 mmol, 1.0 eq) and 1,2-bis(trimethylsiloxy)cyclobutene (1.93 mL, 7.50 mmol, 1.50 eq) were dissolved in CH_2Cl_2 (8.0 mL) and cooled to 0 °C before dropwise addition of boron trifluoride diethyl etherate (0.92 mL, 7.50 mmol, 1.50 eq). The resulting solution was left to stir at room temperature for 18 hours. The reaction mixture was poured over water (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The organic extracts were combined, washed with brine (50 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. The yellow oil was purified by flash chromatography (10-20% EtOAc in petroleum ether) to give spiro[chromane-4,1'-cyclopentane]-2',5'-dione (471 mg, 43%) as a colourless, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.21 – 7.15 (m, 1H), 6.91 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.85 (td, *J* = 7.7, 1.3 Hz, 1H), 6.57 (dd, *J* = 7.7, 1.6 Hz, 1H), 4.35 – 4.31 (m, 2H), 3.11 – 2.90 (m, 4H), 2.10 – 2.06 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 213.7, 155.5, 129.5, 128.1, 121.2, 118.2, 117.8, 61.1, 57.2, 35.6, 29.3. Consistent with data in the literature.[153]

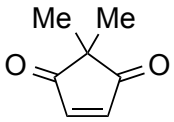
2-Benzyl-2-methylcyclopent-4-ene-1,3-dione (7)



Synthesised according to general procedure 4 using 2-benzyl-2-methylcyclopentane-1,3-dione on a 16.81 mmol scale. Purified by flash chromatography (5-10-15% EtOAc in petroleum ether) to give 2-benzyl-2-methylcyclopent-4-ene-1,3-dione (**7**) as a bright yellow solid (2.99 g, 89% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.18 – 7.12 (m, 3H), 6.98 (s, 2H), 6.94 – 6.91 (m, 2H), 2.99 (s, 2H), 1.25 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 207.4, 148.9, 135.7, 129.8, 127.2, 52.7, 41.1, 19.5. Consistent with data in the literature.[79]

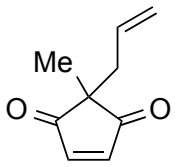
2,2-Dimethylcyclopent-4-ene-1,3-dione



Synthesised according to general procedure 4 using 2,2-Dimethylcyclopentane-1,3-dione on a 13.62 mmol scale. Purified by flash chromatography (10-15-20% EtOAc in petroleum ether) to give 2,2-Dimethylcyclopent-4-ene-1,3-dione as a pale yellow oil (568 mg, 34% yield). **NOTE**: Product volatile.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.17 (s, 2H), 1.12 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 207.8, 147.2, 46.5, 19.7. Consistent with data in the literature.[221]

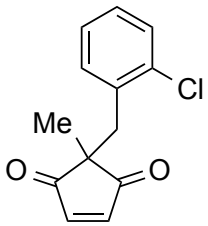
2-Allyl-2-methylcyclopent-4-ene-1,3-dione



Synthesised according to general procedure 4 using 2-allyl-2-methylcyclopentane-1,3-dione on a 16.30 mmol scale. Purified by flash chromatography (2-5-10% EtOAc in petroleum ether) to give 2-allyl-2-methylcyclopent-4-ene-1,3-dione as a bright yellow oil (761 mg, 31% yield). **NOTE**: Product volatile.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.20 (s, 2H), 5.44 (ddt, J = 16.9, 10.1, 7.5 Hz, 1H), 5.01 – 4.92 (m, 2H), 4.97 – 4.95 (m, 1H), 2.34 (d, J = 7.5 Hz, 2H), 1.11 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 207.2, 148.4, 131.5, 119.7, 50.6, 38.8, 18.6. Consistent with data in the literature.[79]

2-(2-Chlorobenzyl)-2-methylcyclopent-4-ene-1,3-dione

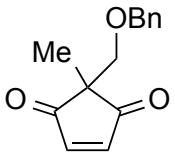


Synthesised according to general procedure 4 using 2-(2-chlorobenzyl)-2-methylcyclopentane-1,3-dione on a 5.93 mmol scale. Purified by flash chromatography (5-10-15% EtOAc in petroleum ether) to give 2-(2-chlorobenzyl)-2-methylcyclopent-4-ene-1,3-dione as a bright yellow solid (1.14 g, 82% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.29 – 7.25 (m, 1H), 7.14 – 7.08 (m, 2H), 7.10 (s, 2H), 7.06 – 7.02 (m, 1H), 3.14 (s, 2H), 1.25 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 206.4,

148.4, 134.5, 133.4, 132.0, 130.1, 128.7, 126.7, 51.5, 37.6, 18.6. Consistent with data in the literature.[79]

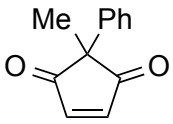
2-((Benzyloxy)methyl)-2-methylcyclopent-4-ene-1,3-dione



Synthesised according to general procedure 4 using 2-((Benzyloxy)methyl)-2-methylcyclopentane-1,3-dione on a 0.81 mmol scale. Purified by flash chromatography (5-10% EtOAc in petroleum ether) to give 2-((Benzyloxy)methyl)-2-methylcyclopent-4-ene-1,3-dione as a yellow oil (118 mg, 63% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.35 – 7.25 (m, 3H), 7.34 (s, 2H), 7.18 – 7.15 (m, 2H), 4.39 (s, 2H), 3.66 (s, 2H), 1.06 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 206.3, 149.3, 137.5, 128.5, 127.8, 127.4, 73.5, 72.1, 51.4, 14.9. Consistent with data in the literature.[78]

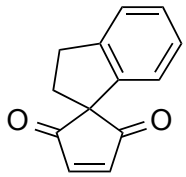
2-Methyl-2-phenylcyclopent-4-ene-1,3-dione



Synthesised according to general procedure 4 using 2-methyl-2-phenylcyclopentane-1,3-dione on a 2.18 mmol scale. Purified by flash chromatography (5-10-20% EtOAc in petroleum ether) to give 2-methyl-2-phenylcyclopent-4-ene-1,3-dione as a bright yellow oil (330 mg, 81% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.37 – 7.26 (m, 5H), 7.35 (s, 2H), 1.59 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 205.1, 148.5, 136.9, 128.9, 127.9, 126.5, 54.5, 19.7. Consistent with data in the literature.[79]

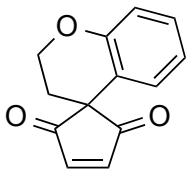
2',3'-Dihydrospiro[cyclopent-4-ene-1,1'-indene]-2,5-dione



Synthesised according to general procedure 4 using 2',3'-Dihydrospiro[cyclopentane-1,1'-indene]-2,5-dione on a 2.25 mmol scale. Purified by flash chromatography (5-10-15% EtOAc in petroleum ether) to give 2',3'-Dihydrospiro[cyclopent-4-ene-1,1'-indene]-2,5-dione as a bright yellow solid (343 mg, 77% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.49 (s, 2H), 7.31 (dp, J = 7.5, 1.0 Hz, 1H), 7.24 (td, J = 7.5, 1.1 Hz, 1H), 7.12 (tq, J = 7.5, 1.0 Hz, 1H), 6.78 (dd, J = 7.5, 0.4 Hz, 1H), 3.23 (t, J = 7.4 Hz, 2H), 2.41 (t, J = 7.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 204.3, 150.3, 145.5, 140.2, 128.6, 126.9, 125.3, 122.3, 63.3, 60.4, 32.0, 31.8, 14.2. Consistent with data in the literature.[222]

Spiro[chromane-4,1'-cyclopent-4-ene]-2',5'-dione

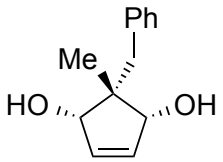


Synthesised according to general procedure 4 using Spiro[chromane-4,1'-cyclopentane]-2',5'-dione on a 2.13 mmol scale. Purified by flash chromatography (10-20-30% EtOAc in

petroleum ether) to give Spiro[chromane-4,1'-cyclopent-4-ene]-2',5'-dione as a bright yellow solid (413 mg, 91% yield).

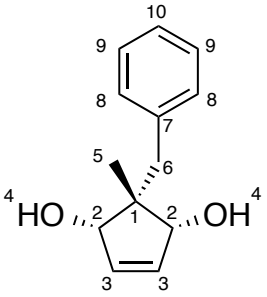
^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.48 (s, 2H), 7.23 – 7.10 (m, 1H), 6.92 (dd, *J* = 8.3, 1.3 Hz, 1H), 6.81 (td, *J* = 7.5, 1.3 Hz, 1H), 6.60 (dd, *J* = 7.8, 1.6 Hz, 1H), 4.43 (t, *J* = 5.3 Hz, 2H), 2.10 (t, *J* = 5.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 204.5, 155.9, 149.9, 129.6, 127.0, 121.1, 118.2, 117.3, 61.9, 50.3, 28.0. Consistent with data in the literature.[221]

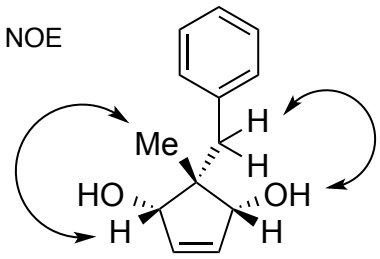
(1*R*,2*S*,3*S*)-2-Benzyl-2-methylcyclopent-4-ene-1,3-diol (8a)



Chemical Formula: $C_{13}H_{16}O_2$
Molecular Weight: 204.2690

Synthesised according to general procedure 5 using 2-Benzyl-2-methylcyclopent-4-ene-1,3-dione on a 5.00 mmol scale. Purified by flash chromatography (40-50% EtOAc in petroleum ether) to give (1*R*,2*S*,3*S*)-2-Benzyl-2-methylcyclopent-4-ene-1,3-diol (**8a**) as a colourless, crystalline solid (489 mg, 48% yield). Stereochemistry confirmed by 2D NOESY.

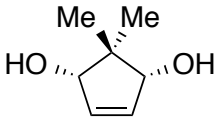




^{1}H NMR (500 MHz, $CDCl_3$) δ_H/ppm: 7.44 – 7.40 (m, 2H, 2ArH-(9)), 7.29 (t, *J* = 7.5 Hz, 2H, 2ArH(8)), 7.21 (tt, *J* = 7.3, 1.3 Hz, 1H, ArH-(10)), 6.19 (dd, *J* = 1.5, 0.9 Hz, 2H, 2CH-(3)),

4.02 (d, J = 7.2 Hz, 2H, 2CH-(2)), 2.97 (s, 2H, CH_2-(6)), 2.27 (d, J = 7.5 Hz, 2H, 2OH-(4)), 0.72 (s, 3H, CH_3-(5)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 139.5 (C(7)), 137.2 (C(3)), 130.7 (C(8)), 128.2 (C(9)), 126.0 (C(10)), 82.1 (C(2)), 48.4 (C(1)), 36.7 (C(6)), 24.1 (C(5)); HRMS (ESI) *m/z* calcd for $C_{13}H_{16}O_2Na$ $[M+Na]^+$: 227.10425, found: 227.10421; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 3275.6 (br. m), 2961.1 (w), 2911.1 (w), 1461.0 (w), 1343.4 (w), 1293.5 (w), 1147.5 (w), 1098.8 (w), 1029.2 (m), 981.4 (m), 931.7 (m), 744.2 (m), 700.15 (m), 623.5 (m). Melting point: 99-102 °C.

***Cis*-2,2-dimethylcyclopent-4-ene-1,3-diol**

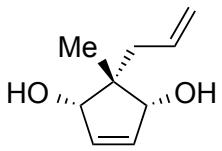


Chemical Formula: $C_7H_{12}O_2$
Molecular Weight: 128.1710

Synthesised according to general procedure 5 using 2,2-dimethylcyclopent-4-ene-1,3-dione on a 3.72 mmol scale. Purified by flash chromatography (1-2% MeOH in EtOAc) to give *cis*-2,2-dimethylcyclopent-4-ene-1,3-diol (single diastereomer) as a colourless, crystalline solid (337 mg, 71% yield).

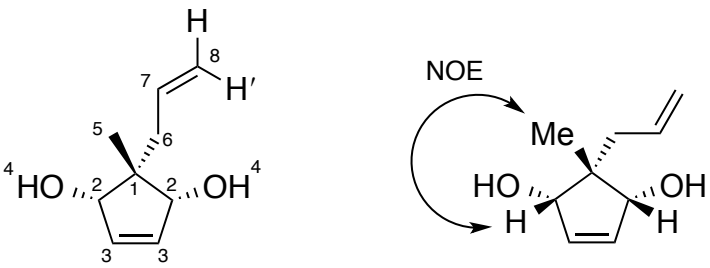
^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 6.00 (d, J = 1.1 Hz, 2H), 4.05 (d, J = 6.8 Hz, 2H), 2.14 (d, J = 7.2 Hz, 2H), 1.02 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 136.1, 82.9, 46.0, 26.9, 16.7. Consistent with data in the literature.[223]

(1*R*,2*S*,3*S*)-2-Allyl-2-methylcyclopent-4-ene-1,3-diol



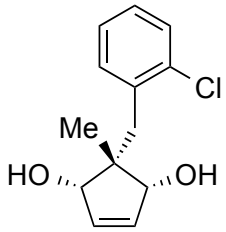
Chemical Formula: $C_9H_{14}O_2$
Molecular Weight: 154.2090

Synthesised according to general procedure 5 using 2-allyl-2-methylcyclopent-4-ene-1,3-dione on a 5.07 mmol scale. Purified by flash chromatography (40-50% EtOAc in petroleum ether) to give (1*R*,2*S*,3*S*)-2-allyl-2-methylcyclopent-4-ene-1,3-diol as a colourless, crystalline solid (334 mg, 43% yield). Stereochemistry confirmed by 2D NOESY.



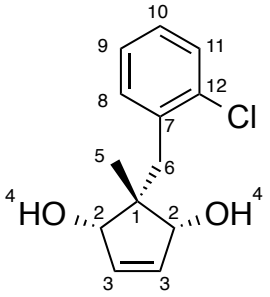
^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 6.07 (d, *J* = 1.6 Hz, 2H, 2CH-(3)), 6.00 (ddt, *J* = 17.3, 10.1, 7.3 Hz, 1H, CH-(7)), 5.15 (ddt, *J* = 17.3, 2.7, 1.4 Hz, 1H, CH***H′***-(8)), 5.10 (ddt, *J* = 10.1, 2.2, 1.1 Hz, 1H, C***H***H′-(8)), 4.00 (d, *J* = 0.7 Hz, 2H, 2CH-(2)), 2.74 (s, 2H, 2OH-(4)), 2.33 (d, *J* = 7.3 Hz, 2H, CH_2-(6)), 0.88 (s, 3H, CH_3-(5)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 136.5 (C(3)), 136.1 (C(7)), 117.4 (C(8)), 82.4 (C(2)), 47.0 (C(1)), 35.9 (C(6)), 24.5 (C(5)); HRMS (ESI) *m/z* calcd for $C_9H_{14}O_2Na$ $[M+Na]^+$: 177.08860, found: 177.08862; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 3309.2 (br. m), 2970.6 (w), 2910.1 (w), 1638.0 (w), 1453.8 (w), 1399.1 (w), 1298.3 (w), 1245.3 (w), 1116.1 (w), 1072.7 (m), 1031.7 (m), 997.9 (m), 987.5 (m), 953.7 (m), 902.5 (m), 828.1 (m), 778.0 (m). Melting point: 70-72 °C.

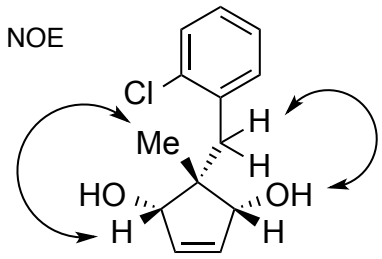
(1*R*,2*S*,3*S*)-2-(2-Chlorobenzyl)-2-methylcyclopent-4-ene-1,3-diol



Chemical Formula: $C_{13}H_{15}ClO_2$
Molecular Weight: 238.7110

Synthesised according to general procedure 5 using 2-(2-chlorobenzyl)-2-methylcyclopent-4-ene-1,3-dione on a 2.14 mmol scale. Purified by flash chromatography (40-50% EtOAc in petroleum ether) to give (1*R*,2*S*,3*S*)-2-(2-chlorobenzyl)-2-methylcyclopent-4-ene-1,3-diol as a colourless, crystalline solid (188 mg, 37% yield). Stereochemistry confirmed by 2D NOESY.

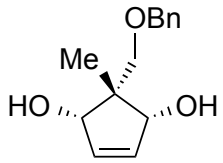




^{1}H NMR (500 MHz, $CDCl_3$) δ_H/ppm: 7.76 (dd, *J* = 7.7, 1.8 Hz, 1H, ArH-(11)), 7.35 (dd, *J* = 7.9, 1.5 Hz, 1H, ArH-(8)), 7.19 (td, *J* = 7.6, 1.5 Hz, 1H, ArH-(10)), 7.13 (td, *J* = 7.6, 1.8 Hz, 1H, ArH-(9)), 6.20 (dd, *J* = 1.5, 0.9 Hz, 2H, 2CH-(3)), 4.09 – 4.05 (m, 2H, 2CH-(2)), 3.20 (s, 2H, CH_2-(6)), 2.55 – 2.51 (m, 2H, 2OH-(4)), 0.71 (s, 3H, CH_3-(5)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 137.7 (C(7)), 137.3 (C(3)), 135.2 (C(12)), 132.3 (C(8)), 129.6 (C(11)), 127.4 (C(10)), 126.9 (C(9)), 82.0 (C(2)), 49.1 (C(1)), 31.7 (C(6)), 22.3 (C(5)); HRMS (ESI) *m/z* calcd for $C_{13}H_{15}O_2{}^{35}ClNa$ $[M+Na]^+$: 261.06528, found: 261.06531; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 3315.1 (br. w), 2980.1 (s), 2888.1 (m), 1461.2 (w), 1382.1 (m), 1251.8 (m), 1151.6

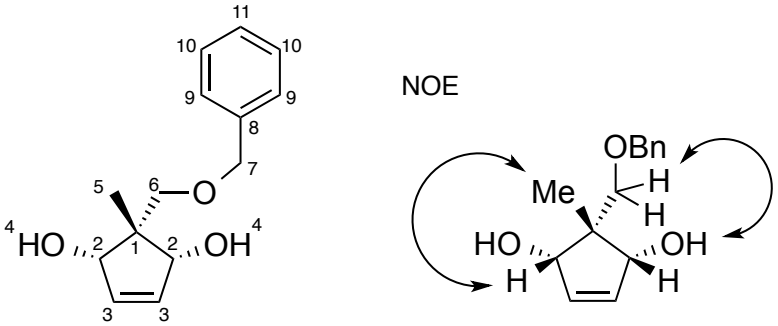
(m), 1087.0 (w), 1040.8 (m), 954.6 (m), 820.7 (w), 750.6 (m), 679.0 (w). Melting point: 126-127 °C.

(1*R*,2*S*,3*S*)-2-((Benzyloxy)methyl)-2-methylcyclopent-4-ene-1,3-diol



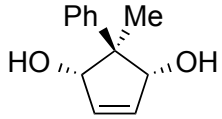
Chemical Formula: $C_{14}H_{18}O_3$
Molecular Weight: 234.2950

Synthesised according to general procedure 5 using 2-((benzyloxy)methyl)-2-methylcyclopent-4-ene-1,3-dione on a 1.27 mmol scale. Purified by flash chromatography (40-50% EtOAc in petroleum ether) to give (1*R*,2*S*,3*S*)-2-((benzyloxy)methyl)-2-methylcyclopent-4-ene-1,3-diol as a colourless oil (137 mg, 46% yield). Stereochemistry confirmed by 2D NOESY.



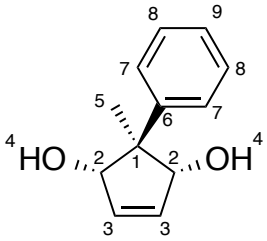
^{1}H NMR (500 MHz, $CDCl_3$) δ_H/ppm: 7.38 – 7.28 (m, 5H, 5ArH-(9-11)), 5.95 (d, *J* = 1.0 Hz, 2H, 2CH-(3)), 4.51 (s, 2H, CH_2-(7)), 4.20 (d, *J* = 8.1 Hz, 2H, 2CH-(2)), 3.72 (s, 2H, CH_2-(6)), 2.79 (d, *J* = 8.8 Hz, 2H, 2OH-(4)), 1.10 (s, 3H, CH_3-(5)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 137.4 (C(8)), 135.7 (C(3)), 128.7 (C(10)), 128.1 (C(11)), 127.8 (C(9)), 83.7 (C(2)), 73.6 (C(6)), 73.0 (7)), 49.1 (C(1)), 23.3 (C(5)); HRMS (ESI) *m/z* calcd for $C_{14}H_{18}O_3Na$ $[M+Na]^+$: 257.11482, found: 257.11469; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 3384.8 (br. m), 2980.5 (s), 2885.4 (m), 1454.3 (w), 1382.8 (m), 1251.4 (w), 1144.4 (m), 1073.6 (m), 1030.6 (m), 955.8 (m), 736.7 (w), 698.1 (w).

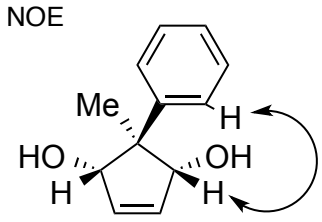
(1*R*,2*R*,3*S*)-2-Methyl-2-phenylcyclopent-4-ene-1,3-diol



Chemical Formula: $C_{12}H_{14}O_2$
Molecular Weight: 190.2420

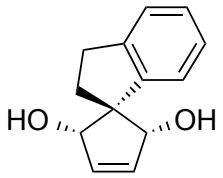
Synthesised according to general procedure 5 using 2-methyl-2-phenylcyclopent-4-ene-1,3-dione on a 1.75 mmol scale. Purified by flash chromatography (3% MeOH in CH_2Cl_2) to give (1*R*,2*S*,3*S*)-2-methyl-2-phenylcyclopent-4-ene-1,3-diol as a colourless, crystalline solid (140 mg, 42% yield). Stereochemistry confirmed by 2D NOESY.



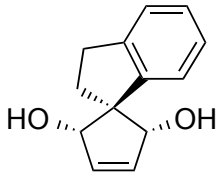


^{1}H NMR (500 MHz, MeOD-d_4) δ_H/ppm: 7.52 – 7.48 (m, 2H, 2ArH-(7)), 7.31 – 7.26 (m, 2H, 2ArH-(8)), 7.20 – 7.14 (m, 1H, ArH-(9)), 5.84 (s, 2H, 2CH-(3)), 4.79 (s, 2H, 2CH-(2)), 1.21 (s, 3H, CH_3-(5)); ^{13}C NMR (101 MHz, MeOD-d_4) δ_c/ppm: 150.3 (C(6)), 134.8 (C(3)), 129.2 (C(8)), 127.5 (C(7)), 126.9 (C(9)), 83.3 (C(2)), 58.8 (C(1)), 17.5 (C(5)); HRMS (EI, 35 ev) *m/z* calcd for $C_{12}H_{14}O_2$ $[M]^+$: 190.0988, found: 190.0995; IR (ATR) ν (cm^{-1}) thin film, MeOD: 3380.2 (br. w), 2507.1 (m), 1495.3 (w), 1395.5 (m), 1032.2 (m), 936.3 (m), 878.0 (m), 790.1 (m), 765.5 (m), 742.4 (w), 700.6 (s), 640.1 (w). Melting point: 176-177 °C.

(1*S*,2*R*,5*S*)-2',3'-Dihydrospiro[cyclopentane-1,1'-inden]-3-ene-2,5-diol and (1*R*,2*R*,5*S*)-2',3'-Dihydrospiro[cyclopentane-1,1'-inden]-3-ene-2,5-diol



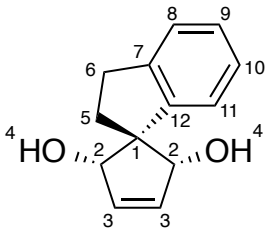
(1*s*,2*R*,5*S*)
Chemical Formula: $C_{13}H_{14}O_2$
Molecular Weight: 202.2530

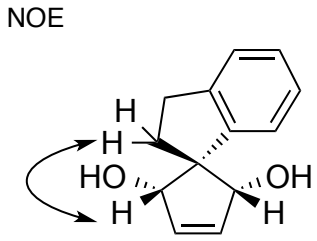


(1*r*,2*R*,5*S*)
Chemical Formula: $C_{13}H_{14}O_2$
Molecular Weight: 202.2530

Synthesised according to general procedure 5 using 2',3'-Dihydrospiro[cyclopentane-1,1'-inden]-3-ene-2,5-dione on a 1.72 mmol scale. Purified by flash chromatography (3% MeOH in CH_2Cl_2) to give (1*S*,2*R*,5*S*)-2',3'-Dihydrospiro[cyclopentane-1,1'-inden]-3-ene-2,5-diol as a colourless, crystalline solid (158 mg, 46% yield, lower polarity) and (1*R*,2*R*,5*S*)-2',3'-Dihydrospiro[cyclopentane-1,1'-inden]-3-ene-2,5-diol as a colourless oil (173 mg, 50% yield, higher polarity, **NOTE**: Unable to remove impurity believed to be the *trans* –diol; used crude in phosphorylation step). Stereochemistry confirmed by 2D NOESY.

Analytical data for (1*S*,2*R*,5*S*)-2',3'-Dihydrospiro[cyclopentane-1,1'-inden]-3-ene-2,5-diol

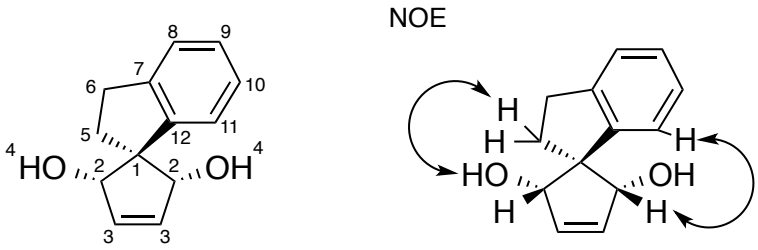




^{1}H NMR (500 MHz, $CDCl_3$) δ_H/ppm: 7.43 – 7.37 (m, 1H, ArH-(8)), 7.34 – 7.31 (m, 1H, ArH-(11)), 7.31 – 7.25 (m, 1H, ArH-(10)), 7.24 – 7.17 (m, 1H, ArH-(9)), 6.17 (d, J = 0.7 Hz, 2H, 2CH-(3)), 4.53 (d, J = 8.7 Hz, 2H, 2CH-(2)), 2.99 (t, J = 7.4 Hz, 2H, CH_2-(6)), 2.25 (t, J = 7.4 Hz, 2H, CH_2-(5)), 1.69 (d, J = 9.0 Hz, 2H, 2OH-(4)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 147.3 (C(12)), 140.0 (C(7)), 136.8 (C(3)), 128.3 (C(8)), 126.4 (C(10)), 126.2 (C(9)), 125.7

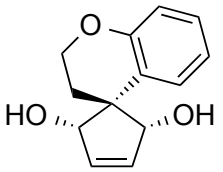
(C(11)), 82.1 (C(2)), 66.3 (C(1)), 36.6 (C(5)), 31.1 (C(6)); HRMS (ESI) *m/z* calcd for $C_{13}H_{14}O_2Na$ $[M+Na]^+$: 225.08860, found: 225.08861; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 3355.8 (br. m), 1479.3 (w), 1293.3 (m), 1031.2 (m), 987.5 (m), 738.4 (m), 632.0 (m). Melting point: 126-130 °C.

Analytical data for (1*R*,2*R*,5*S*)-2',3'-Dihydrospiro[cyclopentane-1,1'-inden]-3-ene-2,5-diol

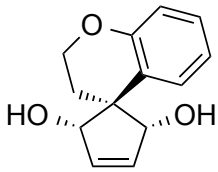


^1H NMR (500 MHz, $CDCl_3$) δ_H/ppm: 7.21 (d, *J* = 7.2 Hz, 1H, ArH-(8)), 7.16 (td, *J* = 7.4, 0.9 Hz, 1H, ArH-(9)), 7.08 (t, *J* = 7.4 Hz, 1H, ArH-(10)), 6.82 (d, *J* = 7.5 Hz, 1H, ArH-(11)), 6.23 (d, *J* = 1.2 Hz, 2H, 2CH-(3)), 4.23 (s, 2H, 2CH-(2)), 3.35 (s, 2H, 2OH-(4)), 2.91 (t, *J* = 7.2 Hz, 2H, CH_2-(6)), 2.28 (t, *J* = 7.2 Hz, 2H, CH_2-(5)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 148.2 (C(12)), 144.1 (C(7)), 137.6 (C(3)), 127.1 (C(8)), 126.4 (C(10)), 124.8 (C(9)), 122.0 (C(11)), 81.7 (C(2)), 62.5 (C(1)), 30.8 (C(6)), 27.9 (C(5)); HRMS (ESI) *m/z* calcd for $C_{13}H_{14}O_2Na$ $[M+Na]^+$: 225.08860, found: 225.08869; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 3324.0 (br. m), 2928.9, (w), 1476.4 (w), 1456.1 (w), 1338.9 (w), 1083.1 (w), 1053.3 (m), 1018.7 (m), 1002.5 (m), 753.7 (m), 723.2 (m).

(2'*R*,4*S*,5'*S*)-Spiro[chromane-4,1'-cyclopentan]-3'-ene-2',5'-diol and (2'*R*,4*R*,5'*S*)-Spiro[chromane-4,1'-cyclopentan]-3'-ene-2',5'-diol



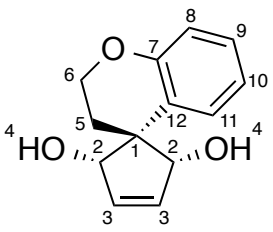
(2'*R*,4*S*,5'*S*)
Chemical Formula: $C_{13}H_{14}O_3$
Molecular Weight: 218.2520

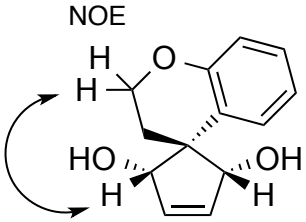


(2'*R*,4*R*,5'*S*)
Chemical Formula: $C_{13}H_{14}O_3$
Molecular Weight: 218.2520

Synthesised according to general procedure 5 using spiro[chromane-4,1'-cyclopent-4-ene]-2',5'-dione on a 1.87 mmol scale. Purified by flash chromatography (2-3% MeOH in CH_2Cl_2) to give (2'*R*,4*S*,5'*S*)-spiro[chromane-4,1'-cyclopentan]-3'-ene-2',5'-diol as a colourless, crystalline solid (121 mg, 30% yield, lower polarity, **NOTE**: Unable to remove unknown impurity) and (2'*R*,4*R*,5'*S*)-spiro[chromane-4,1'-cyclopentan]-3'-ene-2',5'-diol as a colourless oil (124 mg, 30% yield, higher polarity). Stereochemistry confirmed by 2D NOESY.

Analytical data for (2'*R*,4*S*,5'*S*)-Spiro[chromane-4,1'-cyclopentan]-3'-ene-2',5'-diol

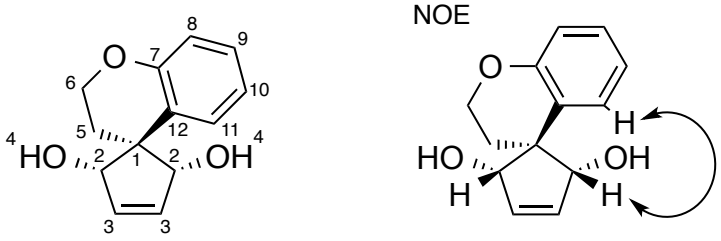




^{1}H NMR (500 MHz, $CDCl_3$) δ_H/ppm: 7.30 (dd, *J* = 7.8, 1.6 Hz, 1H, ArH-(11)), 7.19 (ddd, *J* = 8.3, 7.2, 1.7 Hz, 1H, ArH-(9)), 6.92 (dd, *J* = 8.3, 1.2 Hz, 1H, ArH-(8)), 6.86 (ddd, *J* = 7.8, 7.2, 1.4 Hz, 1H, ArH-(10)), 6.04 (s, 2H, 2CH-(3)), 4.53 (d, *J* = 10.0 Hz, 2H, 2CH-(2)), 4.34 (t, *J* = 5.4 Hz, 2H, CH_2-(6)), 2.26 (t, *J* = 5.4 Hz, 2H, CH_2-(5)), 1.72 (d, *J* = 10.0 Hz, 2H, 2OH-(4)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 157.3 (C(7)), 135.9 (C(3)), 129.4 (C(9)), 128.4 (C(11)), 120.2 (C(10)), 118.8 (C(8)), 117.9 (C(12)), 83.7 (C(2)), 63.7 (C(6)), 54.6 (C(1)), 34.5 (C(5));

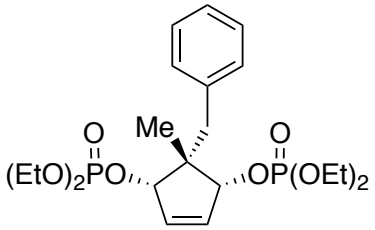
HRMS (ESI) *m/z* calcd for $C_{13}H_{14}O_3Na$ $[M+Na]^+$: 241.08352, found: 241.08354; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 3326.1 (br. m), 1488.0 (w), 1303.5 (w), 1225.4 (m), 1063.9 (m), 1042.7 (m), 1014.3 (w), 973.7 (w), 756.9 (m), 643.9 (w). Melting point: 125-137 °C.

Analytical data for (2'*R*,4*R*,5'*S*)-Spiro[chromane-4,1'-cyclopentan]-3'-ene-2',5'-diol



^1H NMR (500 MHz, $CDCl_3$) δ_H/ppm: 7.10 (ddd, *J* = 8.2, 7.1, 1.7 Hz, 1H ArH-(9)), 6.86 (dd, *J* = 7.9, 1.7 Hz, 1H, ArH-(11)), 6.83 (dd, *J* = 8.2, 1.3 Hz, 1H, ArH-(8)), 6.78 (ddd, *J* = 7.9, 7.1, 1.3 Hz, 1H, ArH-(10)), 6.31 (d, *J* = 1.3 Hz, 2H, 2CH-(3)), 4.53 (d, *J* = 7.3 Hz, 2H, 2CH-(2)), 4.32 (t, *J* = 5.4 Hz, 2H, CH_2-(6)), 2.15 (t, *J* = 5.4 Hz, 2H, CH_2-(5)), 2.07 (d, *J* = 7.9 Hz, 2H, 2OH-(4)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 153.5 (C(7)), 137.3 (C(3)), 128.4 (C(12)), 127.8 (C(9)), 126.2 (C(11)), 120.6 (C(10)), 117.1 (C(8)), 82.8 (C(2)), 64.0 (C(6)), 47.8 (C(1)), 24.0 (C(5)); HRMS (ESI) *m/z* calcd for $C_{13}H_{14}O_3Na$ $[M+Na]^+$: 241.08352, found: 241.08347; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 3346.4 (br. m), 3059.3 (s), 2889.4 (w), 1488.6 (s), 1448.7 (w), 1256.5 (w), 1222.5 (m), 1130.7 (w), 1050.8 (m), 1017.6 (m), 971.5 (w), 754.0 (m).

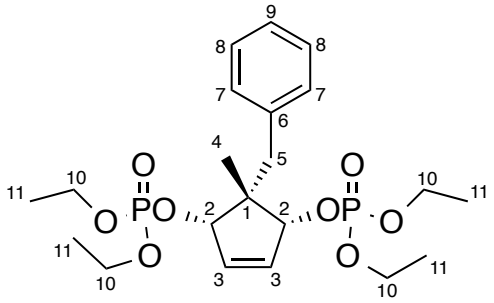
(1*R*,2*S*,3*S*)-2-Benzyl-2-methylcyclopent-4-ene-1,3-bis(diethyl phosphate) (4a)



4a

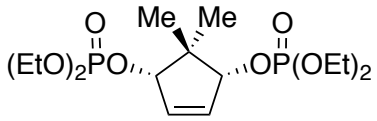
Chemical Formula: $C_{21}H_{34}O_8P_2$
Molecular Weight: 476.4425

Synthesised according to general procedure 6 using (1*R*,2*S*,3*S*)-2-benzyl-2-methylcyclopent-4-ene-1,3-diol on a 12.24 mmol scale. Purified by flash chromatography (1-2-3% MeOH in EtOAc) to give (1*R*,2*S*,3*S*)-2-benzyl-2-methylcyclopent-4-ene-1,3-bis(diethyl phosphate) (**4a**) as a colourless oil (4.614 g, 79%).



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.35 – 7.30 (m, 2H, ArH-(7)), 7.27 – 7.22 (m, 2H, ArH-(8)), 7.17 (tt, *J* = 7.2, 1.4 Hz, 1H, ArH-(9)), 6.33 (s, 2H, 2CH-(3)), 4.66 – 4.63 (m, 2H, 2CH-(2)), 4.16 – 4.03 (m, 8H, 4CH_2-(10)), 2.98 (s, 2H, CH_2-(5)), 1.31 (qd, *J* = 7.1, 1.0 Hz, 12H, 4CH_3-(11)), 0.81 (s, 3H, CH_3-(4)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 138.3 (C(6)), 136.0 (C(3)), 130.7 (C(7)), 128.2 (C(8)), 126.2 (C(9)), 86.2 (C(2)), 63.9 (C(10)), 48.6 (C(1)), 36.2 (C(5)), 24.0 (C(4)), 16.3 (C(11)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_p/ppm: -2.00; HRMS (ESI) *m/z* calcd for $C_{17}H_{35}O_8P_2$ $[M+H]^+$: 477.17291, found: 477.17285; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2985.8 (w), 1368.0 (w), 1260.7 (m), 1162.4 (w), 1021.5 (s), 987.6 (s), 911.1 (m), 821.3 (w), 756.2 (w).

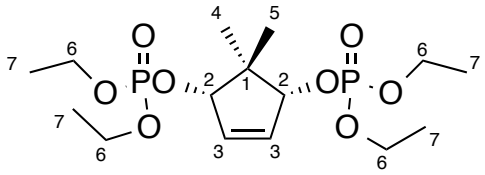
***Cis*-2,2-dimethylcyclopent-4-ene-1,3-bis(diethyl phosphate) (9a)**



9a

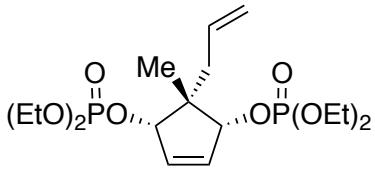
Chemical Formula: $C_{15}H_{30}O_8P_2$
Molecular Weight: 400.3445

Synthesised according to general procedure 6 using *cis*-2,2-dimethylcyclopent-4-ene-1,3-diol on a 1.66 mmol scale. Purified by flash chromatography (2-3-4% MeOH in CH_2Cl_2) to give *cis*-2,2-dimethylcyclopent-4-ene-1,3-bis(diethyl phosphate) (**9a**) as a colourless oil (458 mg, 69%).



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 6.01 (s, 2H, 2CH-(3)), 4.71 (d, J = 6.4 Hz, 2H, 2CH-(2)), 4.06 (ddq, J = 10.6, 8.0, 7.1 Hz, 8H, 4CH_2-(6)), 1.29 (tdd, J = 7.1, 4.4, 1.0 Hz, 12H, 4CH_3-(7)), 1.17 (s, 3H, CH_3-(4)), 1.00 (s, 3H, CH_3-(5)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 133.9 (C(3)), 86.6 (C(2)), 63.8 (C(6)), 47.5 (C1)), 25.9 (C(4)), 17.3 (C5)), 16.2 (C(7)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_p/ppm: -1.65; HRMS (ESI) *m/z* calcd for $C_{15}H_{31}O_8P_2$ $[M+H]^+$: 401.14887, found: 401.14848; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2984.7 (w), 1368.2 (w), 1262.4 (m), 1165.7 (w), 1023.2 (s), 997.1 (s), 951.4 (s), 912.1 (m), 818.4 (w), 755.3 (w).

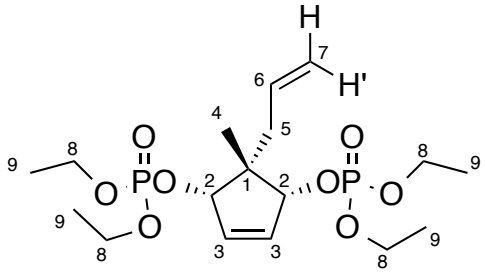
(1*R*,2*S*,3*S*)-2-Allyl-2-methylcyclopent-4-ene-1,3-bis(diethyl phosphate) (10a)



10a

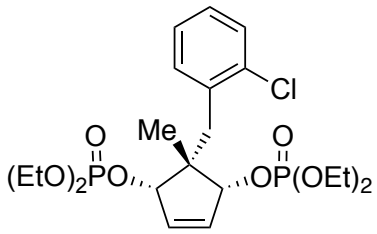
Chemical Formula: $C_{17}H_{32}O_8P_2$
Molecular Weight: 426.3825

Synthesised according to general procedure 6 using (1*R*,2*S*,3*S*)-2-allyl-2-methylcyclopent-4-ene-1,3-diol on a 1.82 mmol scale. Purified by flash chromatography (2-3% MeOH in EtOAc) to give (1*R*,2*S*,3*S*)-2-allyl-2-methylcyclopent-4-ene-1,3-bis(diethyl phosphate) (**10a**) as a colourless oil (632 mg, 81%).



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 6.22 (d, *J* = 0.8 Hz, 2H, 2CH-(3)), 5.89 (ddt, *J* = 17.3, 10.2, 7.2 Hz, 1H, CH-(6)), 5.13 – 5.08 (m, 1H, CH***H′***-(7)), 5.08 – 5.05 (m, 1H, C***H***H′-(7)), 4.68 (d, *J* = 5.6 Hz, 2H, 2CH-(2)), 4.15 – 4.01 (m, 8H, 4CH_2-(8)), 2.37 (d, *J* = 7.2 Hz, 2H, CH_2-(5)), 1.31 (qd, *J* = 7.0, 1.0 Hz, 12H, 4CH_3-(9)), 1.00 (s, 3H, CH_3-(4)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 135.3 (C(3)), 134.8 (C(6)), 117.9 (C(7)), 86.2 (C(2)), 63.9 (C(8)), 47.6 (C(1)), 35.7 (C(5)), 24.3 (C(4)), 16.2 (C(9)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_p/ppm: -1.85; HRMS (ESI) *m/z* calcd for $C_{17}H_{32}O_8NaP_2$ $[M+Na]^+$: 449.14646, found: 449.14596; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2986.5 (w), 1382.2 (w), 1251.9 (m), 1156.7 (w), 1023.2 (s), 996.4 (s), 949.6 (s), 913.2 (m), 816.9 (w), 754.4 (w).

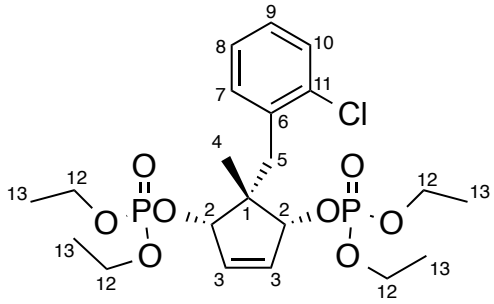
(1*R*,2*S*,3*S*)-2-(2-Chlorobenzyl)-2-methylcyclopent-4-ene-1,3-bis(diethyl phosphate) (11a)



11a

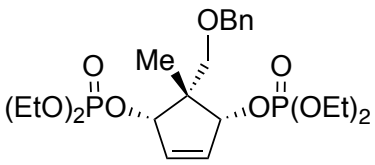
Chemical Formula: $C_{21}H_{33}ClO_8P_2$
Molecular Weight: 510.8845

Synthesised according to general procedure 6 using (1*R*,2*S*,3*S*)-2-(2-chlorobenzyl)-2-methylcyclopent-4-ene-1,3-diol on a 0.79 mmol scale. Purified by flash chromatography (2-3% MeOH in EtOAc) to give (1*R*,2*S*,3*S*)-2-(2-chlorobenzyl)-2-methylcyclopent-4-ene-1,3-bis(diethyl phosphate) (**11a**) as a colourless oil (324 mg, 80%).



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.58 (dd, *J* = 7.6, 1.8 Hz, 1H, ArH-(10)), 7.34 (dd, *J* = 7.8, 1.5 Hz, 1H, ArH-(7)), 7.18 (td, *J* = 7.6, 1.5 Hz, 1H, ArH-(9)), 7.12 (td, *J* = 7.8, 1.8 Hz, 1H, ArH-(8)), 6.36 (s, 2H, 2CH-(3)), 4.72 – 4.69 (m, 2H, 2CH-(2)), 4.18 – 4.04 (m, 8H, 4CH_2-(12)), 3.23 (s, 2H, CH_2-(5)), 1.33 (qd, *J* = 7.1, 1.0 Hz, 12H, 4CH_3-(13)), 0.82 (s, 3H, CH_3-(4)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 136.6 (C(11)), 136.0 (C(3)), 135.4 (C(6)), 131.4 (C(7)), 129.7 (C(10)), 127.6 (C(9)), 127.0 (C(8)), 86.1 (C(2)), 63.9 (C(12)), 48.9 (C(1)), 31.2 (C(5)), 22.3 (C(4)), 16.3 (C(13)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_p/ppm: -2.06; HRMS (ESI) *m/z* calcd for $C_{21}H_{34}O_8{}^{35}ClP_2$ $[M+H]^+$: 511.14120, found: 511.14102; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2986.9 (w), 1369.9 (w), 1262.2 (m), 1163.4 (w), 1023.0 (s), 995.4 (s), 952.1 (s), 909.9 (m), 816.7 (w), 756.5 (w).

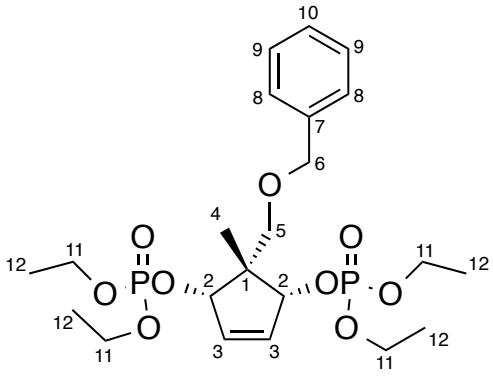
(1*R*,2*S*,3*S*)-2-((Benzyloxy)methyl)-2-methylcyclopent-4-ene-1,3-bis(diethyl phosphate) (12a)



12a

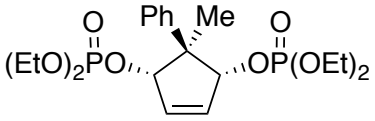
Chemical Formula: $C_{22}H_{36}O_9P_2$
Molecular Weight: 506.4685

Synthesised according to general procedure 6 using (1*R*,2*S*,3*S*)-2-((benzyloxy)methyl)-2-methylcyclopent-4-ene-1,3-diol on a 0.59 mmol scale. Purified by flash chromatography (2-3-4% MeOH in EtOAc) to give (1*R*,2*S*,3*S*)-2-((benzyloxy)methyl)-2-methylcyclopent-4-ene-1,3-bis(diethyl phosphate) (**12a**) as a colourless oil (242 mg, 81%).



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.33 – 7.25 (m, 4H, 4ArH-(8, 9)), 7.25 – 7.19 (m, 1H, ArH-(10)), 6.24 – 6.20 (m, 2H, 2CH-(3)), 4.76 – 4.73 (m, 2H, 2CH-(2)), 4.51 (s, 2H, CH_2-(6)), 4.06 – 3.95 (m, 8H, 4CH_2-(11)), 3.62 (s, 2H, CH_2-(5)), 1.23 (qd, J = 7.1, 1.0 Hz, 12H, 4CH_3-(12)), 1.15 (s, 3H, CH_3-(4)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 138.7 (C(7)), 135.3 (C(3)), 128.2 (C(9)), 127.4 (C(10)), 127.3 (C(8)), 85.8 (C(2)), 73.4 (C(5)), 69.7 (C(6)), 63.7 (C(11)), 48.4 (C(1)), 22.6 (C(4)), 16.1 (C(12)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_p/ppm: -1.83; HRMS (ESI) *m/z* calcd for $C_{27}H_{37}O_9P_2$ $[M+H]^+$: 507.19073, found: 507.19021; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2980.8 (w), 1392.9 (w), 1262.5 (m), 1164.6 (w), 1098.7 (w), 1072.2 (w), 1021.0 (s), 965.3 (s), 919.7 (w), 879.9 (w), 742.3 (w), 700.0 (w).

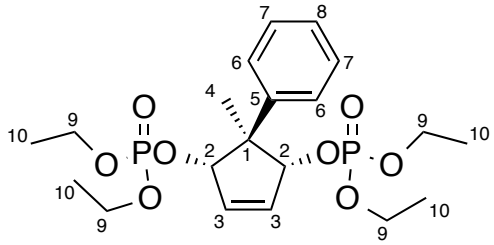
(1*R*,2*R*,3*S*)-2-Methyl-2-phenylcyclopent-4-ene-1,3-bis(diethyl phosphate) (13a)



13a

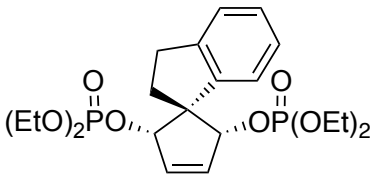
Chemical Formula: $C_{20}H_{32}O_8P_2$
Molecular Weight: 462.4155

Synthesised according to general procedure 5 using (1*R*,2*R*,3*S*)-2-methyl-2-phenylcyclopent-4-ene-1,3-diol on a 0.74 mmol scale. Purified by flash chromatography (1-2-3% MeOH in EtOAc) to give (1*R*,2*R*,3*S*)-2-methyl-2-phenylcyclopent-4-ene-1,3-bis(diethyl phosphate) (**13a**) as a colourless oil (304 mg, 89%).



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.47 – 7.43 (m, 2H, 2ArH-(6)), 7.34 – 7.28 (m, 2H, 2ArH-(7)), 7.24 – 7.18 (m, 1H, ArH-(8)), 6.12 (s, 2H, 2CH-(3)), 5.37 (d, *J* = 6.8 Hz, 2H, 2CH-(2)), 4.12 – 3.92 (m, 8H, 4CH_2-(9)), 1.36 (s, 3H, CH_3-(4)), 1.23 (dtd, *J* = 15.2, 7.1, 1.0 Hz, 6H, 2CH_3-(10)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 145.4 (C(5)), 132.9 (C(3)), 128.7 (C(6)), 126.9 (C(8)), 126.2 (C(7)), 86.7 (C(2)), 64.0 (C(9)), 56.5 (C(1)), 17.6 (C(4)), 16.1 (C(10)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_p/ppm: -2.09; HRMS (ESI) *m/z* calcd for $C_{20}H_{33}O_8P_2$ $[M+H]^+$: 463.16448, found: 463.16452; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2982.3 (w), 1392.9 (w), 1265.3 (m), 1029.5 (s), 1001.8 (s), 960.2 (s), 919.7 (w), 703.7 (w).

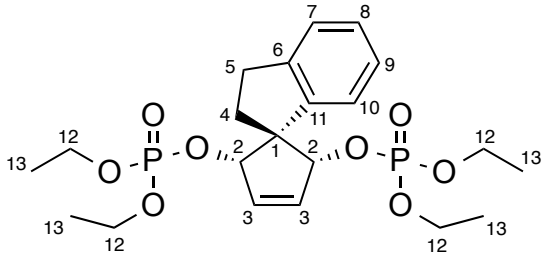
(1*S*,2*R*,5*S*)-2',3'-Dihydrospiro[cyclopentane-1,1'-inden]-3-ene-2,5-bis(diethyl phosphate) (14a)



14a

Chemical Formula: $C_{21}H_{32}O_8P_2$
Molecular Weight: 474.42652

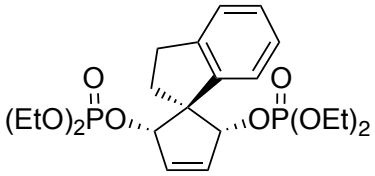
Synthesised according to general procedure 6 using (1*S*,2*R*,5*S*)-2',3'-dihydrospiro[cyclopentane-1,1'-inden]-3-ene-2,5-diol on a 0.72 mmol scale. Purified by flash chromatography (1-2-3% MeOH in EtOAc) to give (1*S*,2*R*,5*S*)-2',3'-dihydrospiro[cyclopentane-1,1'-inden]-3-ene-2,5-bis(diethyl phosphate) (**14a**) as a colourless oil (221 mg, 65%).



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.32 (d, *J* = 7.6 Hz, 1H, ArH-(7)), 7.18 – 7.14 (m, 1H, ArH-(10)), 7.12 (td, *J* = 7.1, 1.3 Hz, 1H, ArH-(9)), 7.05 (td, *J* = 7.6, 7.1, 0.8 Hz, 1H, ArH-(8)), 6.26 – 6.25 (m, 2H, 2CH-(3)), 5.11 – 5.08 (m, 2H, 2CH-(2)), 3.90 – 3.79 (m, 4H, 2CH_2-(12)), 3.63 – 3.54 (m, 4H, 2CH_2-(12)), 2.97 (t, *J* = 7.3 Hz, 2H, CH_2-(5)), 2.31 (t, *J* = 7.3 Hz, 2H, CH_2-(4)), 1.20 – 1.15 (m, 6H, 2CH_3-(13)), 1.06 – 1.01 (m, 6H, 2CH_3-(13)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 145.4 (C(11)), 139.9 (C(6)), 135.2 (C(3)), 128.4 (C(7)), 127.4 (C(9)), 125.2 (C(8)), 124.1 (C(10)), 85.6 (C(2)), 63.9 (C(1)), 63.6 (C(12)), 37.5 (C(4)), 30.7 (C(5)), 16.0 (C(13)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_p/ppm: -2.29; HRMS (ESI) *m/z* calcd for $C_{21}H_{33}O_8P_2$ $[M+H]^+$: 475.16452, found: 475.16455; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2981.6 (w),

1262.6 (m), 1165.4 (w), 1009.2 (s), 953.5 (s), 902.6 (w), 883.4 (w), 818.6 (w), 803.3 (w), 760.3 (w).

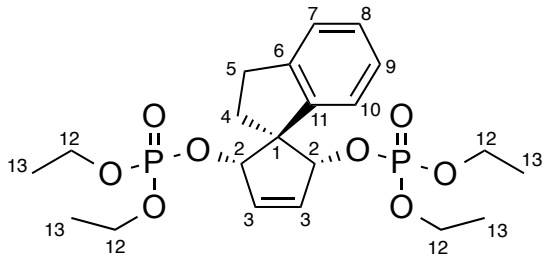
(1*R*,2*R*,5*S*)-2',3'-Dihydrospiro[cyclopentane-1,1'-inden]-3-ene-2,5-bis(diethyl phosphate) (15a)



15a

Chemical Formula: $C_{21}H_{32}O_8P_2$
Molecular Weight: 474.4265

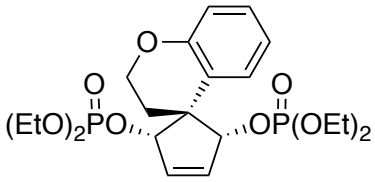
Synthesised according to general procedure 6 using (1*R*,2*R*,5*S*)-2',3'-dihydrospiro[cyclopentane-1,1'-inden]-3-ene-2,5-diol on a 1.68 mmol scale. Purified by flash chromatography (1-2-% MeOH in EtOAc) to give (1*R*,2*R*,5*S*)-2',3'-dihydrospiro[cyclopentane-1,1'-inden]-3-ene-2,5-bis(diethyl phosphate) (**15a**) as a colourless oil (514 mg, 64%).



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.23 – 7.19 (m, 1H, ArH-(7)), 7.17 (td, *J* = 7.4, 1.3 Hz, 1H, ArH-(8)), 7.14 – 7.08 (m, 1H, ArH-(9)), 6.98 (d, *J* = 7.4 Hz, 1H, ArH-(10)), 6.33 (d, *J* = 1.0 Hz, 2H, 2CH-(3)), 5.04 (dd, *J* = 7.2, 0.9 Hz, 2H, 2CH-(2)), 4.07 – 3.87 (m, 8H, 4CH_2-(12)), 2.96 (t, *J* = 7.2 Hz, 2H, CH_2-(5)), 2.41 (t, *J* = 7.2 Hz, 2H, CH_2-(4)), 1.24 (td, *J* = 7.1, 1.0 Hz, 6H, 2CH_3-(13)), 1.19 (td, *J* = 7.1, 1.0 Hz, 6H, 2CH_3-(13)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 145.0 (C(11)), 144.8 (C(6)), 135.6 (C(3)), 127.9 (C(7)), 126.7 (C(9)), 125.0 (C(8)), 122.1 (C(10)), 85.5 (C(2)), 63.8 (C(12)), 62.9 (C(1)), 30.8 (C(4)), 27.9 (C(5)), 16.1 (C(13));

^{31}P NMR (162 MHz, $CDCl_3$) δ_p/ppm: -1.91; HRMS (ESI) *m/z* calcd for $C_{21}H_{33}O_8P_2$ $[M+H]^+$: 475.16452, found: 475.16489; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2981.0 (w), 1392.9 (w), 1262.9 (m), 1164.7 (w), 1010.9 (s), 967.3 (s), 888.1 (w), 799.4 (w), 803.3 (w), 760.1 (w).

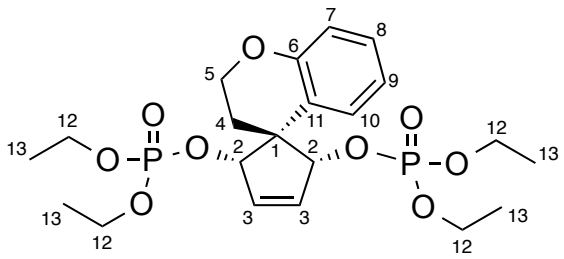
(2'*R*,4*S*,5'*S*)-Spiro[chromane-4,1'-cyclopentan]-3'-ene-2',5'-bis(diethyl phosphate) (16a)



16a

Chemical Formula: $C_{21}H_{32}O_9P_2$
Molecular Weight: 490.4255

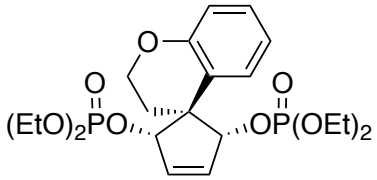
Synthesised according to general procedure 6 using (2'*R*,4*S*,5'*S*)-spiro[chromane-4,1'-cyclopentan]-3'-ene-2',5'-diol on a 0.57 mmol scale. Purified by flash chromatography (3-4-5% MeOH in EtOAc) to give (2'*R*,4*S*,5'*S*)-spiro[chromane-4,1'-cyclopentan]-3'-ene-2',5'-bis(diethyl phosphate) (**16a**) as a colourless oil (193 mg, 69%).



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.17 (dd, *J* = 7.9, 1.5 Hz, 1H, ArH-(10)), 7.03 (td, *J* = 7.1, 1.7 Hz, 1H, ArH-(8)), 6.76 – 6.69 (m, 2H, 2ArH-(7, 9)), 6.19 (s, 2H, 2CH-(3)), 5.10 (dd, *J* = 7.2, 1.0 Hz, 2H, 2CH-(2)), 4.30 (t, *J* = 5.4 Hz, 2H, CH_2-(5)), 3.91 – 3.81 (m, 4H, $2CH_2$-(12)), 3.63 – 3.53 (m, 4H, $2CH_2$-(12)), 2.32 (t, *J* = 5.4 Hz, 2H, CH_2-(4)), 1.19 (td, *J* = 7.1, 1.0 Hz, 6H, $2CH_3$-(13)), 1.03 (td, *J* = 7.1, 1.1 Hz, 6H, $2CH_3$-(13)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 155.7 (C(6)), 134.3 (C(3)), 132.1 (C(10)), 128.2 (C(8)), 118.7 (C(9)), 118.0 (C(11)), 116.9 (C(7)), 86.7 (C(2)), 63.8 (C(12)), 63.1 (C(5)), 52.3 (C(1)), 34.8 (C(4)), 16.0 (C(13)); ^{31}P

NMR (162 MHz, $CDCl_3$) δ_p/ppm: -2.29; HRMS (ESI) *m/z* calcd for $C_{21}H_{33}O_9P_2$ $[M+H]^+$: 491.15943, found: 491.15935; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2981.5 (w), 1490.2 (w), 1450.9 (w), 1308.6 (m), 1261.2 (w), 1009.0 (s), 957.5 (s), 889.0 (w), 818.3 (w), 803.8 (w), 754.5 (m).

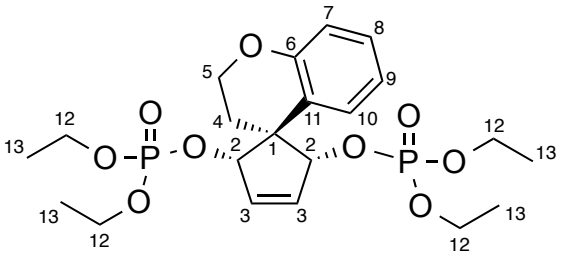
(2'*R*,4*R*,5'*S*)-Spiro[chromane-4,1'-cyclopentan]-3'-ene-2',5'-bis(diethyl phosphate) (17a)



17a

Chemical Formula: $C_{21}H_{32}O_9P_2$
Molecular Weight: 490.4255

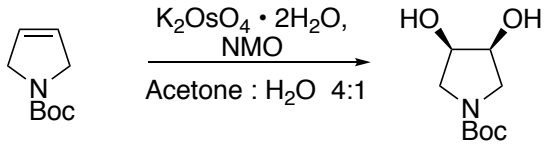
Synthesised according to general procedure 6 using (2'*R*,4*R*,5'*S*)-spiro[chromane-4,1'-cyclopentan]-3'-ene-2',5'-diol on a 0.56 mmol scale. Purified by flash chromatography (3-4-5% MeOH in EtOAc) to give (2'*R*,4*R*,5'*S*)-spiro[chromane-4,1'-cyclopentan]-3'-ene-2',5'-bis(diethyl phosphate) (**17a**) as a colourless oil (203 mg, 74%).



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.09 (td, *J* = 7.6, 7.1, 1.6 Hz, 1H, ArH-(8)), 6.89 (dd, *J* = 8.3, 1.7 Hz, 1H, ArH-(10)), 6.81 – 6.77 (m, 2H, 2ArH-(7, 9)), 6.37 (d, *J* = 1.1 Hz, 2H, 2CH-(3)), 5.14 (dd, *J* = 7.0, 1.0 Hz, 2H, 2CH-(2)), 4.25 (t, *J* = 5.4 Hz, 2H, CH_2-(5)), 4.08 – 3.90 (m, 8H, 4CH_2-(12)), 2.21 (t, *J* = 5.4 Hz, 2H, CH_2-(4)), 1.26 – 1.18 (m, 12H, 4CH_3-(13)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 154.5 (C(6)), 135.7 (C(3)), 128.6 (C(10)), 126.4 (C(8)), 125.3 (C(11)), 120.9 (C(9)), 117.6 (C(7)), 86.9 (C(2)), 64.0 (C(12)), 63.7 (C(5)), 48.6 (C(1)), 24.0

(C(4)), 16.1 (C(13)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_p/ppm: -1.80; HRMS (ESI) *m/z* calcd for $C_{21}H_{33}O_9P_2$ $[M+H]^+$: 491.15943, found: 491.15935; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2981.9 (w), 1490.6 (w), 1448.8 (w), 1260.9 (m), 1225.5 (w), 1013.8 (s), 961.7 (s), 889.5 (w), 855.8 (w), 756.5 (m).

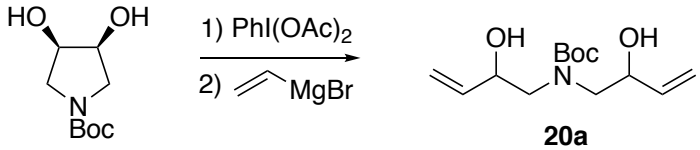
***tert*-Butyl (3*R*,4*S*)-3,4-dihydroxypyrrolidine-1-carboxylate (19a)**



To a solution of N-Boc-2,5-dihydro-1*H*-pyrrole (2.50 g, 14.77 mmol, 1 eq) in acetone (24 mL) and water (6 mL) was added NMO (2.60 g, 22.19 mmol, 1.5 eq) followed by potassium osmate(VI) dihydrate (163 mg, 0.44 mmol, 0.03 eq). The resulting orange/brown suspension was left to stir at room temperature overnight. The resulting mixture was quenched by addition of sat. aq. $Na_2S_2O_3$ (100 mL). The mixture was extracted with EtOAc (3 x 100 mL). The organic extracts were combined, washed with brine (150 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. The yellow oil was purified by flash chromatography (0-10% MeOH in CH_2Cl_2) to give *tert*-butyl (3*R*,4*S*)-3,4-dihydroxypyrrolidine-1-carboxylate (**19a**) (2.98g, 99%) as a clear amorphous solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H/ppm: 4.20 – 4.15 (m, 2H), 3.77 (s, 2H), 3.50 (dd, *J* = 11.0, 5.2 Hz, 2H), 3.29 (dd, *J* = 11.0, 4.0 Hz, 2H), 1.41 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ_c/ppm: 155.0, 80.1, 71.0, 50.5, 28.6. Consistent with data in the literature.[224]

***tert*-Butyl bis(2-hydroxybut-3-en-1-yl)carbamate (20a)**

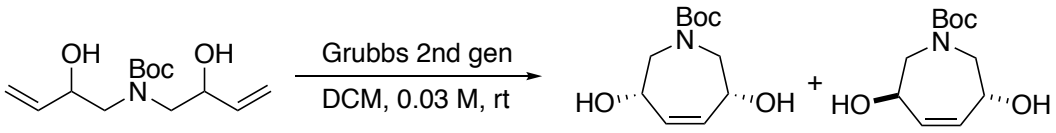


20a

tert-Butyl (3*R*,4*S*)-3,4-dihydroxypyrrolidine-1-carboxylate (**19a**) (3.57 g, 16.7 mmol, 1 eq) was dissolved in CH_2Cl_2 (35 mL) and cooled to 0 ˚C before addition of $PhI(OAc)_2$ (8.05 g, 25.0 mmol, 1.5 eq). the resulting mixture was allowed to warm to room temperature and stir for 2 hours. The mixture was cooled to –78 ˚C and vinylmagnesium bromide (1.0 M in THF, 100 mL, 100 mmol, 6 eq) was added slowly via canula. The resulting mixture was warmed to 0 ˚C and left to stir for 1 hour and then poured over sat. aq. NH_4Cl (150 mL). The mixture was extracted with EtOAc (3 x 100 mL). The organic extracts were combined, washed with brine (150 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. The yellow oil was purified by flash chromatography (40-50% EtOAc in petroleum ether) to give *tert*-butyl bis(2-hydroxybut-3-en-1-yl)carbamate (**20a**) (3.59 g, 84%) as a colourless oil. NMR shows a mixture of rotamers.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H/ppm: 5.88 – 5.72 (m, 2H), 5.38 – 5.24 (m, 2H), 5.14 (d, J = 10.6 Hz, 2H), 4.58 – 4.28 (m, 2H), 4.00 (s, 2H), 3.74 – 2.77 (m, 4H), 1.45 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ_c/ppm: 157.1, 156.4, 138.3, 138.1, 115.9, 80.6, 72.8, 72.2, 72.1, 57.4, 57.1, 55.7, 55.4, 28.5, 28.5. Consistent with data in the literature.[225]

***tert*-Butyl (3*R*,6*S*)-3,6-dihydroxy-2,3,6,7-tetrahydro-1*H*-azepine-1-carboxylate (21a)**

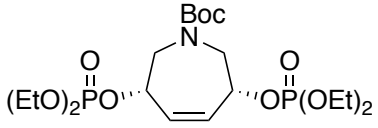


21a **22a**

To a solution of *tert*-butyl bis(2-hydroxybut-3-en-1-yl)carbamate (**20a**) (3.09 g, 12.01 mmol, 1.0 eq) in CH_2Cl_2 (400 ml) was added Grubbs Catalyst 2nd Generation (307 mg, 0.36 mmol, 3 mol%). The resulting solution was left to stir at room temperature for 5 days. The reaction mixture was concentrated *in vacuo* to give a brown oil. The brown oil was purified by flash chromatography (75% EtOAc in petroleum ether) to give *tert*-butyl *cis*-3,6-dihydroxy-2,3,6,7-tetrahydro-1*H*-azepine-1-carboxylate (**21a**) (less polar, eluted first, 472 mg, 17%) and *tert*-butyl *trans*-3,6-dihydroxy-2,3,6,7-tetrahydro-1*H*-azepine-1-carboxylate (**22a**) (more polar, eluted second, 469 mg, 17%) as brown oils. Both obtained as a mixture of rotamers. *Cis*-diol characterised.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 5.75 (s, 2H), 4.40 – 4.24 (m, 2H), 3.87 (br. s, 1H), 3.82 – 3.71 (m, 2H), 3.30 (br. s, 1H), 3.22 – 3.14 (m, 2H), 1.44 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ_c/ppm: 155.8, 133.9, 80.7, 69.0, 53.3, 28.4. Consistent with data in the literature.[225]

***tert*-Butyl (3*R*,6*S*)-3,6-bis((diethoxyphosphoryl)oxy)-2,3,6,7-tetrahydro-1*H*-azepine-1-carboxylate (23a)**

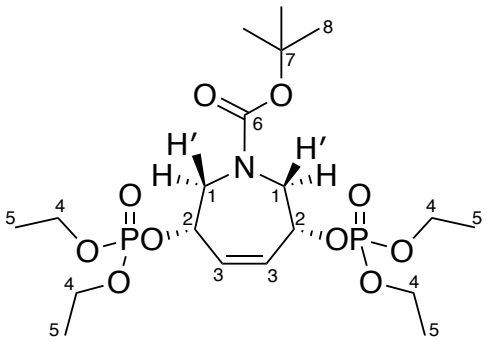


23a

Chemical Formula: $C_{19}H_{37}NO_{10}P_2$
Molecular Weight: 501.44952

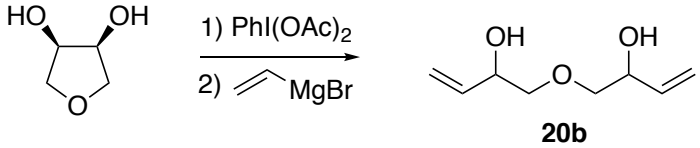
To a solution of *tert*-butyl *cis*-3,6-dihydroxy-2,3,6,7-tetrahydro-1*H*-azepine-1-carboxylate (**21a**) (470 mg, 2.05 mmol, 1.0 eq) in CH_2Cl_2 (8.2 mL) was added NEt_3 (0.86 mL, 6.15 mmol,

3.0 eq) and DMAP (124 mg, 1.01 mmol, 0.5 eq). The resulting solution was cooled to 0 °C before dropwise addition of diethylchlorophosphate (0.89 mL, 6.15 mmol, 3.0 eq). The resulting mixture was left to stir at room temperature for 16 hours. The mixture was then quenched with H_2O (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The organic extracts were combined, washed with brine (50 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. The yellow oil was purified by flash chromatography (50-100% EtOAc in heptane) to give *tert*-Butyl (3*R*,6*S*)-3,6-bis((diethoxyphosphoryl)oxy)-2,3,6,7-tetrahydro-1*H*-azepine-1-carboxylate (**23a**) as a pale yellow oil (494 mg, 48% yield). Obtained as a mixture of rotamers.



^{1}H NMR (400 MHz, DMSO-d_6, 338K) δ_H/ppm: 5.83 (s, 2H, 2CH-(3)), 4.92 – 4.86 (m, 2H, 2CH-(2)), 4.11 – 4.03 (m, 8H, 4CH_2-(4)), 4.02 (dd, *J* = 13.6, 4.3 Hz, 2H, 2CH***H′***-(1)), 3.22 (dd, *J* = 13.6, 9.5 Hz, 2H, 2C***H***H′-(1)), 1.46 (s, 9H, 3CH_3-(8)), 1.29 (t, *J* = 6.9 Hz, 12H, 4CH_3-(5)); ^{13}C NMR (126 MHz, $CDCl_3$) δ_c/ppm: 154.41 (C(6)), 131.95 (C(3)), 131.69 (C(3)), 81.00 (C(2)), 74.18 (C(1)), 73.79 (C(1)), 64.13 (C(4)), 52.12 (C(7)), 51.33 (C(7)), 28.39 (C(8)), 16.25 (C(5)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: –1.50; HRMS (ESI) *m/z* calcd for $C_{19}H_{37}NO_{10}P$ $[M+H]^+$: 501.18927, found: 501.19836; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2888.4 (w), 1693.7 (s), 1465.7 (w), 1367.8 (w), 1254.0 (m), 1027.8 (s), 989.6 (m), 806.3 (w), 701.2 (w)

1,1'-Oxybis(but-3-en-2-ol) (20b)

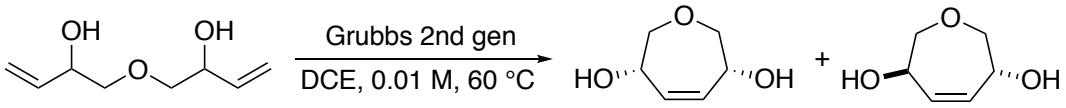


20b

1,4-Anhydroerythritol (1.37 mL, 16.7 mmol, 1 eq) was dissolved in CH_2Cl_2 (35 mL) and cooled to 0 ˚C before addition of $PhI(OAc)_2$ (8.05 g, 25.0 mmol, 1.5 eq). the resulting mixture was allowed to warm to room temperature and stir for 2 hours. The mixture was cooled to –78 ˚C and vinylmagnesium bromide (1.0 M in THF, 100 mL, 100 mmol, 6 eq) was added slowly via canula. The resulting mixture was warmed to 0 ˚C and left to stir for 1 hour and then poured over sat. aq. NH_4Cl (150 mL). The mixture was extracted with EtOAc (3 x 100 mL). The organic extracts were combined, washed with brine (150 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. The yellow oil was purified by flash chromatography (40-50% EtOAc in petroleum ether) to give 1,1'-oxybis(but-3-en-2-ol) (**20b)** (1.644 g, 62%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H/ppm: 5.81 (dddd, J = 17.2, 10.6, 5.7, 3.4 Hz, 2H), 5.34 (d, J = 17.2 Hz, 2H), 5.17 (dd, J = 10.6, 1.4 Hz, 2H), 4.36 – 4.31 (m, 2H), 3.57 (dd, J = 10.0, 3.1 Hz, 1H), 3.53 (dd, J = 10.1, 3.1 Hz, 1H), 3.45 (s, 2H), 3.42 (dd, J = 10.1, 7.9 Hz, 1H), 3.37 (dd, J = 10.0, 8.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ_c/ppm: 136.6, 116.6, 75.4, 71.6. Consistent with data in the literature.[224]

***Cis*-2,3,6,7-tetrahydrooxepine-3,6-diol (21b)**

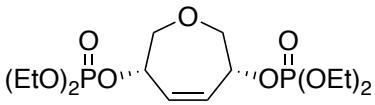


21b **22b**

To a solution of 1,1'-oxybis(but-3-en-2-ol) (**20b**) (1.36 g, 8.60 mmol, 1.0 eq) in 1,2-dichloroethane (860 ml) was added Grubbs Catalyst 2nd Generation (146 mg, 0.172 mmol, 2 mol%). The resulting solution was left to stir at 60 ˚C for 24 hours. Another portion of Grubbs Catalyst 2nd Generation (146 mg, 0.172 mmol, 2 mol%) was added and the reaction was left to stir at 60 ˚C for a further 24 hours. The reaction mixture was concentrated *in vacuo* to give a brown oil. The brown oil was purified by flash chromatography (75% EtOAc in petroleum ether) to give *cis*-2,3,6,7-tetrahydrooxepine-3,6-diol (**21b**) (less polar, eluted first, 204 mg, 18%) and *trans*-2,3,6,7-tetrahydrooxepine-3,6-diol (**22b**) (more polar, eluted second, 203 mg, 18%) as brown oils. *Cis*-diol characterised.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 5.91 (dd, J = 3.1, 1.5 Hz, 2H), 4.14 (s, 2H), 3.88 (dd, J = 12.4, 5.1 Hz, 4H), 3.63 (dd, J = 12.4, 2.3 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ_c/ppm: 133.5, 76.2, 69.9. Consistent with data in the literature.[225]

Tetraethyl ((3*R*,6*S*)-2,3,6,7-tetrahydrooxepine-3,6-diyl) bis(phosphate) (24a)

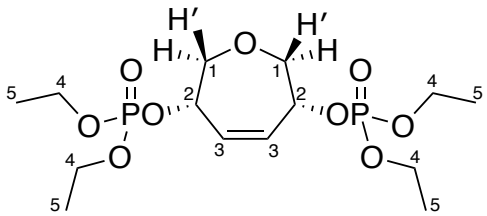


24a

Chemical Formula: $C_{14}H_{28}O_9P_2$
Molecular Weight: 402.31652

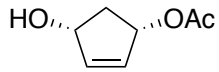
Cis-2,3,6,7-tetrahydrooxepine-3,6-diol (**21b**) (204 mg, 1.57 mmol, 1.0 eq) was dissolved in THF (10 mL) before addition of DABCO (527 mg, 4.70 mmol, 3.0 eq). The resulting solution was cooled to 0 ˚C before dropwise addition of diethyl chlorophosphate (0.68 mL, 4.70 mmol, 3.0 eq). The resulting mixture was allowed to warm to room temperature and stir for 17 hours

before being poured over sat. aq. $NaHCO_3$ (50 mL). The mixture was extracted with EtOAc (3 x 50 mL). The organic extracts were combined, washed with brine (100 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. The yellow oil was purified by flash chromatography (0-1-2% MeOH in CH_2Cl_2) to give tetraethyl ((3*R*,6*S*)-2,3,6,7-tetrahydrooxepine-3,6-diyl) bis(phosphate) (**24a**) (289 mg, 46%) as a colourless oil.



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 5.86 (s, 2H, 2CH-(3)), 5.03 – 4.95 (m, 2H, 2CH-(2)), 4.16 – 4.03 (m, 8H, 4CH_2-(4)), 4.03 (dd, *J* = 11.7, 4.2 Hz, 2H, 2CH***H′***-(1)), 3.51 (dd, *J* = 11.7, 9.2 Hz, 2H, 2C***H***H′-(1)), 1.32 (tt, *J* = 7.1, 1.3 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ_c/ppm: 138.9 (C(3)), 75.2 (C(2)), 74.0 (C(1)), 64.2 (C(4)), 16.2 (C(5)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: –1.48; HRMS (ESI) *m/z* calcd for $C_{14}H_{28}O_9NaP$ $[M+Na]^+$: 425.11008, found: 425.10994; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2889.3 (w), 1461.4 (w), 1389.2 (w), 1263.0 (m), 1029.9 (s), 988.5 (s), 808.4 (w), 701.6 (w).

(1*S*,4*R*)-4-hydroxycyclopent-2-en-1-yl acetate (32)



32

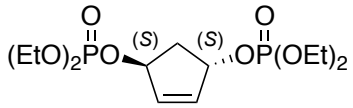
Chemical Formula: $C_7H_{10}O_3$
Molecular Weight: 142.15400

To a solution of *cis*-4-cyclopentene-1,3-diol (200 mg, 2.00 mmol, 1.0 eq) in THF (5.33 mL) was added NEt_3 (0.195 mL, 1.40 mmol, 0.7 eq) and vinyl acetate (1.29 mL, 14.0 mmol, 7.0 eq). PPL lipase (400 mg) was then added, and the resulting beige suspension was left to stir at room temperature for 22 hours. The reaction mixture was filtered through Celite and evaporated *in vacuo* to give a yellow oil. The oil was purified on silica (30-40-50% EtOAc in petroleum ether) to give a white solid. The white solid was recrystallised using a 3:1 mixture of pentane : Et_2O to give (1*S*,4*R*)-4-hydroxycyclopent-2-en-1-yl acetate (**32**) as colourless needles (126 mg, 44%). **NOTE**: Diacetate by-product (135 mg, 37%) obtained from column and recycled.

GC analysis indicated an enantiomeric excess of >99% [Beta DEX 325 (Supelco) column; initial temperature 80 ˚C, initial hold time 5 min, progress rate 5 ˚C/min, final temperature 160 ˚C, final hold time 10 min; Flow rate 2 mL/min; minor enantiomer, t_R = 14.789 min; major enantiomer, t_R = 15.175 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 6.10 (d, *J* = 5.5 Hz, 1H), 5.97 (d, *J* = 5.5 Hz, 1H), 5.61 – 5.19 (m, 1H), 4.71 (s, 1H), 2.79 (dt, *J* = 14.6, 7.3 Hz, 1H), 2.04 (s, 3H), 1.64 (dt, *J* = 14.6, 3.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 170.9, 138.6, 132.7, 77.2, 74.9, 40.6, 21.3. Consistent with data found in the literature.[164]

(1*S*,3*S*)-Cyclopent-4-ene-1,3-diyl tetraethyl bis(phosphate) (31)



31

Chemical Formula: $C_{13}H_{26}O_8P_2$
Molecular Weight: 372.29052

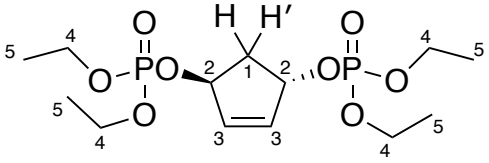
(1*S*,4*R*)-4-hydroxycyclopent-2-en-1-yl acetate (**32**) (529 mg, 3.72 mmol, 1.0 eq) and PPh_3 (1.95 g, 7.44 mmol, 2.0 eq) were dissolved in toluene (10.5 mL) before addition of HCO_2H (288 µL, 7.63 mmol, 2.05 eq). The resulting solution was cooled to 0 °C before dropwise addition of DIAD (1.46 mL, 7.44 mmol, 2.00 eq). The resulting solution was left to stir at 0 °C for 4 hours 40 mins, before being poured over sat. aq. $NaHCO_3$ (50 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL). The organic extracts were combined, washed with brine (30 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. The oil was filtered through a short plug of silica, washing with CH_2Cl_2. The filtrate was evaporated *in vacuo* to give the crude diester (518 mg) which was used immediately in the next step.

The diester was dissolved in MeOH (21 mL) before addition of H_2O (323 µL, 18.27 mmol, 6.0 eq) and LiOH (437 mg, 18.27 mmol, 6.0 eq). The resulting mixture was left to stir at room temperature for 13 hours. The mixture was evaporated *in vacuo* and the resulting residue was filtered through a short plug of silica, rinsing with 5% MeOH in CH_2Cl_2. The filtrate was evaporated *in vacuo* to give the crude alcohol (290 mg) that was used immediately in the next step.

To a solution of the alcohol in CH_2Cl_2 (13 mL) was added NEt_3 (1.21 mL, 8.69 mmol, 3.0 eq) and DMAP (172 mg, 1.45 mmol, 0.5 eq). The resulting solution was cooled to 0 °C before dropwise addition of diethylchlorophosphate (1.26 mL, 8.69 mmol, 3.0 eq). The resulting mixture was left to stir at room temperature for 16 hours. The mixture was then quenched with

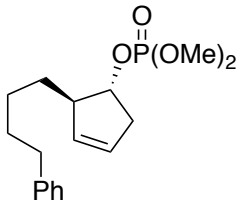
H_2O (30 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The organic extracts were combined, washed with brine (20 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. The yellow oil was purified by flash chromatography (2-3% MeOH in EtOAc) to give (1*S*,3*S*)-cyclopent-4-ene-1,3-diyl tetraethyl bis(phosphate) (**31**) as colourless oil (948 mg, 68% yield over 3 steps). **NOTE**: Procedure used to produce racemic **±31** from racemic 4-hydroxycyclopent-2-en-1-yl acetate.

Enantiomeric excess of **31** determined by use in General Procedure 1a.



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 6.16 (d, *J* = 1.0 Hz, 2H, 2CH-(3)), 5.54 (m, *J* = 5.2 Hz, 2H, 2CH-(2)), 4.08 (m, *J* = 7.9, 7.1, 5.1 Hz, 8H, 4CH_2-(4)), 2.36 (t, *J* = 4.9 Hz, 2H, CH_2-(1)), 1.32 (tdd, *J* = 7.1, 3.0, 1.0 Hz, 12H, 4CH_3-(5)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 136.1 (C(3)), 81.2 (C(2)), 63.9 (C(4)), 40.0 (C(1)), 16.3 (C(5)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.53; HRMS (ESI) *m/z* calcd for $C_{13}H_{26}O_8P_2Na$ $[M+Na]^+$: 395.09951, found: 395.09958; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2984.8 (w), 1445.1 (w), 1371.8 (w), 1262.7 (m), 1165.9 (w), 1028.0 (s), 978.1 (s), 804.2 (w), 754.9 (w). $[\alpha]^{25}_{589}$ = -123.2 (c=1.0 in $CHCl_3$, >99% ee)

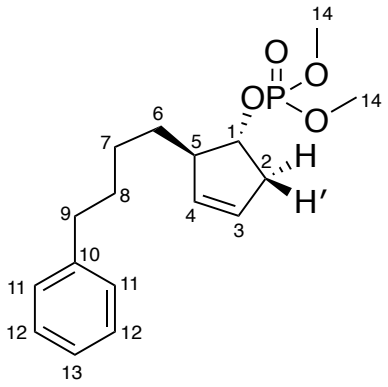
Dimethyl ((1*R*,2*R*)-2-(4-phenylbutyl)cyclopent-3-en-1-yl) phosphate



Chemical Formula: $C_{17}H_{25}O_4P$
Molecular Weight: 324.3568

Synthesised according to general procedure 1b, using *meso*-4-cyclopentene-1,3-bisdimethylphosphate and 4-phenyl-1-butene as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (20-50% EtOAc in petroleum ether) to give dimethyl ((1*R*,2*R*)-2-(4-phenylbutyl)cyclopent-3-en-1-yl) phosphate as a yellow oil (71 mg, 55%).

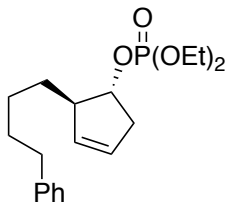
HPLC analysis indicated an enantiomeric excess of 86% [Chiralpak® IA; flow: 1 mL/min; hexane/iPrOH: 94:6; λ = 210 nm; major enantiomer, t_R = 8.075 min; minor enantiomer, t_R = 10.003 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.33 – 7.24 (m, 2H, ArH-(12)), 7.21 – 7.14 (m, 3H, ArH-(11, 13)), 5.77 – 5.58 (m, 2H, 2CH-(3, 4)), 4.68 (tt, *J* = 6.3, 2.9 Hz, 1H, CH-(1)), 3.74 (dd, *J* = 11.1, 0.9 Hz, 6H, $2CH_3$-(14)), 2.87 – 2.71 (m, 2H, C***H***H′-(2), CH-(5)), 2.66 – 2.57 (m, *J* = 7.7 Hz, 2H, CH_2-(9)), 2.54 – 2.44 (m, *J* = 17.8 Hz, 1H, C H***H′***-(2)), 1.73 – 1.58 (m, 2H, CH_2-(6)), 1.53 – 1.27 (m, 4H, $2CH_2$-(7, 8).; ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 142.7 (C(10)), 132.8

(C(4)), 128.5 (C(12)), 128.4 (C(11)), 127.3 (C(3)), 125.8 (C(13)), 83.5 (C(1)), 54.3 (C(14)), 53.06 (C(5)), 39.9 (C(2)), 36.0 (C(9)), 32.7 (C(6)), 31.7 (C(8)), 27.2 (C(7)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: 0.76; HRMS (ESI) *m/z* calcd for $C_{17}H_{25}O_4P$ $[M+H]^+$: 325.149, found: 325.1569; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2929.8 (w), 2584.7 (w), 1453.9 (w), 1218.4 (m), 1186.0 (w), 1035.0 (s), 922.3 (w), 848.1 (m), 750.0 (w), 700.8 (w); $[\alpha]^{25}_{589}$ = -72.6 (c=1.0 in $CHCl_3$, 86% ee).

Diethyl ((1*R*,2*R*)-2-(4-phenylbutyl)cyclopent-3-en-1-yl) phosphate (1b)

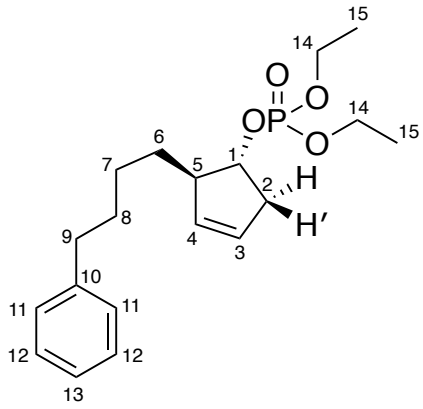


1b

Chemical Formula: $C_{19}H_{29}O_4P$
Molecular Weight: 352.4108

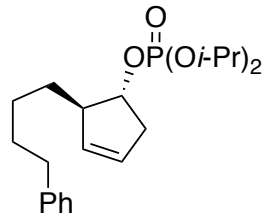
Synthesised according to general procedure 1b, using *meso*-4-cyclopentene-1,3-bisdiethylphosphate (**1a**) and 4-phenyl-1-butene as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (20-40% EtOAc in petroleum ether) to give **1b** as a yellow oil (93 mg, 66%).

HPLC analysis indicated an enantiomeric excess of 90% [Chiralpak® IA; flow: 1.0 mL/min; hexane/iPrOH: 95:5; λ = 210 nm; major enantiomer, t_R = 8.687 min; minor enantiomer, t_R = 10.302 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.31 – 7.22 (m, 2H, ArH-(12)), 7.22 – 7.13 (m, 3H, ArH-(11, 13)), 5.66 (dq, *J* = 6.0, 1.8 Hz, 2H, 2CH-(3, 4)), 4.67 (tt, *J* = 6.4, 3.0 Hz, 1H, CH-(1)), 4.09 (p, *J* = 7.2 Hz, 4H, $2CH_2$-(14)), 2.86 – 2.69 (m, 2H, C***H***H′-(2), CH-(5)), 2.67 – 2.57 (m, *J* = 7.7 Hz, 2H, CH_2-(9)), 2.53 – 2.46 (m, 1H, CH***H′***-(2)), 1.72 – 1.56 (m, 2H, CH_2-(6)), 1.56 – 1.38 (m, 4H, $2CH_2$-(7, 8)), 1.33 (t, *J* = 7.3 Hz, 6H, $2CH_3$-(15)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 142.7 (C(10)), 132.7 (C(4)), 128.4 (C(12)), 128.3 (C(11)), 127.3 (C(3)), 125.7 (C(13)), 83.1 (C(1)), 63.6 (C(14)), 53.0 (C(5)), 39.9 (C(2)), 35.9 (C(9)), 32.6 (C(6)), 31.7 (C(8)), 27.2 (C(7)), 16.3 (C(15)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.45; HRMS (ESI) *m/z* calcd for $C_{19}H_{29}O_4P$ $[M+H]^+$: 353.1803, found: 353.1883; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2930.2 (w), 2586.7 (w), 1453.8 (w), 1369.2 (w), 1262.6 (m), 1165.9 (w), 1028.6 (s), 976.8 (m), 820.8 (w), 748.9 (w), 700.4 (w); $[\alpha]^{25}_{589}$ = -65.6 (c=1.0 in $CHCl_3$, 90% ee).

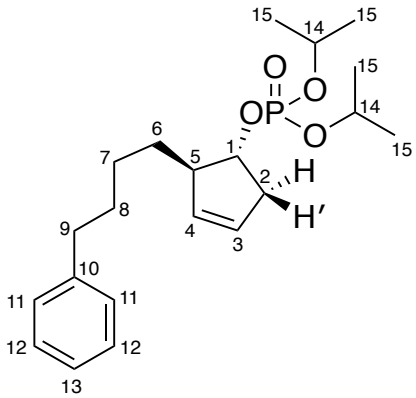
Diisopropyl ((1*R*,2*R*)-2-(4-phenylbutyl)cyclopent-3-en-1-yl) phosphate



Chemical Formula: $C_{21}H_{33}O_4P$
Molecular Weight: 380.4648

Synthesised according to general procedure 1b, using *meso*-4-cyclopentene-1,3-bisdiisopropylphosphate and 4-phenyl-1-butene as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (30-40% EtOAc in petroleum ether) to give diisopropyl ((1*R*,2*R*)-2-(4-phenylbutyl)cyclopent-3-en-1-yl) phosphate as a yellow oil (69 mg, 45%).

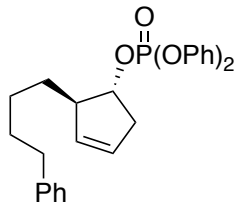
HPLC analysis indicated an enantiomeric excess of 84% [Chiralpak® IA; flow: 1 mL/min; hexane/iPrOH: 96:4; λ = 210 nm; major enantiomer, t_R = 7.985 min; minor enantiomer, t_R = 10.348 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.30 – 7.24 (m, 2H, ArH-(12)), 7.20 – 7.13 (m, 3H, 2ArH-(11, 13)), 5.65 (dq, *J* = 6.0, 1.9 Hz, 2H, 2CH-(3, 4)), 4.69 – 4.57 (m, 3H, 3CH-(1, 14)), 2.81 – 2.70 (m, 2H, C***H***H′-(2), CH-(5)), 2.64 – 2.57 (m, 2H, CH_2-(9)), 2.50 (dd, *J* = 17.5, 1.8

Hz, 1H, CH***H′***-(2)), 1.64 – 1.58 (m, 2H, CH_2-(6)), 1.53 – 1.38 (m, 4H, $2CH_2$-(7, 8)), 1.32 (d, *J* = 6.3 Hz, 12H, $4CH_3$-(15)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 142.7 (C(10)), 132.7 (C(4)), 128.5 (C(12)), 128.4 (C(11)), 127.4 (C(3)), 125.8 (C(13)), 82.9 (C(1)), 72.3 (C(14)), 53.0 (C(5)), 39.9 (C(2)), 36.0 (C(9)), 32.8 (C(6)), 31.8 (C(8)), 27.3 (C(7)), 23.8 (C(15)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -3.05; HRMS (ESI) *m/z* calcd for $C_{21}H_{33}O_4NaP$ $[M+Na]^+$: 403.2009, found: 403.2002; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2980.6 (m), 2931.3 (w), 1454.3 (w), 1385.4 (w), 1260.3 (m), 1143.1 (w), 999.2 (s), 700.1 (w).; $[\alpha]^{25}_{589}$ = -63.1 (c=1.0 in $CHCl_3$, 84% ee).

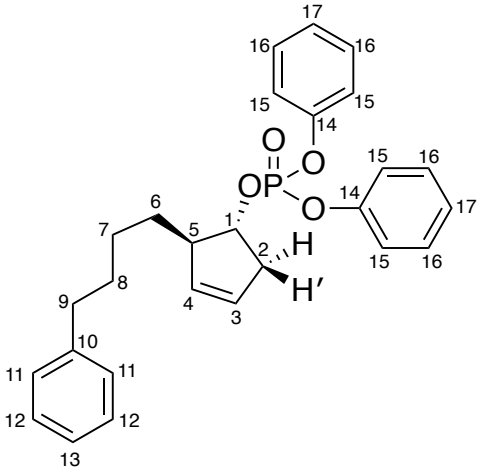
Diphenyl ((1*R*,2*R*)-2-(4-phenylbutyl)cyclopent-3-en-1-yl) phosphate



Chemical Formula: $C_{27}H_{29}O_4P$
Molecular Weight: 448.4988

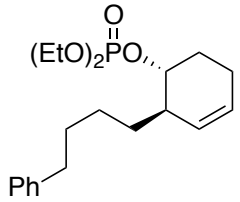
Synthesised according to general procedure 1b, using *meso*-4-cyclopentene-1,3-bisdiphenylphosphate and 4-phenyl-1-butene as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (10% EtOAc in petroleum ether with 1% NEt_3) on silica which was pre-washed with 2% NEt_3 in petroleum ether solution to give diphenyl ((1*R*,2*R*)-2-(4-phenylbutyl)cyclopent-3-en-1-yl) phosphate as a yellow oil (121 mg, 68%).

HPLC analysis indicated an enantiomeric excess of 70% [Chiralpak® IA; flow: 1 mL/min; hexane/iPrOH: 90:10; λ = 210 nm; major enantiomer, t_R = 13.473 min; minor enantiomer, t_R = 17.902 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.35 – 7.12 (m, 15H, ArH-(11, 12, 13, 15, 16, 17)), 5.65 (dq, *J* = 6.0, 1.8 Hz, 2H, 2CH-(3, 4)), 4.94 – 4.88 (m, *J* = 6.4, 3.8, 2.9 Hz, 1H, CH-(1)), 2.82 – 2.71 (m, 2H, C***H***H′-(2), CH-(5)), 2.58 – 2.53 (m, 2H, CH_2-(9)), 2.53 – 2.46 (m, 1H, CH***H′***-(2)), 1.62 – 1.52 (m, 2H, CH_2-(6)), 1.43 – 1.25 (m, 4H, 2CH_2-(7, 8)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 150.6 (C(14)), 142.6 (C(10), 132.6 (C(4)), 129.8 (C(12)), 128.4 (C(11)), 128.3 (C(13)), 127.1 (C(3)), 125.7 (C(16)), 125.3 (C(17)), 120.2 (C(15)), 85.1 (C(1)), 52.9 (C(5)), 39.7 (C(2)), 35.8 (C(9)), 32.4 (C(6)), 31.6 (C(8)), 27.1 (C(7)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -12.3; HRMS (ESI) *m/z* calcd for $C_{27}H_{29}O_4NaP$ $[M+Na]^+$: 471.1696, found: 471.1688; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2929.9 (w), 2856.3 (w), 1591.2 (w), 1489.3 (m), 1455.3 (w), 1286.5 (m), 1221.1 (w), 1190.9 (s), 1163.1 (w), 1022.4 (m), 948.6 (s), 753.9 (m), 689.2 (m); $[\alpha]^{25}_{589}$ = -36.1 (c=1.0 in $CHCl_3$, 70% ee).

Diethyl ((1*R*,2*R*)-2-(4-phenylbutyl)cyclohex-3-en-1-yl) phosphate (2b)

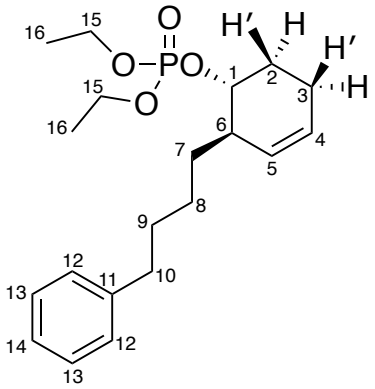


2b

Chemical Formula: $C_{20}H_{31}O_4P$
Molecular Weight: 366.4378

Synthesised according to general procedure 1b, using *meso*-5-cyclohexene-1,4-bisdiethylphosphate (**2a**) and 4-phenyl-1-butene as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (40-50% EtOAc in petroleum ether) to give **2b** as a yellow oil (102 mg, 79%).

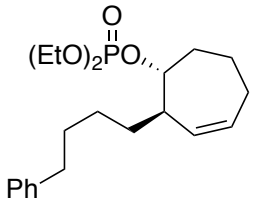
HPLC analysis indicated an enantiomeric excess of 91% [Chiralpak® IB; flow: 1 mL/min; hexane/iPrOH: 98:2; λ = 210 nm; major enantiomer, t_R = 9.164 min; minor enantiomer, t_R = 9.966 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.31 – 7.23 (m, 2H, ArH-(13), 7.20 – 7.13 (m, 3H, ArH-(12, 14)), 5.69 – 5.61 (m, 1H, CH-(4)), 5.54 – 5.47 (m, 1H, CH-(5)), 4.33 (dtd, *J* = 9.4, 6.7, 2.9 Hz, 1H, CH-(1)), 4.09 (p, *J* = 7.1 Hz, 4H, 2CH_2-(15)), 2.61 (t, *J* = 7.7 Hz, 2H, CH_2-(10)), 2.30 – 2.20 (m, 1H, CH-(6)), 2.20 – 2.13 (m, 1H, C***H***H′-(3)), 2.13 – 2.07 (m, 1H, CH***H′***-(3)), 2.07

– 1.99 (m, 1H, C***H***H´-(2)), 1.87 – 1.76 (m, 1H, CH***H´***-(2)), 1.68 – 1.34 (m, 6H, 3CH_2-(7, 8, 9)), 1.32 (tdd, *J* = 7.1, 2.8, 1.0 Hz, 6H, 2CH_3-(16)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 142.7 (C(11)), 128.5 (C(13)), 128.4 (C(12)), 128.1 (C(5)), 126.4 (C(4)), 125.7 (C(14)), 78.4 (C(1)), 63.6 (C(15)), 41.8 (C(6)), 36.0 (C(10)), 32.5 (C(7)), 31.9 (C(9)), 27.8 (C(2)), 26.1 (C(8)), 23.3 (C(3)), 16.2 (C(16)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.47; HRMS (ESI) *m/z* calcd for $C_{20}H_{31}O_4NaP$ $[M+Na]^+$: 389.18522, found: 389.18602; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2981.0 (w), 2931.1 (w), 2858.5 (w), 1262.0 (m), 1030.7 (s), 1010.4 (s), 967.4 (m), 817.8 (w), 784.2 (w), 700.0 (w); $[\alpha]^{25}_{589}$ = -70.2 (c=1.0 in $CHCl_3$, 95% ee).

Diethyl ((1*R*,2*R*)-2-(4-phenylbutyl)cyclohept-3-en-1-yl) phosphate (3b)

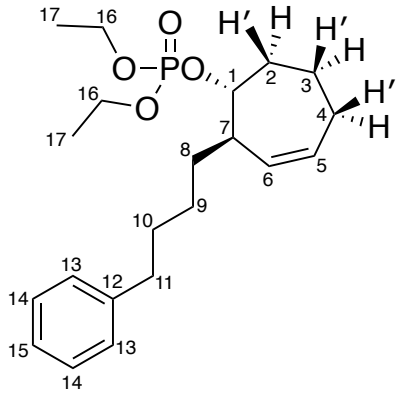


3b

Chemical Formula: $C_{21}H_{33}O_4P$
Molecular Weight: 380.4648

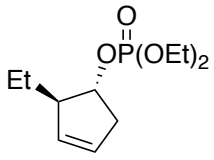
Synthesised according to general procedure 1b, using *meso*-6-cycloheptene-1,5-bisdiethylphosphate (**3a**) and 4-phenyl-1-butene as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (40-50% EtOAc in petroleum ether) to give **3b** as a yellow oil (92 mg, 60%).

HPLC analysis indicated an enantiomeric excess of 92% [Chiralpak® IC; flow: 1 mL/min; hexane/iPrOH: 96:4; λ = 210 nm; major enantiomer, t_R = 26.044 min; minor enantiomer, t_R = 29.793 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.30 – 7.24 (m, 2H, ArH-(14)), 7.21 – 7.14 (m, 3H, ArH-(13, 15)), 5.84 (dtd, *J* = 11.2, 6.3, 1.6 Hz, 1H, CH-(5)), 5.41 (dd, *J* = 11.2, 4.6 Hz, 1H, CH-(6)), 4.26 (qd, *J* = 8.1, 3.1 Hz, 1H, CH-(1)), 4.08 (pd, *J* = 7.4, 3.1 Hz, 4H, $2CH_2$-(16)), 2.60 (td, *J* = 8.1, 2.3 Hz, 2H, CH_2-(11)), 2.57 – 2.49 (m, 1H, CH-(7)), 2.25 – 2.18 (m, 1H, C***H***H′-(2)), 2.09 (q, *J* = 6.0 Hz, 2H, C***HH′***-(4)), 1.97 – 1.88 (m, 1H, CH***H′***-(2)), 1.78 – 1.69 (m, 1H, C***H***H′-(3)), 1.68 – 1.57 (m, 3H, $2CH_2$-(8, 9)), 1.54 – 1.38 (m, 3H, CH***H′***(3), $3CH_2$-(9, 10)), 1.32 (tt, *J* = 7.1, 1.2 Hz, 6H, $2CH_3$-(17)) 1.32 - 1.24 (m, 1H, CH_2-(10)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 142.8 (C(12)), 133.0 (C(5)), 131.4 (C(6)), 128.5 (C(13)), 128.4 (C(14)), 125.7 (C(15)), 79.5 (C(1)), 63.6 (C(16)), 44.5 (C(7)), 36.4 (C(2)), 36.0 (C(11)), 31.84 (C(9)), 31.76 (C(8)), 28.1 (C(4)), 26.7 (C(10)), 23.0 (C(3)), 16.3 (C(17)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.74; HRMS (ESI) *m/z* calcd for $C_{21}H_{33}O_4NaP$ $[M+Na]^+$: 403.20087, found: 403.20154; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2930.1 (w), 2858.0 (w), 1453.3 (w), 1392.8 (w), 1261.0 (m), 1032.3 (s), 997.3 (s), 802.3 (w), 748.7 (w), 699.9 (w); $[\alpha]^{25}_{589}$ = -41.3 (c=1.0 in $CHCl_3$, 92% ee).

Diethyl ((1*R*,2*R*)-2-ethylcyclopent-3-en-1-yl) phosphate (1c)



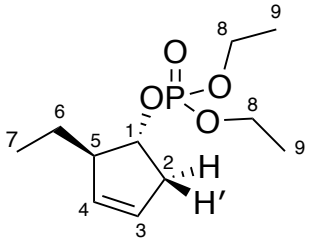
1c

Chemical Formula: $C_{11}H_{21}O_4P$
Molecular Weight: 248.2588

Synthesised according to general procedure 1b, using *meso*-4-cyclopentene-1,3-bisdiethylphosphate (**1a**) and ethylene as the alkene partner (hydrozirconation and reaction carried out under an ethylene atmosphere). Purified by flash chromatography (30-50% EtOAc in petroleum ether) to give **1c** as a yellow oil (81 mg, 82%).

The product was derivatised according to general procedure 2 for HPLC analysis.

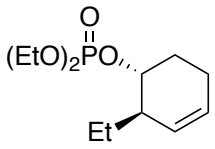
HPLC analysis indicated an enantiomeric excess of 90% [Chiralpak® ID; flow: 0.7 mL/min; hexane/iPrOH: 99:1; λ = 210 nm; minor enantiomer, t_R = 14.157 min; major enantiomer, t_R = 14.785 min].



^{1}H NMR (500 MHz, $CDCl_3$) δ_H/ppm: 5.68 – 5.65 (m, 1H, CH-(4)), 5.64 – 5.61 (m, 1H, CH-(3)), 4.66 (tt, *J* = 6.6, 3.1 Hz, 1H, CH-(1)), 4.08 (dtd, *J* = 14.6, 7.1, 3.2 Hz, 4H, $2CH_2$-(8)), 2.77 – 2.72 (m, 1H, C***H***H′-(2)), 2.73 – 2.67 (m, 1H, CH-(5)), 2.51 – 2.44 (m, 1H, CH***H′***-(2)), 1.52 – 1.39 (m, 1H, CHH′-(6)), 1.39 – 1.33 (m, 1H, CHH′-(6)), 1.31 (tdd, *J* = 7.1, 2.3, 1.0 Hz, 6H, CH_3-(9)), 0.93 (t, *J* = 7.5 Hz, 3H, $2CH_3$-(7)); ^{13}C NMR (126 MHz, $CDCl_3$) δ_c/ppm: 132.5

(C(4)), 127.3 (C(3)), 82.9 (C(1), 63.7 (C(8)), 54.6 (C(5)), 40.0 (C(2)), 25.6 (C(6)), 16.3 (C(9)), 11.8 (C(7)); ^{31}P NMR (202 MHz, $CDCl_3$) δ_P/ppm: -1.46; HRMS (ESI) *m/z* calcd for $C_{21}H_{33}O_4NaP$ $[M+Na]^+$: 271.10697, found: 271.10697; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2980.1 (w), 1460.5 (w), 1392.7 (w), 1263.4 (m), 1166.2 (w), 1026.8 (s), 974.6 (s), 887.0 (w), 820.82 (w), 715.4 (w); $[\alpha]^{25}_{589}$ = -71.1 (c=1.0 in $CHCl_3$, 90% ee). Optical rotation value consistent with those found in the literature.[127]

Diethyl ((1*R*,2*R*)-2-ethylcyclohex-3-en-1-yl) phosphate (2c)



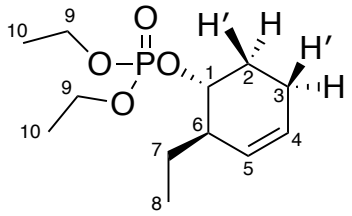
2c

Chemical Formula: $C_{12}H_{23}O_4P$
Molecular Weight: 262.2858

Synthesised according to general procedure 1b, using *meso*-5-cyclohexene-1,4-bisdiethylphosphate (**2a**) and ethylene as the alkene partner (hydrozirconation and reaction carried out under an ethylene atmosphere). Purified by flash chromatography (30-50% EtOAc in petroleum ether) to give **2c** as a yellow oil (83 mg, 79%).

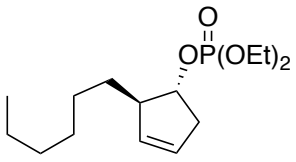
The product was derivatised according to general procedure 2 for HPLC analysis.

HPLC analysis indicated an enantiomeric excess of 97% [Chiralpak® ID; flow: 0.7 mL/min; hexane/iPrOH: 99:1; λ = 210 nm; major enantiomer, t_R = 13.323 min ; minor enantiomer, t_R = 14.305 min].



^{1}H NMR (500 MHz, $CDCl_3$) δ_H/ppm: 5.69 – 5.63 (m, 1H, CH-(4)), 5.54 – 5.48 (m, 1H, CH-(5)), 4.36 – 4.30 (m, 1H, CH-(1)), 4.14 – 4.05 (m, 4H, $2CH_2$-(9)), 2.23 – 2.17 (m, 1H, CH-(6)), 2.17 – 2.13 (m, 1H, C***H***H′-(3)), 2.12 – 2.07 (m, 1H, CH***H′***-(3)), 2.07 – 2.01 (m, 1H, C***H***H′-(2)), 1.84 – 1.76 (m, 1H, CH***H′***-(2)), 1.65 – 1.55 (m, 1H, CH_2-(7)), 1.42 – 1.35 (m, 1H, CH_2-(7)), 1.33 (td, J = 7.1, 1.0 Hz, 6H, $2CH_3$-(10)), 0.93 (t, J = 7.5 Hz, 3H, CH_3-(8)); ^{13}C NMR (126 MHz, $CDCl_3$) δ_c/ppm: 128.0 (C(5)), 126.5 (C(4)), 78.0 (C(1)), 63.7 (C(9)), 43.3 (C(6)), 28.0 (C(2)), 25.2 (C(7)), 23.5 (C(3)), 16.3 (C(10)), 10.7 (C(8)); ^{31}P NMR (202 MHz, $CDCl_3$) δ_P/ppm: -1.49; HRMS (ESI) *m/z* calcd for $C_{21}H_{33}O_4NaP$ $[M+Na]^+$: 285.12262, found: 285.12257; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 3024.8 (w), 2934.2 (w), 1444.3 (w), 1262.7 (m), 1166.6 (w), 1100.9 (w), 1026.5 (s), 1008.2 (s), 987.3 (m), 819.0 (w), 726.3 (w), 682.0 (w); $[\alpha]^{25}_{589}$ = -51.8 (c=1.0 in $CHCl_3$, 97% ee). Optical rotation value consistent with those found in the literature.[127]

Diethyl ((1*R*,2*R*)-2-hexylcyclopent-3-en-1-yl) phosphate (1d)



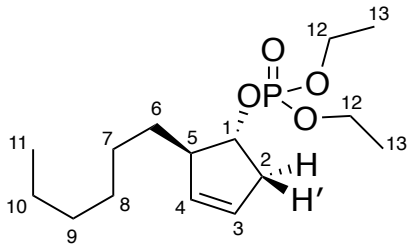
1d

Chemical Formula: $C_{15}H_{29}O_4P$
Molecular Weight: 304.3668

Synthesised according to general procedure 1b, using *meso*-4-cyclopentene-1,3-bisdiethylphosphate (**1a**) and 1-hexene as the alkene partner (hydrozirconation time 20 mins).

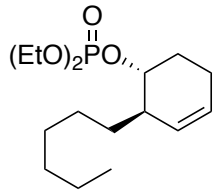
Purified by flash chromatography (20-40% EtOAc in petroleum ether) to give **1d** as a yellow oil (78 mg, 64%).

GC analysis indicated an enantiomeric excess of 90% [Astec Chiraldex ß-DA (Supelco) column; initial temperature 140 ˚C, initial hold time 5 min, progress rate 0.5 ˚C/min, final temperature 160 ˚C, final hold time 15 min; Flow rate 2 mL/min; minor enantiomer, t_R = 46.800 min; major enantiomer, t_R = 47.341 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 5.71 – 5.66 (m, 1H, CH-(4)), 5.66 – 5.62 (m, 1H, CH-(3)), 4.67 (tt, *J* = 6.4, 3.0 Hz, 1H, CH-(1)), 4.10 (pd, *J* = 7.2, 2.7 Hz, 4H, 2CH_2-(12)), 2.80 – 2.71 (m, 2H, C***H***H′-(2), CH-(5)), 2.54 – 2.45 (m, 1H, CH***H′***-(2)), 1.33 (tdd, *J* = 7.1, 2.2, 1.0 Hz, 6H, 2CH_3-(13)), 1.47 – 1.18 (m, 10H, 5CH_2-(6, 7, 8, 9, 10)), 0.90 – 0.84 (m, 3H, CH_3-(11)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 132.9 (C(4)), 127.2 (C(3)), 83.2 (C(1)), 63.7 (C(12)), 53.2 (C(5)), 40.0 (C(2)), 32.9 (C(6)), 31.9 (C(9)), 29.6 (C(8)), 27.5 (C(7)), 22.8 (C(10)), 16.3 (C(13)), 14.2 (C(11)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.46; HRMS (ESI) *m/z* calcd for $C_{15}H_{29}O_4NaP$ $[M+Na]^+$: 327.16957, found: 327.16953; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2926.9 (w), 2856.2 (w), 1459.2 (w), 1392.7 (w), 1263.7 (m), 1165.8 (w), 1030.2 (s), 973.6 (m), 820.6 (w), 712.4 (w); $[\alpha]^{25}_{589}$ = -63.5 (c=1.0 in $CHCl_3$, 90% ee).

Diethyl ((1*R*,2*R*)-2-hexylcyclohex-3-en-1-yl) phosphate (2d)

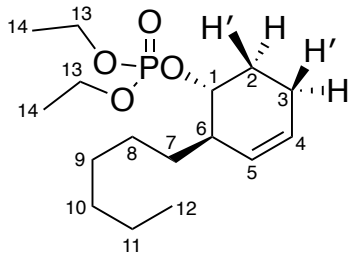


2d

Chemical Formula: $C_{16}H_{31}O_4P$
Molecular Weight: 318.3938

Synthesised according to general procedure 1b, using *meso*-5-cyclohexene-1,4-bisdiethylphosphate (**2a**) and 1-hexene as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (20-40% EtOAc in petroleum ether) to give **2d** as a yellow oil 111 mg, 87%).

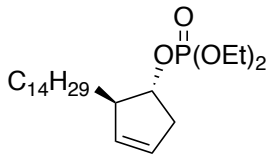
GC analysis indicated an enantiomeric excess of 97% [Astec Chiraldex ß-DA (Supelco) column; initial temperature 160 ˚C, initial hold time 5 min, progress rate 0.1 ˚C/min, final temperature 165 ˚C, final hold time 10 min; Flow rate 2 mL/min; minor enantiomer, t_R = 44.980 min; major enantiomer, t_R = 45.671 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 5.68 – 5.60 (m, 1H, CH-(4)), 5.56 – 5.48 (m, 1H, CH-(5)), 4.33 (dtd, *J* = 9.3, 6.7, 2.9 Hz, 1H, CH-(1)), 4.16 – 4.03 (m, 4H, 2CH_2-(13)), 2.29 – 2.20 (m, 1H, CH-(6)), 2.20 – 2.12 (m, 1H, C***H***H′-(3)), 2.11 – 2.06 (m, 1H, CH***H′***-(3)), 2.06 – 1.97 (m, 1H, C***H***H′-(2)), 1.86 – 1.75 (m, 1H, CH***H′***-(2)), 1.59 – 1.16 (m, 10H, 5CH_2-(7, 8, 9, 10, 11)), 1.33 (td, *J* = 7.1, 1.0 Hz, 6H, 2CH_3-(14)), 0.91 – 0.84 (m, 3H, CH_3-(12)); ^{13}C NMR (101

MHz, $CDCl_3$) δ_c/ppm: 128.3 (C(5)), 126.3 (C(4)), 78.4 (C(1)), 63.6 (C(13)), 41.8 (C(6)), 32.7 (C(7)), 31.9 (C(10)), 29.7 (C(9)), 27.7 (C(2)), 26.3 (C(8)), 23.3 (C(3)), 22.8 (C(11)), 16.3 (C(14)), 14.2 (C(12)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.49; HRMS (ESI) *m/z* calcd for $C_{16}H_{31}O_4NaP$ $[M+Na]^+$: 341.18522, found: 341.18537; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2928.1 (m), 2857.7 (w), 1458.2 (w), 1393.3 (w), 1263.1 (m), 1166.1 (w), 1011.0 (s), 974.6 (m), 817.9 (w), 726.3 (w); $[\alpha]^{25}_{589}$ = -71.5 (c=1.0 in $CHCl_3$, 97% ee).

Diethyl ((1*R*,2*R*)-2-tetradecylcyclopent-3-en-1-yl) phosphate (1e)



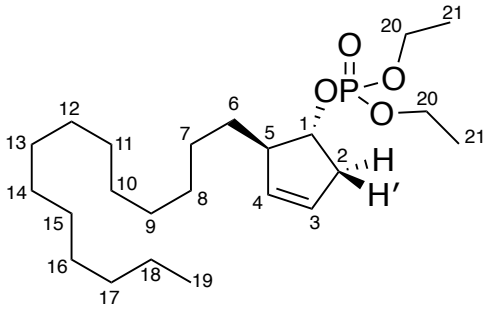
1e

Chemical Formula: $C_{23}H_{45}O_4P$
Molecular Weight: 416.5828

Synthesised according to general procedure 1b, using *meso*-4-cyclopentene-1,3-bisdiethylphosphate (**1a**) and 1-tetradecene as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (15-35% EtOAc in petroleum ether) to give **1e** as a yellow oil (92 mg, 55%).

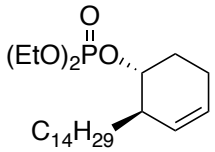
The product was derivatised according to general procedure 2 for HPLC analysis.

HPLC analysis indicated an enantiomeric excess of 90% [Chiralpak® IC; flow: 0.7 mL/min; hexane/iPrOH: 99:1; λ = 210 nm; major enantiomer, t_R = 11.584 min ; minor enantiomer, t_R = 12.143 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 5.71 – 5.66 (m, 1H, CH-(4)), 5.65 – 5.61 (m, 1H, CH-(3)), 4.66 (tt, *J* = 6.4, 3.0 Hz, 1H, (CH-(1)), 4.09 (pd, *J* = 7.2, 2.7 Hz, 4H, 2CH_2-(20)), 2.81 – 2.71 (m, 2H, C***H***H′-(2), CH-(5)), 2.53 – 2.44 (m, 1H, CH***H′***-(2)), 1.37 – 1.30 (m, 6H, 2CH_3-(21)), 1.46 – 1.21 (m, 26H, 13CH_2-(6-18)), 0.92 – 0.83 (m, 3H, CH_3-(19)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 132.9 (C(4)), 127.2 (C(3)), 83.3 (C(1)), 63.7 (C(20)), 53.2 (C(5)), 40.0 (C(2)), 32.9 (C(6)), 32.1 (C(7-18), 29.9 (C(7-18)), 29.8 (C(7-18)), 29.8 (C(7-18)), 29.8 (C(7-18)), 29.7 (C(7-18), 29.5 (C(7-18)), 27.6 (C(7-18)), 22.8 (C(7-18)), 16.3 (C(21)), 14.3 (C(19)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.46; HRMS (ESI) *m/z* calcd for $C_{23}H_{45}O_4NaP$ $[M+Na]^+$: 439.29477, found: 439.29420; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2923.1(m), 2853.2 (w), 1465.9 (w), 1369.6 (w), 1264.1 (m), 1166.2 (w), 1030.3 (s), 974.4 (m), 820.6 (w), 712.6 (w); $[\alpha]^{25}_{589}$ = -56.0 (c=1.0 in $CHCl_3$, 90% ee).

Diethyl ((1*R*,2*R*)-2-tetradecylcyclohex-3-en-1-yl) phosphate (2e)



2e

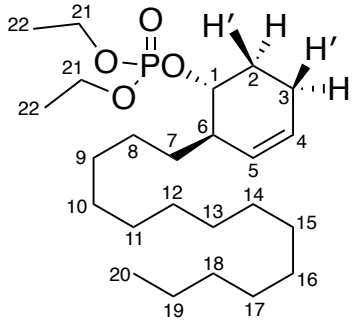
Chemical Formula: $C_{24}H_{47}O_4P$
Molecular Weight: 430.6098

Synthesised according to general procedure 1b, using *meso*-5-cyclohexene-1,4-bisdiethylphosphate (**2a**) and 1-tetradecene as the alkene partner (hydrozirconation time 20

mins). Purified by flash chromatography (15-35% EtOAc in petroleum ether) to give **2e** as a yellow oil (128 mg, 74%).

The product was derivatised according to general procedure 2 for HPLC analysis.

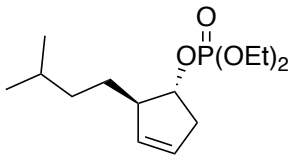
HPLC analysis indicated an enantiomeric excess of 95% [Chiralpak® IC; flow: 0.7 mL/min; hexane/iPrOH: 99:1; λ = 210 nm; major enantiomer, t_R = 11.101 min ; minor enantiomer, t_R = 11.933 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 5.68 – 5.62 (m, 1H, CH-(4)), 5.55 – 5.49 (m, 1H, CH-(5)), 4.33 (dtd, *J* = 9.3, 6.7, 2.9 Hz, 1H, CH-(1)), 4.10 (pd, *J* = 7.2, 3.2 Hz, 4H, 2CH_2-(21)), 2.29 – 2.21 (m, 1H, CH-(6)), 2.21 – 2.12 (m, 1H, C***H***H′-(3)), 2.12 – 2.06 (m, 1H, CH***H′***-(3)), 2.03 – 1.98 (m, 1H, C***H***H′-(2)), 1.86 – 1.75 (m, 1H, CH***H′***-(2)), 1.46 – 1.21 (m, 26H, 13CH_2-(7-19)) 1.33 (td, *J* = 7.1, 1.0 Hz, 6H, 2CH_3-(22)), 0.92 – 0.84 (m, 3H, CH_3-(20)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 128.3 (C(5)), 126.3 (C(4)), 78.4 (C(1)), 63.6 (C(21)), 41.8 (C(6)), 32.8 (C(7)), 32.1 (C(8-19)), 30.0 (C(8-19)), 29.8 (C(8-19), 29.8 (C(8-19)), 29.8 (C(8-19)), 29.7 (C(8-19)), 29.5 (C(8-19)), 27.7 (C(2)), 26.4 (C(8-19)), 23.3 (C(3)), 22.8 (C(8-19)), 16.3 (C(22)), 14.3 (C(20)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.49; HRMS (ESI) *m/z* calcd for $C_{24}H_{47}O_4NaP$ $[M+Na]^+$: 453.31042, found: 453.31042; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$:

2923.5 (m), 2853.4 (m), 1466.1 (w), 1264.3 (w), 1166.7 (w), 1034.2 (s), 1012.2 (s), 976.8 (m), 817.6 (w), 724.2 (w); $[\alpha]^{25}_{589}$ = -44.5 (c=1.0 in $CHCl_3$, 95% ee).

Diethyl ((1*R*,2*R*)-2-isopentylcyclopent-3-en-1-yl) phosphate (1f)

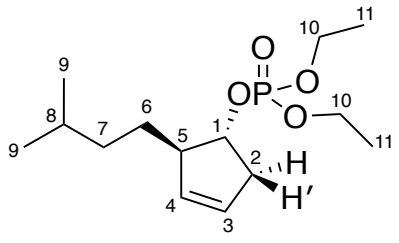


1f

Chemical Formula: $C_{14}H_{27}O_4P$
Molecular Weight: 290.3398

Synthesised according to general procedure 1b, using *meso*-4-cyclopentene-1,3-bisdiethylphosphate (**1a**) and 3-methyl-1-butene (reagent bottle under an Ar atmosphere and cooled to -78 ˚C before adding to flask **B**) as the alkene partner (hydrozirconation time 30 mins). Purified by flash chromatography (15-40% EtOAc in petroleum ether) to give **1f** as a yellow oil (70 mg, 60%).

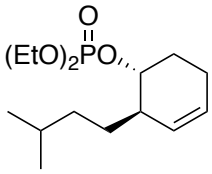
GC analysis indicated an enantiomeric excess of 90% [Astec Chiraldex ß-DA (Supelco) column; initial temperature 120 ˚C, initial hold time 5 min, progress rate 2 ˚C/min, final temperature 170 ˚C, final hold time 10 min; Flow rate 3 mL/min; minor enantiomer, t_R = 27.398 min; major enantiomer, t_R = 27.708 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 5.70 – 5.66 (m, 1H, CH-(4)), 5.66 – 5.61 (m, 1H, CH-(3)), 4.66 (tt, *J* = 6.5, 3.0 Hz, 1H, CH-(1)), 4.16 – 4.03 (m, 4H, 2CH_2-(10)), 2.80 – 2.70 (m,

2H, C***H***H´-(2), CH-(5)), 2.53 – 2.44 (m, 1H, CH***H´***-(2)), 1.57 – 1.47 (m, 1H, CH-(8)), 1.47 – 1.16 (m, 4H, $2CH_2$-(6, 7)) 1.33 (tdd, *J* = 7.1, 2.2, 1.0 Hz, 6H, $2CH_3$-(11)), 0.86 (dd, *J* = 6.7, 1.2 Hz, 6H, $2CH_3$-(9)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 132.9 (C(4)), 127.2 (C(3)), 83.3 (C(1)), 63.7 (C(10)), 53.3 (C(5)), 40.0 (C(2)), 36.7 (C(7)), 30.6 (C(8)), 28.3 (C(6)), 22.7 (C(9)), 16.2 (C(11)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.47; HRMS (ESI) *m/z* calcd for $C_{14}H_{27}O_4NaP$ $[M+Na]^+$: 313.15392, found: 313.15373; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2928.1 (w), 2869.4 (w), 1468.3 (w), 1367.5 (w), 1263.8 (m), 1167.4 (w), 1029.3 (s), 977.0 (m), 820.9 (w), 712.0 (w); $[\alpha]^{25}_{589}$ = -75.9 (c=1.0 in $CHCl_3$, 90% ee).

Diethyl ((1*R*,2*R*)-2-isopentylcyclohex-3-en-1-yl) phosphate (2f)

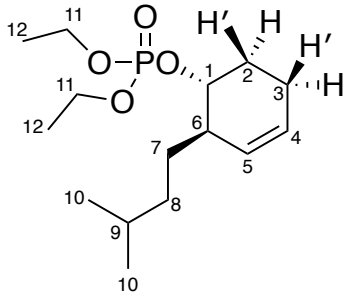


2f

Chemical Formula: $C_{15}H_{29}O_4P$
Molecular Weight: 304.3668

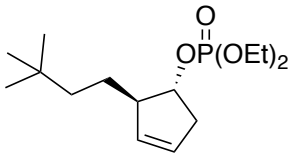
Synthesised according to general procedure 1b, using *meso*-5-cyclohexene-1,4-bisdiethylphosphate (**2a**) and 3-methyl-1-butene (reagent bottle under an Ar atmosphere and cooled to -78 ˚C before adding to flask **B**) as the alkene partner (hydrozirconation time 30 mins). Purified by flash chromatography (15-40% EtOAc in petroleum ether) to give **2f** as a yellow oil (95 mg, 78%).

GC analysis indicated an enantiomeric excess of 96% [Astec Chiraldex ß-DA (Supelco) column; initial temperature 120 ˚C, initial hold time 5 min, progress rate 2 ˚C/min, final temperature 170 ˚C, final hold time 10 min; Flow rate 3 mL/min; minor enantiomer, t_R = 33.344 min; major enantiomer, t_R = 33.699 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 5.68 – 5.61 (m, 1H, CH-(4)), 5.54 – 5.48 (m, 1H, CH-(5)), 4.33 (dtd, *J* = 9.3, 6.7, 2.9 Hz, 1H, CH-(1)), 4.10 (pd, *J* = 7.2, 3.9 Hz, 4H, $2CH_2$-(11)), 2.27 – 2.18 (m, 1H, CH-(6)), 2.18 – 2.12 (m, 1H, C***H***H′-(3)), 2.12 – 2.05 (m, 1H, CH***H′***-(3)), 2.05 – 1.99 (m, 1H, C***H***H′-(2)), 1.86 – 1.74 (m, 1H, CH***H′***-(2)), 1.61 – 1.45 (m, 2H, CHH′ (7), CH-(9)), 1.36 – 1.12 (m, 3H, CHH′-(7) CH_2-(8)), 1.33 (td, *J* = 7.1, 1.0 Hz, 6H, $2CH_3$-(10)), 0.87 (dd, *J* = 6.6, 1.8 Hz, 6H, $2CH_3$-(12)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 128.3 (C(5)), 126.3 (C(4)), 78.4 (C(1)), 63.6 (C(13)), 42.0 (C(6)), 35.5 (C(8)), 30.5 (C(9)), 28.4 (C(7)), 27.8 (C(2)), 23.3 (C(3)), 22.7 (C(10)), 16.3 (C(12)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.49; HRMS (ESI) *m/z* calcd for $C_{15}H_{29}O_4NaP$ $[M+Na]^+$: 327.16957, found: 327.16949; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2955.5 (w), 1458.1 (w), 1367.8 (w), 1263.6 (m), 1166.4 (w), 1011.0 (s), 973.9 (m), 817.5 (w), 726.0 (w); $[\alpha]^{25}_{589}$ = -76.8 (c=1.0 in $CHCl_3$, 96% ee).

Diethyl (1*R*,2*R*)-2-(3,3-dimethylbutyl)cyclopent-3-en-1-yl) phosphate (1g)



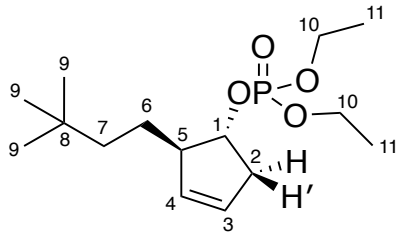
1g

Chemical Formula: $C_{15}H_{29}O_4P$
Molecular Weight: 304.3668

Synthesised according to general procedure 1b, using *meso*-4-cyclopentene-1,3-bisdiethylphosphate (**1a**) and 3,3-dimethyl-1-butene as the alkene partner (hydrozirconation

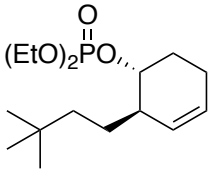
time 1hr 15 mins). Purified by flash chromatography (20-40% EtOAc in petroleum ether) to give **1g** as a yellow oil (59 mg, 48%).

GC analysis indicated an enantiomeric excess of 91% [Astec Chiraldex ß-DA (Supelco) column; initial temperature 120 ˚C, initial hold time 5 min, progress rate 4 ˚C/min, final temperature 170 ˚C, final hold time 5 min; Flow rate 3 mL/min; minor enantiomer, t_R = 22.524 min; major enantiomer, t_R = 22.903 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 5.70 – 5.66 (m, 1H, CH-(4)), 5.65 – 5.61 (m, 1H, CH-(3)), 4.66 (tt, *J* = 6.5, 3.0 Hz, 1H, CH-(1)), 4.09 (pd, *J* = 7.1, 3.0 Hz, 4H, 4CH_2-(10)), 2.80 – 2.67 (m, 2H, C***H***H′-(2), CH-(5)), 2.53 – 2.45 (m, 1H, CH***H′***-(2)), 1.33 (tdd, *J* = 7.1, 2.3, 0.9 Hz, 6H, 2CH_3-(11)), 1.44 – 1.17 (m, 4H, 2CH_2-(6, 7)), 0.85 (s, 9H, 3CH_3-(9)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 132.9 (C(4)), 127.2 (C(3)), 83.2 (C(1)), 63.7 (C(10)), 53.7 (C(5)), 41.7 (C(8)), 40.0 (C(2)), 30.3 (C(7)), 29.4 (C(9)), 27.8 (C(6)), 16.3 (C(11)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.49; HRMS (ESI) *m/z* calcd for $C_{15}H_{29}O_4NaP$ $[M+Na]^+$: 327.16957, found: 327.16945; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2952.4 (w), 2866.8 (w), 1476.1 (w), 1364.6 (w), 1263.0 (m), 1166.9 (w), 1033.9 (s), 1011.9 (s), 979.8 (m), 817.6 (w), 725.7 (w); $[\alpha]^{25}_{589}$ = -35.2 (c=1.0 in $CHCl_3$, 91% ee).

Diethyl (1*R*,2*R*)-2-(3,3-dimethylbutyl)cyclohex-3-en-1-yl) phosphate (2g)

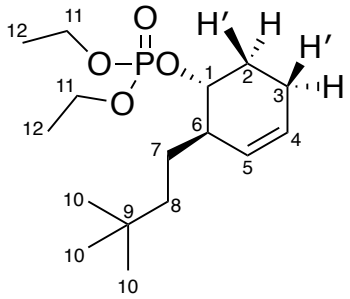


2g

Chemical Formula: $C_{16}H_{31}O_4P$
Molecular Weight: 318.3938

Synthesised according to general procedure 1b, using *meso*-5-cyclohexene-1,4-bisdiethylphosphate (**2a**) and 3,3-dimethyl-1-butene as the alkene partner (hydrozirconation time 1hr 15 mins). Purified by flash chromatography (20-40% EtOAc in petroleum ether) to give **2g** as a yellow oil (80 mg, 63%).

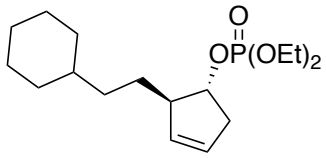
GC analysis indicated an enantiomeric excess of 96% [Astec Chiraldex ß-DA (Supelco) column; initial temperature 120 ˚C, initial hold time 5 min, progress rate 4 ˚C/min, final temperature 170 ˚C, final hold time 15 min; Flow rate 3 mL/min; minor enantiomer, t_R = 28.911 min; major enantiomer, t_R = 29.547 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 5.68 – 5.62 (m, 1H, CH-(4)), 5.53 – 5.47 (m, 1H, CH-(5)), 4.34 (dtd, *J* = 9.3, 6.7, 2.9 Hz, 1H, CH-(1)), 4.15 – 4.05 (m, 4H, 2CH_2-(11)), 2.24 – 2.17 (m, 1H, CH-(6)), 2.17 – 2.12 (m, 1H, C***H***H′-(3)), 2.11 – 2.06 (m, 1H, CH***H′***-(3)), 2.06 – 2.00 (m, 1H, C***H***H′-(2)), 1.87 – 1.72 (m, 1H, CH***H′***-(2)), 1.60 – 1.47 (m, 1H, CHH′-(7)), 1.37 – 1.28 (m, 6H, 2CH_3-(12)), 1.37 – 1.08 (m, 3H, CHH′-(7), CH_2-(8)), 0.86 (s, 9H, 3CH_3-(10)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 128.3 (C(5)), 126.3 (C(4)), 78.4 (C(1)), 63.6 (C(11)),

42.3 (C(6)), 40.4 (C(9)), 30.4 (C(8)), 29.5 (C(10)), 27.9 (C(2)), 27.4 (C(7)), 23.4 (C(3)), 16.3 (C(12)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.49; HRMS (ESI) *m/z* calcd for $C_{16}H_{31}O_4NaP$ $[M+Na]^+$: 341.18522, found: 341.18521; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2952.8 (w), 2867.0 (w), 1475.9 (w), 1393.6 (w), 1364.6 (w), 1262.9 (m), 1166.5 (w), 1033.0 (s), 1011.9 (s), 979.0 (m), 817.6 (w), 725.6 (w); $[\alpha]^{25}_{589}$ = -58.5 (c=1.0 in $CHCl_3$, 96% ee).

Diethyl (1*R*,2*R*)-2-(2-cyclohexylethyl)cyclopent-3-en-1-yl phosphate (1h)

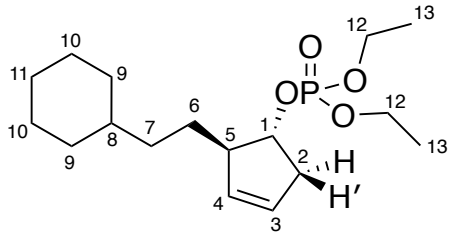


1h

Chemical Formula: $C_{17}H_{31}O_4P$
Molecular Weight: 330.4048

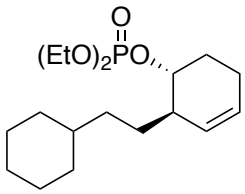
Synthesised according to general procedure 1b, using *meso*-4-cyclopentene-1,3-bisdiethylphosphate (**1a**) and vinylcyclohexane as the alkene partner (hydrozirconation time 30 mins). Purified by flash chromatography (15-40% EtOAc in petroleum ether) to give **1h** as a yellow oil (74 mg, 56%).

GC analysis indicated an enantiomeric excess of 91% [Astec Chiraldex ß-DA (Supelco) column; initial temperature 180 ˚C, initial hold time 5 min, progress rate 0.5 ˚C/min, final temperature 205 ˚C, final hold time 10 min; Flow rate 2 mL/min; minor enantiomer, t_R = 35.635 min; major enantiomer, t_R = 36.243 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 5.70 – 5.65 (m, 1H, CH-(4)), 5.65 – 5.61 (m, 1H, CH-(3)), 4.66 (tt, *J* = 6.5, 2.9 Hz, 1H, CH-(1)), 4.16 – 4.03 (m, 4H, $2CH_2$-(12)), 2.79 – 2.69 (m, 2H, C***H***H´-(2), CH-(5)), 2.53 – 2.44 (m, 1H, CH***H´***-(2)), 1.73 – 1.58 (m, 5H, CH-(8), $2CH_2$-(9)), 1.48 – 1.04 (m, 8H, $4CH_2$-(6, 7, 10)), 1.33 (tdd, *J* = 7.1, 2.5, 1.0 Hz, 6H, $2CH_3$-(13)), 0.86 (m, 2H, CH_2-(11)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 132.9 (C(4)), 127.2 (C(3)), 83.3 (C(1)), 63.7 (C(12)), 53.4 (C(5)), 39.9 (C(2)), 38.0 (C(9)), 35.2 (C(7)), 33.5 (C(8)), 30.1 (C(6)), 26.8 (C(11)), 26.5 (C(10)), 16.3 (C(13)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.47; HRMS (ESI) *m/z* calcd for $C_{17}H_{31}O_4NaP$ $[M+Na]^+$: 353.18522, found: 353.18493; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2981.1 (w), 2922.0 (m), 2851.3 (w), 1448.1 (w), 1369.5 (m), 1263.4 (m), 1165.6 (w), 1029.3 (s), 974.7 (m), 820.6 (w), 712.0 (w); $[\alpha]^{25}_{589}$ = -73.4 (c=1.0 in $CHCl_3$, 91% ee).

Diethyl (1*R*,2*R*)-2-(2-cyclohexylethyl)cyclohex-3-en-1-yl phosphate (2h)



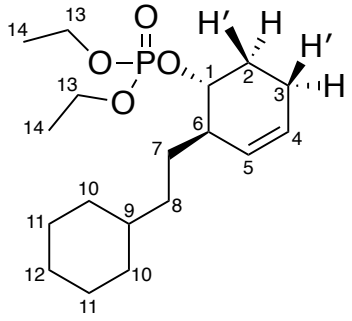
2h

Chemical Formula: $C_{18}H_{33}O_4P$
Molecular Weight: 344.4318

Synthesised according to general procedure 1b, using *meso*-5-cyclopentene-1,4-bisdiethylphosphate (**2a**) and vinylcyclohexane as the alkene partner (hydrozirconation time 30 mins). Purified by flash chromatography (15-40% EtOAc in petroleum ether) to give **2h** as a yellow oil (94 mg, 64%).

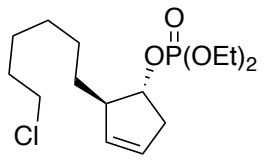
GC analysis indicated an enantiomeric excess of 95% [Astec Chiraldex ß-DA (Supelco) column; initial temperature 180 ˚C, initial hold time 5 min, progress rate 0.5 ˚C/min, final

temperature 205 ˚C, final hold time 10 min; Flow rate 2 mL/min; minor enantiomer, t_R = 46.528 min; major enantiomer, t_R = 47.237 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 5.69 – 5.61 (m, 1H, CH-(4)), 5.54 – 5.47 (m, 1H, CH-(5)), 4.33 (dtd, *J* = 9.3, 6.7, 2.9 Hz, 1H, CH-(1)), 4.17 – 4.03 (m, 4H, 2CH_2-(11)), 2.25 – 2.18 (m, 1H, CH-(6)), 2.18 – 2.12 (m, 1H, C***H***H′-(3)), 2.12 – 2.05 (m, 1H, CH***H′***-(3)), 2.05 – 1.98 (m, 1H, C***H***H′-(2)), 1.86 – 1.75 (m, 1H, CH***H′***-(2)), 1.74 – 1.50 (m, 7H, CH-(9), CHH′-(7), 2CH_2-(10)), 1.33 (dt, *J* = 7.1, 1.0 Hz, 6H, 2CH_3-(14)), 1.31 – 1.09 (m, 7H, CHH′-(7), 3CH_2-(8, 11)), 0.94 – 0.79 (m, 2H, CH_2-(12)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 128.3 (C(5)), 126.3 (C(4)), 78.4 (C(1)), 63.7 (C(13)), 42.0 (C(6)), 38.1 (C(10)), 34.0 (C(8)), 33.5 (C(9)), 30.0 (C(6)), 27.8 (C(2)), 26.8 (C(12)), 26.5 (C(11)), 23.3 (C(3)), 16.3 (C(14)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.49; HRMS (ESI) *m/z* calcd for $C_{18}H_{33}O_4NaP$ $[M+Na]^+$: 367.20087, found: 367.20042; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2980.56 (w), 2922.3 (m), 2850.9 (w), 1447.8 (w), 1393.3 (w), 1263.2 (m), 1165.7 (w), 1034.3 (s), 1011.9 (s), 817.8 (w), 725.6 (w); $[\alpha]^{25}_{589}$ = -66.2 (c=1.0 in $CHCl_3$, 96% ee).

(1*R*,2*R*)-2-(6-chlorohexyl)cyclopent-3-en-1-yl diethyl phosphate (1i)



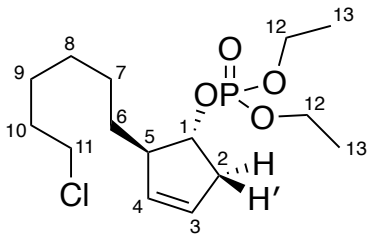
1i

Chemical Formula: $C_{15}H_{28}ClO_4P$
Molecular Weight: 338.8088

Synthesised according to general procedure 1b, using *meso*-4-cyclopentene-1,3-bisdiethylphosphate (**1a**) and 6-chloro-1-hexene as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (20-40% EtOAc in petroleum ether) to give **1i** as a yellow oil (61 mg, 45%).

The product was derivatised according to general procedure 2 for HPLC analysis.

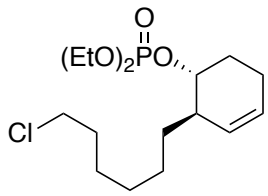
HPLC analysis indicated an enantiomeric excess of 91% [Chiralpak® IC; flow: 0.8 mL/min; hexane/iPrOH: 98:2; λ = 210 nm; minor enantiomer, t_R = 17.579 min ; major enantiomer, t_R = 18.652 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 5.70 – 5.66 (m, 1H, CH-(4)), 5.66 – 5.62 (m, 1H, CH-(3)), 4.67 (tt, *J* = 6.5, 3.0 Hz, 1H, CH-(1)), 4.16 – 4.03 (m, 4H, $2CH_2$-(12)), 3.52 (t, *J* = 6.7 Hz, 2H, CH_2-(11)), 2.81 – 2.71 (m, 2H, C***H***H'-(2) CH-(5)), 2.54 – 2.45 (m, 1H, CH***H′***-(2)), 1.81 – 1.71 (m, 2H, CH_2-(10)), 1.50 – 1.25 (m, 8H, $4CH_2$-(6, 7, 8, 9)), 1.33 (tdd, *J* = 7.1, 1.8, 1.0 Hz, 6H, $2CH_3$-(13)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 132.8 (C(4)), 127.3 (C(3)), 83.2 (C(1)),

63.7 (C(12)), 53.1 (C(5)), 45.2 (C(11)), 39.9 (C(2)), 32.72 (C(10)) 32.70 (C(6)), 29.1 (C(7-9)), 27.4 (C(7-9)), 26.9 (C(7-9)), 16.3 (C(13)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.46; HRMS (ESI) *m/z* calcd for $C_{15}H_{28}O_4{}^{35}ClNaP$ $[M+Na]^+$: 361.13059, found: 361.13063; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2930.2 (w), 2856.1 (w), 1443.8 (w), 1263.8 (m), 1166.9 (w), 1029.2 (s), 821.2 (w), 714.1 (w); $[\alpha]^{25}{}_{589}$ = -63.1 (c=1.0 in $CHCl_3$, 91% ee).

(1*R*,2*R*)-2-(6-chlorohexyl)cyclohex-3-en-1-yl diethyl phosphate (2i)



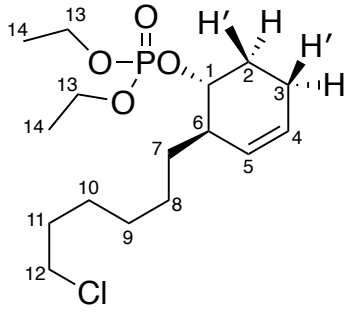
2i

Chemical Formula: $C_{16}H_{30}ClO_4P$
Molecular Weight: 352.8358

Synthesised according to general procedure 1b, using *meso*-5-cyclohexene-1,4-bisdiethylphosphate (**2a**) and 6-chloro-1-hexene as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (20-40% EtOAc in petroleum ether) to give **2i** as a yellow oil (95 mg, 67%).

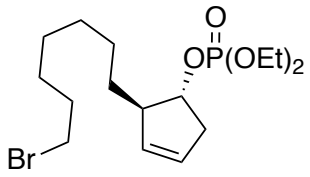
The product was derivatised according to general procedure 2 for HPLC analysis.

HPLC analysis indicated an enantiomeric excess of 95% [Chiralpak® IC; flow: 0.8 mL/min; hexane/iPrOH: 98:2; λ = 210 nm; major enantiomer, t_R = 25.573 min ; minor enantiomer, t_R = 27.726 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 5.69 – 5.62 (m, 1H, CH-(4)), 5.55 – 5.47 (m, 1H, CH-(5)), 4.32 (dtd, *J* = 9.4, 6.7, 2.9 Hz, 1H, CH-(1)), 4.10 (pd, *J* = 7.1, 3.2 Hz, 4H, 2CH_2-(13)), 3.52 (t, J = 6.7 Hz, 2H, CH_2-(12)), 2.29 – 2.21 (m, 1H, CH-(6)), 2.21 – 2.12 (m, 1H, C***H***H′-(3)), 2.12 – 2.05 (m, 1H, CH***H′***-(3)), 2.05 – 1.98 (m, 1H, C***H***H′-(2)), 1.86 – 1.75 (m, 1H, C***H***H′-(2)), 1.79 – 1.71 (m, 2H, CH_2-(11)), 1.59 – 1.25 (m, 8H, 4CH_2-(7, 8, 9, 10)) 1.33 (td, *J* = 7.1, 1.1 Hz, 6H, 2CH_3-(14)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 128.1 (C(5)), 126.4 (C(4)), 78.3 (C(1)), 63.7 (C(13)), 45.2 (C(12)), 41.7 (C(6)), 32.7 (C(11)), 32.6 (C(7)), 29.2 (C(8-10)), 27.8 (C(2)), 26.9 (C(8-10)), 26.2 (C(8-10)), 23.4 (C(3)), 16.3 (C(14)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.46; HRMS (ESI) *m/z* calcd for $C_{16}H_{30}O_4{}^{35}ClNaP$ $[M+Na]^+$: 375.14636, found: 35.14624; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2930.6 (w), 2856.2 (w), 1444.0 (w), 1274.0 (w), 1167.1 (w), 1030.0 (s), 821.1 (w), 713.8 (w); $[\alpha]^{25}{}_{589}$ = -61.3 (c=1.0 in $CHCl_3$, 95% ee).

(1*R*,2*R*)-2-(7-bromoheptyl)cyclopent-3-en-1-yl diethyl phosphate (1j)



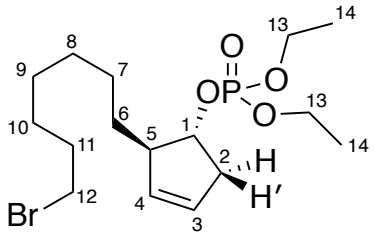
1j

Chemical Formula: $C_{16}H_{30}BrO_4P$
Molecular Weight: 397.2898

Synthesised according to general procedure 1b, using *meso*-4-cyclopentene-1,3-bisdiethylphosphate (**1a**) and 7-bromo-1-heptene as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (15-40% EtOAc in petroleum ether) to give **1j** as a yellow oil (44 mg, 28%).

The product was derivatised according to general procedure 2 for HPLC analysis.

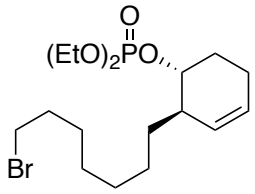
HPLC analysis indicated an enantiomeric excess of 88% [Chiralpak® ID; flow: 0.8 mL/min; hexane/iPrOH: 98:2; λ = 210 nm; minor enantiomer, t_R = 17.072 min ; major enantiomer, t_R = 19.663 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 5.70 – 5.66 (m, 1H, CH-(4)), 5.66 – 5.62 (m, 1H, CH-(3)), 4.66 (tt, *J* = 6.4, 3.0 Hz, 1H, CH-(1)), 4.16 – 4.03 (m, 4H, $2CH_2$-(13)), 3.52 (t, *J* = 6.8 Hz, 2H, CH_2-(12)), 2.81 – 2.70 (m, 2H, C***H***H'-(2) CH-(5)), 2.53 – 2.44 (m, 1H, CH***H′***-(2)), 1.89 – 1.79 (m, 2H, CH_2-(11)), 1.47 – 1.22 (m, 10H, $5CH_2$-(6, 7, 8, 9, 10)), 1.33 (tdd, *J* = 7.1, 1.8, 1.0 Hz, 6H, $2CH_3$-(14)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 132.8 (C(4)), 127.3 (C(3)), 83.2

(C(1)), 63.7 (C(12)), 53.1 (C(5)), 39.9 (C(2)), 34.1 (C(12)), 32.9 (C(6-11)), 32.8 (C(6-11)), 29.7 (C(6-11)), 28.78 (C(6-11)), 28.3 (C(6-11)), 27.4 (C(6-11)), 16.3 (C(13)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.46; HRMS (ESI) *m/z* calcd for $C_{16}H_{30}O_4{}^{79}BrNaP$ $[M+Na]^+$: 419.09753, found: 419.09548; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2928.7 (w), 2855.5 (w), 1443.0 (w), 1369.3 (w), 1273.1 (m), 1166.0 (w), 1030.8 (s), 975.6 (m), 821.0 (w), 713.5 (w); $[\alpha]^{25}{}_{589}$ = -42.1 (c=1.0 in $CHCl_3$, 88% ee).

(1*R*,2*R*)-2-(7-bromoheptyl)cyclohex-3-en-1-yl diethyl phosphate (2j)



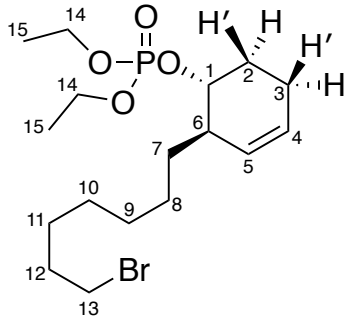
2j

Chemical Formula: $C_{17}H_{32}BrO_4P$
Molecular Weight: 411.3168

Synthesised according to general procedure 1b, using *meso*-5-cyclohexene-1,4-bisdiethylphosphate (**3**) and 6-bromo-1-heptene as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (15-40% EtOAc in petroleum ether) to give **14b** as a yellow oil (39 mg, 24%).

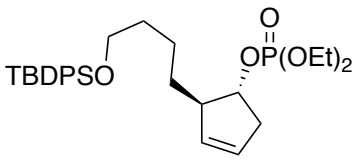
The product was derivatised according to general procedure 2 for HPLC analysis.

HPLC analysis indicated an enantiomeric excess of 90% [Chiralpak® IC; flow: 0.8 mL/min; hexane/iPrOH: 98:2; λ = 210 nm; major enantiomer, t_R = 22.900 min ; minor enantiomer, t_R = 25.200 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 5.69 – 5.62 (m, 1H, CH-(4)), 5.55 – 5.48 (m, 1H, CH-(5)), 4.33 (dtd, *J* = 9.3, 6.7, 2.9 Hz, 1H, CH-(1)), 4.10 (pd, *J* = 7.1, 3.2 Hz, 4H, 2CH_2-(14)), 3.40 (t, *J* = 6.8 Hz, 2H, CH_2-(13)), 2.29 – 2.21 (m, 1H, CH-(6)), 2.21 – 2.12 (m, 1H, C***H***H′-(3)), 2.12 – 2.05 (m, 1H, CH***H′***-(3)), 2.05 – 1.98 (m, 1H, C***H***H′-(2)), 1.89 – 1.75 (m, 3H, CH***H′***-(2), CH_2-(12)), 1.60 – 1.22 (m, 10H, 5CH_2-(7, 8, 9, 10, 11)), 1.33 (td, *J* = 7.1, 1.0 Hz, 6H, 2CH_3-(15)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 128.2 (C(5)), 126.4 (C(4)), 78.3 (C(1)), 63.7 (C(14)), 41.7 (C(6)), 34.1 (C(13)), 32.9 (C(7)), 32.7 (C(8-12)), 29.8 (C(8-12)), 28.8 (C(8-12)), 28.3 (C(8-12)), 27.7 (C(2)), 26.3 (C(8-12)), 23.3 (C(3)), 16.3 (C(15)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.47; HRMS (ESI) *m/z* calcd for $C_{17}H_{32}O_4{}^{79}BrNaP$ $[M+Na]^+$: 433.11138, found: 433.11094; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2930.2 (w), 2856.3 (w), 1442.1 (w), 1262.7 (w), 1166.2 (w), 1034.6 (s), 1011.8 (s), 817.8 (w), 725.9 (w); $[\alpha]^{25}{}_{589}$ = -44.0 (c=1.0 in $CHCl_3$, 90% ee).

(1*R*,2*R*)-2-(4-((*tert*-butyldiphenylsilyl)oxy)butyl)cyclopent-3-en-1-yl diethyl phosphate (1k)

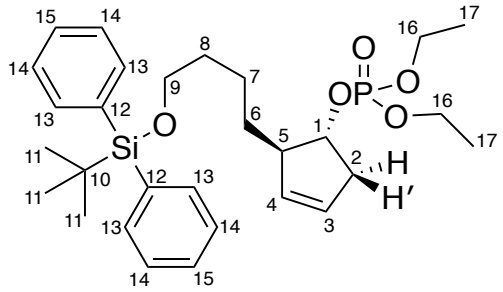


1k

Chemical Formula: $C_{29}H_{43}O_5PSi$
Molecular Weight: 530.7168

Synthesised according to general procedure 1b, using *meso*-4-cyclopentene-1,3-bisdiethylphosphate (**1a**) and (but-3-en-1-yloxy)(*tert*-butyl)diphenylsilane as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (15-40% EtOAc in petroleum ether) to give **1k** as a yellow oil (109 mg, 51%).

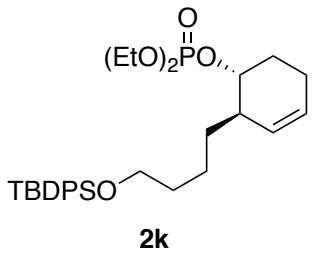
HPLC analysis indicated an enantiomeric excess of 89% [Chiralpak® ID; flow: 1.0 mL/min; hexane/iPrOH: 97:3; λ = 210 nm; major enantiomer, t_R = 21.054 min; minor enantiomer, t_R = 24.276 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.70 – 7.63 (m, 4H, ArH-(14)), 7.46 – 7.34 (m, 6H, ArH-(13, 15)), 5.71 – 5.61 (m, 2H, 2CH-(3, 4)), 4.65 (tt, *J* = 6.4, 2.9 Hz, 1H, CH-(1)), 4.09 (p, *J* = 7.1 Hz, 4H, 2CH_2-(16)), 3.65 (t, *J* = 6.5 Hz, 2H, CH_2-(9)), 2.80 – 2.70 (m, 2H, C***H***H′-(2), CH-(5)), 2.54 – 2.46 (m, 1H, CH***H′***-(2)), 1.64 – 1.51 (m, 2H, CH_2-(6)), 1.48 – 1.26 (m, 4H, 2CH_2-(7, 8)), 1.32 (tdd, *J* = 7.1, 2.8, 1.0 Hz, 6H, 2CH_3-(17)), 1.04 (s, 9H, 3CH_3-(11)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 135.7 (C(12)), 134.2 (C(15)), 132.7 (C(4)), 128.7 (C(13)), 127.7

(C(14)), 127.3 (C(3)), 83.2 (C(1)), 63.9 (C(9)), 63.7 (C(16)), 53.1 (C(5)), 39.9 (C(2)), 32.8 (C(8)), 32.7 (C(6)), 27.0 (C(11)), 23.8 (C(7)), 19.4 (C(10)), 16.3 (C(17)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.47; HRMS (ESI) *m/z* calcd for $C_{29}H_{43}O_5NaPSi$ $[M+Na]^+$: 553.25096, found: 553.25022; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 3069.8 (w), 2931.9 (w), 2857.9 (w), 1473.0 (w), 1428.4 (w), 1391.0 (w), 1361.8 (w), 1263.5 (w), 1166.1 (w), 1110.4 (m), 1031.7 (s), 977.2 (m), 822.8 (w), 741.3 (w), 703.6 (m), 613.9 (w); $[\alpha]^{25}_{589}$ = -46.2 (c=1.0 in $CHCl_3$, 89% ee).

(1*R*,2*R*)-2-(4-((*tert*-butyldiphenylsilyl)oxy)butyl)cyclohex-3-en-1-yl diethyl phosphate (2k)

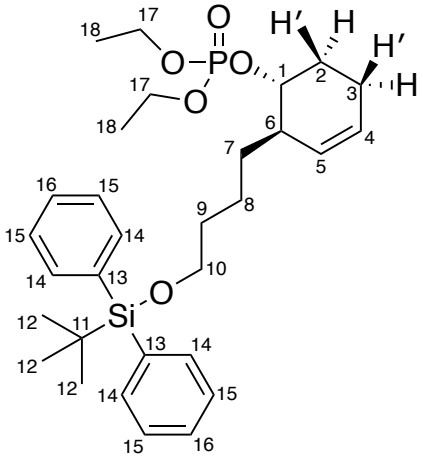


2k

Chemical Formula: $C_{30}H_{45}O_5PSi$
Molecular Weight: 544.7438

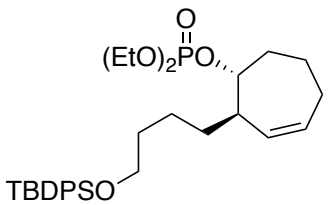
Synthesised according to general procedure 1b, using *meso*-5-cyclohexene-1,4-bisdiethylphosphate (**2a**) and (but-3-en-1-yloxy)(*tert*-butyl)diphenylsilane as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (15-40% EtOAc in petroleum ether) to give **2k** as a yellow oil (139 mg, 64%).

HPLC analysis indicated an enantiomeric excess of 92% [Chiralpak® IC; flow: 0.8 mL/min; hexane/iPrOH: 96:4; λ = 210 nm; major enantiomer, t_R = 18.135 min; minor enantiomer, t_R = 19.126 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.69 – 7.64 (m, 4H, ArH-(15)), 7.45 – 7.34 (m, 6H, ArH-(14, 16)), 5.69 – 5.63 (m, 1H, CH-(4)), 5.55 – 5.49 (m, 1H, CH-(5)), 4.32 (dtd, *J* = 9.1, 6.6, 2.8 Hz, 1H, CH-(1)), 4.09 (pd, *J* = 7.2, 2.2 Hz, 4H, $2CH_2$-(17)), 3.40 (t, *J* = 6.8 Hz, 2H, CH_2-(10)), 2.28 – 2.20 (m, 1H, CH-(6)), 2.20 – 2.13 (m, 1H, C***H***H´-(3)), 2.13 – 2.05 (m, 1H, CH***H´***-(3)), 2.05 – 1.98 (m, 1H, C***H***H´-(2)), 1.87 – 1.76 (m, 1H, CH***H´***-(2)), 1.65 – 1.24 (m, 6H, $3CH_2$-(7, 8, 9)), 1.31 (qd, *J* = 7.1, 1.0 Hz, 6H, $2CH_3$-(18)), 1.04 (s, 9H, $3CH_3$-(12)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 135.7 (C(13)), 134.2 (C(16)), 129.6 (C(14)), 128.0 (C(5)), 127.7 (C(15)), 126.4 (C(4)), 78.4 (C(1)), 63.9 (C(10)), 63.7 (C(17)), 41.8 (C(6)), 32.9 (C(9)), 32.5 (C(7)), 27.7 (C(2)), 27.0 (C(12)), 23.3 (C(3)), 22.7 (C(8)), 19.4 (C(11)), 16.3 (C(18)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.49; HRMS (ESI) *m/z* calcd for $C_{30}H_{45}O_5NaPSi$ $[M+Na]^+$: 567.26661, found: 567.26490; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 3069.8 (w), 2931.9 (w), 2857.9 (w), 1473.0 (w), 1428.4 (w), 1391.0 (w), 1361.8 (w), 1263.5 (w), 1166.1 (w), 1110.4 (m), 1031.7 (s), 977.2 (m), 822.8 (w), 741.3 (w), 703.6 (m), 613.9 (w); $[\alpha]^{25}_{589}$ = -43.3 (c=1.0 in $CHCl_3$, 95% ee).

(1*R*,2*R*)-2-(4-((*tert*-butyldiphenylsilyl)oxy)butyl)cyclohept-3-en-1-yl diethyl phosphate (3k)

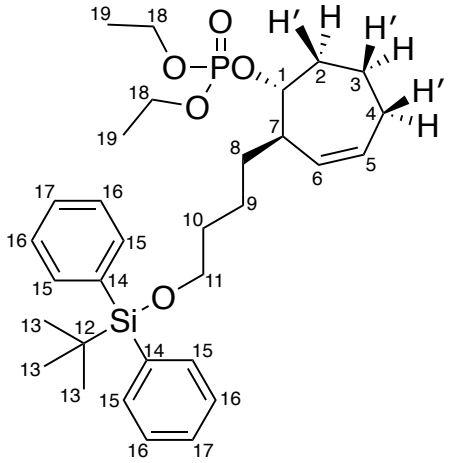


3k

Chemical Formula: $C_{31}H_{47}O_5PSi$
Molecular Weight: 558.7708

Synthesised according to general procedure 1b, using *meso*-6-cycloheptene-1,5-bisdiethylphosphate (**3a**) and (but-3-en-1-yloxy)(*tert*-butyl)diphenylsilane as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (20-40% EtOAc in petroleum ether) to give **3k** as a yellow oil (134 mg, 60%).

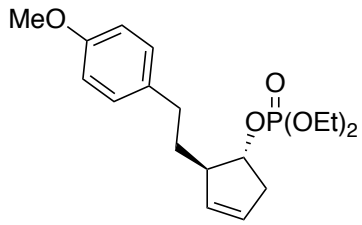
HPLC analysis indicated an enantiomeric excess of 91% [Chiralpak® IC; flow: 1.0 mL/min; hexane/iPrOH: 96:4; λ = 210 nm; major enantiomer, t_R = 15.451 min; minor enantiomer, t_R = 16.874 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.69 – 7.63 (m, 4H, ArH-(16)), 7.45 – 7.33 (m, 3H, ArH-(15, 17)), 5.84 (dtd, *J* = 11.2, 6.2, 1.5 Hz, 1H, CH-(5)), 5.41 (dd, *J* = 11.2, 5.3 Hz, 1H, CH-

(6)), 4.25 (qd, *J* = 7.9, 3.1 Hz, 1H, CH-(1)), 4.08 (p, *J* = 7.1 Hz, 4H, 2CH_2-(18)), 3.65 (t, *J* = 6.4 Hz, 2H, CH_2-(11)), 2.58 – 2.48 (m, 1H, CH-(7)), 2.24 – 2.16 (m, 1H, C***H***H′-(2)), 2.09 (q, *J* = 5.9 Hz, 2H, C***HH′***-(4)), 1.99 – 1.88 (m, 1H, CH***H′***-(2)), 1.79 – 1.69 (m, 1H, C***H***H′-(3)), 1.64 – 1.21 (m, 6H, 3CH_2-(8, 9, 10)), 1.31 (qd, *J* = 7.1, 1.0 Hz, 6H, 2CH_3-(19)), 1.04 (s, 9H, 3CH_3-(13)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 135.7 (C(14)), 134.2 (C(17)), 133.0 (C(5)), 131.4 (C(6)), 129.6 (C(15)), 127.7 (C(16)), 79.5 (C(1)), 64.0 (C(11)), 63.6 (C(18)), 44.6 (C(7)), 36.3 (C(2)), 32.9 (C(10)), 31.6 (C(8)), 28.1 (C(4)), 27.00 (C(13)), 23.2 (C(9)), 23.0 (C(3)), 19.4 (C(12)), 16.3 (C(19)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.76; HRMS (ESI) *m/z* calcd for $C_{31}H_{47}O_5NaPSi$ $[M+Na]^+$: 581.28226, found: 581.28170; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2931.3 (w), 2858.4 (w), 1472.9 (w), 1428.3 (w), 1390.6 (w), 1261.5 (m), 1166.0 (w), 1110.1 (m), 1033.5 (s), 998.1 (s), 822.4 (w), 741.6 (w), 703.1 (m), 613.6 (w); $[\alpha]^{25}_{589}$ = -20.7 (c=1.0 in $CHCl_3$, 91% ee).

Diethyl ((1*R*,2*R*)-2-(4-methoxyphenethyl)cyclopent-3-en-1-yl) phosphate (1l)

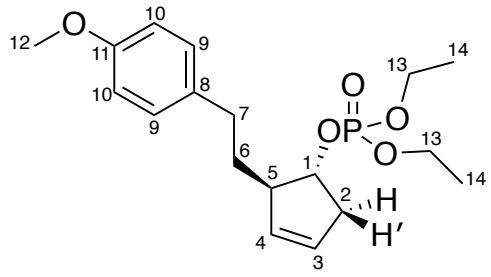


1l

Chemical Formula: $C_{18}H_{27}O_5P$
Molecular Weight: 354.3828

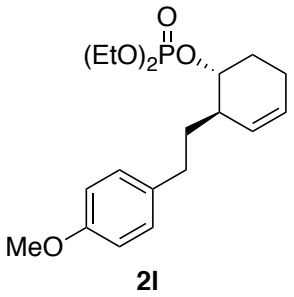
Synthesised according to general procedure 1b, using *meso*-4-cyclopentene-1,3-bisdiethylphosphate (**1a**) and 4-methoxystyrene as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (25-50% EtOAc in petroleum ether) to give **1l** as a yellow oil (99 mg, 70%). **NOTE**: Compound unstable in air and should be stored under an Ar atmosphere in a freezer.

HPLC analysis indicated an enantiomeric excess of 91% [Chiralpak® ID; flow: 1.0 mL/min; hexane/iPrOH: 90:10; λ = 210 nm; major enantiomer, t_R = 22.170 min; minor enantiomer, t_R = 24.908 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.10 (d, *J* = 8.7 Hz, 2H, ArH-(10)), 6.81 (d, *J* = 8.7 Hz, 2H, ArH-(9)), 5.74 – 5.69 (m, 1H, CH-(4)), 5.69 – 5.65 (m, 1H, CH-(3)), 4.74 (tt, *J* = 6.4, 3.0 Hz, 1H, CH-(1)), 4.09 (pd, *J* = 7.4, 3.2 Hz, 4H, $2CH_2$-(13)), 3.78 (s, 3H, CH_3-(12)), 2.85 – 2.74 (m, 2H, C***H***H′-(2), CH-(5)), 2.63 (t, *J* = 7.4 Hz, 2H, CH_2-(7)), 2.56 – 2.47 (m, 1H, CH***H′***-(2)), 1.78 – 1.54 (m, 2H, CHH′-(6)), 1.32 (tdd, *J* = 7.1, 2.6, 1.0 Hz, 6H, $2CH_3$-(14)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 157.9 (C(11)), 134.2 (C(9)), 132.5 (C(4)), 129.4 (C(10)), 127.6 (C(3)), 113.9 (C(8)), 83.1 (C(1)), 63.7 (C(13)), 55.4 (C(12)), 52.6 (C(5)), 39.9 (C(2)), 34.9 (C(7)), 32.9 (C(6)), 16.3 (C(14)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.44; HRMS (ESI) *m/z* calcd for $C_{18}H_{27}O_5NaP$ $[M+Na]^+$: 377.14883, found: 377.14877; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 3058.8 (w), 2931.8 (w), 2853.3 (w), 1612.0 (w), 1512.7 (m), 1456.3 (w), 1246.7 (m), 1178.1 (w), 1031.4 (s), 977.9 (m), 821.2 (w), 752.5 (w); $[\alpha]^{25}_{589}$ = -62.8 (c=1.0 in $CHCl_3$, 91% ee).

Diethyl ((1*R*,2*R*)-2-(4-methoxyphenethyl)cyclohex-3-en-1-yl) phosphate (2l)

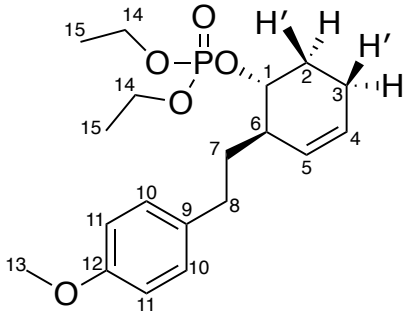


2l

Chemical Formula: $C_{19}H_{29}O_5P$
Molecular Weight: 368.4098

Synthesised according to general procedure 1b, using *meso*-5-cyclohexene-1,4-bisdiethylphosphate (**2a**) and 4-methoxystyrene as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (25-50% EtOAc in petroleum ether) to give **2l** as a yellow oil (103 mg, 70%). **NOTE**: Compound unstable in air and should be stored under an Ar atmosphere in a freezer.

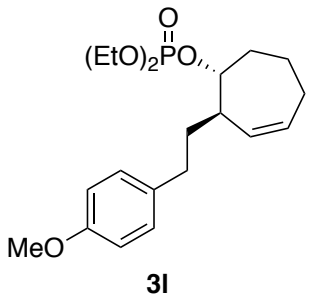
SFC analysis indicated an enantiomeric excess of 99% [Chiralpak® IG; flow: 1.5 mL/min; MeOH/CO_2: 1% to 30%; λ = 210 nm; major enantiomer, t_R = 3.393 min; minor enantiomer, t_R = 3.462 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.11 (d, *J* = 8.6 Hz, 2H, ArH-(11)), 6.81 (d, *J* = 8.6 Hz, 2H, ArH-(10)), 5.73 – 5.67 (m, 1H, CH-(4)), 5.57 (dd, *J* = 10.0, 1.8 Hz, 1H, CH-(5)), 4.40 (dtd, *J* = 9.3, 6.7, 2.9 Hz, 1H, CH-(1)), 4.08 (pd, *J* = 7.2, 2.2 Hz, 4H, 2CH_2-(14)), 3.77 (s, 3H, CH_2-(13)), 2.70 (ddd, *J* = 13.8, 10.6, 5.5 Hz, 1H, CHH′-(8)), 2.55 (ddd, *J* = 13.8, 10.4, 6.1 Hz, 1H,

CHH′-(8)), 2.36 – 2.27 (m, 1H, CH-(6)), 2.27 – 2.16 (m, 1H, C***H***H′-(3)), 2.16 – 2.07 (m, 1H, CH***H′***-(3)), 2.07 – 2.01 (m, 1H, C***H***H′-(2)), 1.89 – 1.77 (m, 2H, CH***H′***-(2) CHH′-(7)), 1.68 – 1.57 (m, 1H, CHH′-(7)), 1.31 (qd, J = 7.1, 1.0 Hz, 6H, 2CH_3-(15)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 157.8 (C(12)), 134.4 (C(10)), 129.3 (C(11)), 127.8 (C(5)), 126.8 (C(4)) 113.9 (C(9)), 78.4 (C(1)), 63.7 (C(14)), 55.4 (C(13)), 41.3 (C(6)), 34.8 (C(8)), 31.6 (C(7)), 27.8 (C(2)), 23.4 (C(3)), 16.3 (C(18)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.44; HRMS (ESI) *m/z* calcd for $C_{19}H_{29}O_5NaP$ $[M+Na]^+$: 391.16448, found: 391.16517; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 3649.5 (w), 2980.7 (m), 1612.1 (w), 1512.6 (m), 1457.5 (w), 1392.8 (w), 1247.5 (m), 1176.5 (w), 1032.5 (s), 972.5 (m), 818.1 (w), 726.4 (w); $[\alpha]^{25}_{589}$ = -55.9 (c=1.0 in $CHCl_3$, 97% ee).

Diethyl ((1*R*,2*R*)-2-(4-methoxyphenethyl)cyclohept-3-en-1-yl) phosphate (3l)

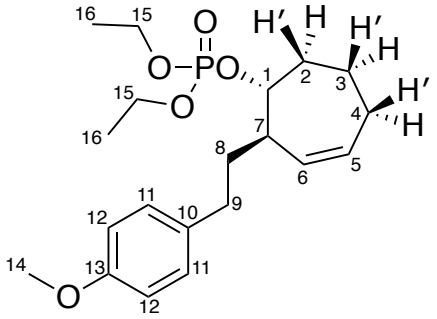


3l

Chemical Formula: $C_{20}H_{31}O_5P$
Molecular Weight: 382.4368

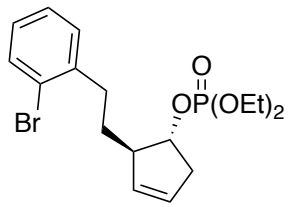
Synthesised according to general procedure 1b, using *meso*-6-cycloheptene-1,5-bisdiethylphosphate (**3a**) and 4-methoxystyrene as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (25-50% EtOAc in petroleum ether) to give **3l** as a yellow oil (80 mg, 52%). **NOTE**: Compound unstable in air and should be stored under an Ar atmosphere in a freezer.

HPLC analysis indicated an enantiomeric excess of 94% [Chiralpak® IA; flow: 1.0 mL/min; hexane/iPrOH: 93:7; λ = 210 nm; major enantiomer, t_R = 11.108 min; minor enantiomer, t_R = 11.960 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.10 (d, *J* = 6.1 Hz, 2H, ArH-(12)), 6.81 (d, *J* = 8.7 Hz, 2H, ArH-(11)), 5.91 (dtd, *J* = 11.2, 6.23, 1.5 Hz, 1H, CH-(5)), 5.52 (dd, *J* = 11.2, 5.3 Hz, 1H, CH-(6)), 4.31 (qd, *J* = 7.9, 3.0 Hz, 1H, CH-(1)), 4.11 – 4.02 (m, 4H, 2CH_2-(15)), 3.78 (s, 3H, CH_3-(14)), 2.71 (ddd, *J* = 13.8, 10.7, 4.9 Hz, 1H, CHH′-(9)), 2.63 – 2.55 (m, 1H, CH-(7)), 2.50 (ddd, *J* = 13.8, 10.4, 6.4 Hz, 1H, CHH′-(9)), 2.24 – 2.17 (m, 1H, C***H***H′-(2)), 2.11 (q, *J* = 5.6 Hz, 2H, C***HH′***-(4)), 1.98 – 1.84 (m, 2H, CH***H′***-(2), CHH′-(8)), 1.78 – 1.66 (m, 2H, C***H***H′-(3), CHH′-(8)), 1.55 – 1.42 (m, 1H, CH***H′***-(3)), 1.30 (dtd, *J* = 10.9, 7.1, 1.0 Hz, 6H, 2CH_3-(16)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 157.8 (C(13)), 134.5 (C(12)), 133.4 (C(5)), 131.1 (C(6)), 129.4 (C(11)), 113.8 (C(10)), 79.2 (C(1)), 63.6 (C(15)), 55.4 (C(14)), 44.0 (C(7)), 36.4 (C(2)), 34.0 (C(9)), 32.2 (C(8)), 28.1 (C(4)), 23.0 (C(3)), 16.3 (C(16)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.73; HRMS (ESI) *m/z* calcd for $C_{20}H_{31}O_5NaP$ $[M+Na]^+$: 405.18013, found: 405.17959; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2932.2 (w), 1612.0 (w), 1512.6 (m), 1444.4 (w), 1392.8 (w), 1246.9 (m), 1177.9 (w), 1032.7 (s), 998.9 (s), 819.5 (w), 700.5 (w); $[\alpha]^{25}_{589}$ = -34.3 (c=1.0 in $CHCl_3$, 94% ee).

(1*R*,2*R*)-2-(2-bromophenethyl)cyclopent-3-en-1-yl diethyl phosphate (1m)

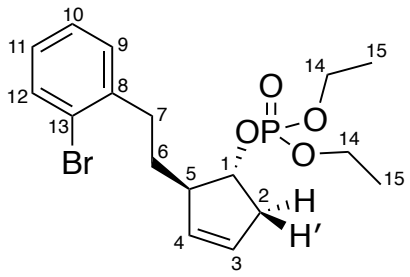


1m

Chemical Formula: $C_{17}H_{24}BrO_4P$
Molecular Weight: 403.2528

Synthesised according to general procedure 1b, using *meso*-4-cyclopentene-1,3-bisdiethylphosphate (**1a**) and 2-bromostyrene as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (25-50% EtOAc in petroleum ether) to give **1m** as a yellow oil (85 mg, 53%).

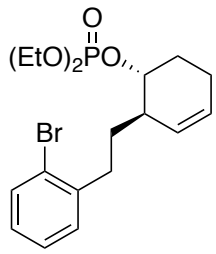
HPLC analysis indicated an enantiomeric excess of 83% [Chiralpak® ID; flow: 1.0 mL/min; hexane/iPrOH: 90:10; λ = 210 nm; major enantiomer, t_R = 17.193 min; minor enantiomer, t_R = 18.143 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.56 – 7.50 (m, 1H, ArH-(12)), 7.28 – 7.21 (m, 2H, ArH-(9, 10)), 7.10 – 7.05 (m, 1H, ArH-(11)), 5.78 (d, *J* = 6.0, 1.9 Hz, 1H, CH-(4)), 5.73 (d, *J* = 6.0, 2.0 Hz, 1H, CH-(3)), 4.82 (tt, *J* = 6.5, 3.1 Hz, 1H, CH-(1)), 4.09 (pd, *J* = 7.1, 3.2 Hz, 4H, $2CH_2$-(14)), 2.94 – 2.74 (m, 4H, C***H***H′-(2), CH-(5), CH_2-(7)), 2.57 (dd, *J* = 17.5, 2.0 Hz, 1H, CH***H′***-(2)), 1.82 – 1.59 (m, 2H, CHH′-(6)), 1.36 (tt, *J* = 7.1, 0.8 Hz, 6H, $2CH_3$-(15)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 141.4 (C(8)), 132.9 (C(4)), 132.3 (C(12)), 130.5 (C(10)), 127.9 (C(3)),

127.8 (C(9)), 127.6 (C(11)), 124.4 (C(13)), 82.9 (C(1)), 63.8 (C(14)), 52.9 (C(5)), 40.0 (C(2)), 34.2 (C(7)), 33.0 (C(6)), 16.3 (C(15)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.48; HRMS (ESI) *m/z* calcd for $C_{17}H_{24}O_4{}^{79}BrNaP$ $[M+Na]^+$: 425.04878, found: 425.04845; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 3649.2 (w), 3059.2 (w), 2980.7 (m), 1471.8 (w), 1440.7 (w), 1392.4 (w), 1263.4 (m), 1164.2 (w), 1027.2 (s), 970.6 (m), 821.2 (w), 753.1 (w), 658.2 (w); $[\alpha]^{25}{}_{589}$ = -66.9 (c=1.0 in $CHCl_3$, 83% ee).

(1*R*,2*R*)-2-(2-bromophenethyl)cyclohex-3-en-1-yl diethyl phosphate (2m)

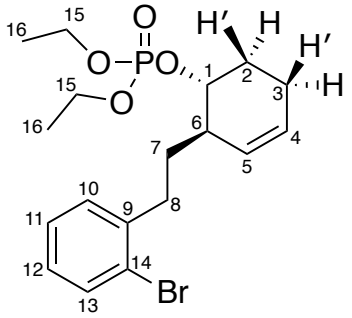


2m

Chemical Formula: $C_{18}H_{26}BrO_4P$
Molecular Weight: 417.2798

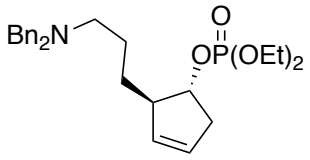
Synthesised according to general procedure 1b, using *meso*5-cyclohexene-1,4-bisdiethylphosphate (**2a**) and 2-bromostyrene as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (25-50% EtOAc in petroleum ether) to give **2m** as a yellow oil (102 mg, 61%).

HPLC analysis indicated an enantiomeric excess of 91% [Chiralpak® IA; flow: 0.7 mL/min; hexane/iPrOH: 99:1; λ = 210 nm; major enantiomer, t_R = 45.337 min; minor enantiomer, t_R = 54.833 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.50 (dd, *J* = 8.0, 1.2 Hz, 1H, ArH-(13)), 7.28 – 7.18 (m, 2H, ArH-(10, 11)), 7.08 – 7.00 (m, 1H, ArH-(12)), 5.77 – 5.67 (m, 1H, CH-(4)), 5.67 – 5.62 (m, 1H, CH-(5)), 4.42 (dtd, *J* = 9.7, 7.0, 3.0 Hz, 1H, CH-(1)), 4.15 – 4.05 (m, 4H, $2CH_2$-(15)), 2.85 (ddd, *J* = 13.6, 11.2, 5.4 Hz, 1H, CHH′-(8)), 2.75 (ddd, *J* = 13.6, 10.9, 5.6 Hz, 1H, CHH′-(8)), 2.41 – 2.31 (m, 1H, CH-(6)), 2.26 – 2.16 (m, 1H, C***H***H′-(3)), 2.16 – 2.09 (m, 1H, CH***H′***-(3)), 2.09 – 2.03 (m, 1H, C***H***H′-(2)), 1.96 – 1.78 (m, 2H, CH***H′***-(2) CHH′-(7)), 1.69 – 1.55 (m, 1H, CHH′-(7)), 1.31 (qd, *J* = 7.0, 1.0 Hz, 6H, $2CH_3$-(16)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 141.7 (C(9)), 132.9 (C(13)), 130.5 (C(11)), 127.7 (C(5)), 127.6 (C(10)), 127.6 (C(12)), 126.9 (C(4)) 124.5 (C(14)), 78.0 (C(1)), 63.7 (C(15)), 41.7 (C(6)), 33.0 (C(8)), 32.8 (C(7)), 27.8 (C(2)), 23.5 (C(3)), 16.3 (C(16)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.49; HRMS (ESI) *m/z* calcd for $C_{18}H_{26}O_4{}^{79}BrNaP$ $[M+Na]^+$: 439.06443, found: 439.06403; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2983.7 (w), 2932.2 (w), 1472.0 (w), 1439.0 (w), 1262.8 (m), 1165.5 (w), 1023.1 (s), 979.7 (m), 818.1 (w), 752.3 (w); $[\alpha]^{25}{}_{589}$ = -44.4 (c=1.0 in $CHCl_3$, 91% ee).

(1*R*,2*R*)-2-(3-(dibenzylamino)propyl)cyclopent-3-en-1-yl diethyl phosphate (1n)

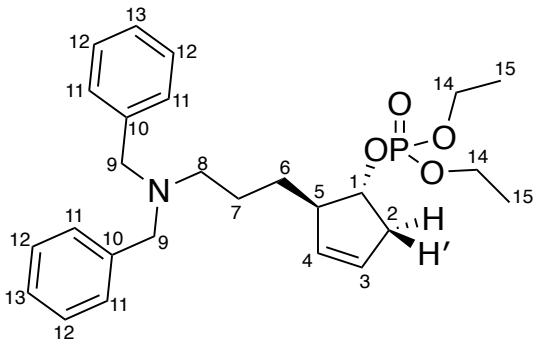


1n

Chemical Formula: $C_{26}H_{36}NO_4P$
Molecular Weight: 457.5508

Synthesised according to general procedure 1b, using *meso*-4-cyclopentene-1,3-bisdiethylphosphate (**1a**) and *N*,*N*-dibenzylprop-2-en-1-amine as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (15-40% EtOAc in petroleum ether (with 1% NEt_3)) to give **1n** as a yellow oil (175 mg, 89%).

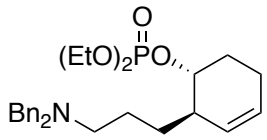
HPLC analysis indicated an enantiomeric excess of 37% [Chiralpak® IA; flow: 0.8 mL/min; hexane/iPrOH: 95:5; λ = 210 nm; major enantiomer, t_R = 13.181 min; minor enantiomer, t_R = 15.096 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.39 – 7.28 (m, 8H, ArH-(11, 12)), 7.25 – 7.20 (m, 2H, ArH-(13)), 5.64 (s, 2H, 2CH-(3, 4)), 4.64 (tt, *J* = 6.5, 3.0 Hz, 1H, CH-(1)), 4.08 (pd, *J* = 7.1 Hz, 1.8 Hz, 4H, $2CH_2$-(14)), 3.55 (s, 4H, $2CH_2$-(9)), 2.79 – 2.69 (m, 2H, C***H***H′-(2), CH-(5)), 2.49 (dd, *J* = 16.4, 3.0 Hz, 1H, CH***H′***-(2)), 2.43 (td, *J* = 7.6, 2.3 Hz, 2H, $2CH_2$-(8)), 1.66 – 1.50 (m, 2H, CH_2-(6)), 1.47 – 1.29 (m, 2H, CH_2-(7)), 1.32 (tdd, *J* = 7.1, 3.9, 1.0 Hz, 6H, $2CH_3$-(15)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 140.0 (C(10)), 132.7 (C(4)), 128.8 (C(11)), 128.2 (C(12)), 127.3 (C(3)), 126.8 (C(13)), 83.1 (C(1)), 63.6 (C(14)), 58.4 (C(9)), 53.6 (C(8)), 52.9

(C(5)), 39.9 (C(2)), 30.3 (C(6)), 25.0 (C(7)), 16.2 (C(15)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.46; HRMS (ESI) *m/z* calcd for $C_{26}H_{37}O_4NP$ $[M+H]^+$: 458.24547, found: 458.24541; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 3060.7 (w), 2980.7 (w), 2795.9 (w), 2341.6 (w), 1601.9 (w), 1494.2 (w), 1453.2 (w), 1369.4 (w), 1262.0 (m), 1165.2 (w), 1128.7 (w), 1027.9 (s), 972.2 (m), 820.7 (w), 745.6 (w), 699.0 (m), 668.3 (w); $[\alpha]^{25}_{589}$ = -24.8 (c=1.0 in $CHCl_3$, 37% ee).

(1*R*,2*R*)-2-(3-(dibenzylamino)propyl)cyclohex-3-en-1-yl diethyl phosphate (2n)

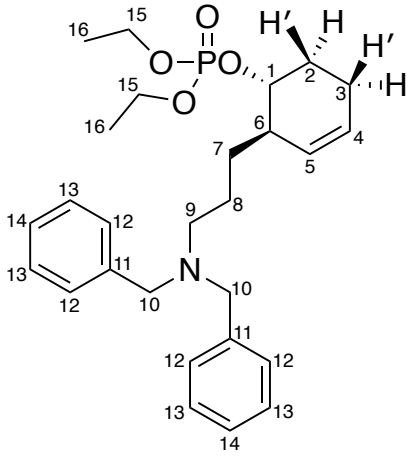


2n

Chemical Formula: $C_{27}H_{38}NO_4P$
Molecular Weight: 471.5778

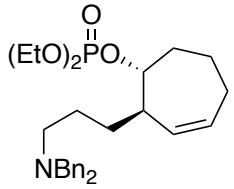
Synthesised according to general procedure 1b, using *meso*-5-cyclohexene-1,4-bisdiethylphosphate (**3**) and *N*,*N*-dibenzylprop-2-en-1-amine as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (15-40% EtOAc in petroleum ether (with 1% NEt_3)) to give **2n** as a yellow oil (156 mg, 83%).

SFC analysis indicated an enantiomeric excess of 86% [Chiralpak® IG; flow: 2.0 mL/min; CO_2/MeOH: 92:8; λ = 210 nm; major enantiomer, t_R = 2.715 min; minor enantiomer, t_R = 2.995 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.39 – 7.28 (m, 8H, ArH-(12, 13)), 7.27 – 7.18 (m, 2H, ArH-(14)), 5.68 – 5.61 (m, 1H, CH-(4)), 5.47 (dd, *J* = 10.0, 2.0 Hz, 1H, CH-(5)), 4.32 (dtd, *J* = 9.4, 6.7, 2.9 Hz, 1H, CH-(1)), 4.14 – 3.99 (m, 4H, 2CH_2-(15)), 3.43 (t, *J* = 6.9 Hz, 2H, CH_2-(10)), 2.27 – 2.19 (m, 1H, CH-(6)), 2.19 – 2.12 (m, 1H, C***H***H′-(3)), 2.12 – 2.05 (m, 1H, CH***H′***-(3)), 2.05 – 1.99 (m, 1H, C***H***H′-(2)), 1.86 – 1.75 (m, 1H, CH***H′***-(2), 1.72 – 1.60 (m, 1H, CHH′-(7)), 1.60 – 1.48 (m, 2H, 2CHH′, (7, 8)), 1.37 – 1.31 (m, 1H, CHH′ (8)), 1.30 (dtd, *J* = 18.0, 7.1, 1.0 Hz, 6H, 2CH_3-(16)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 140.0 (C(11)), 128.8 (C(12)), 128.2 (C(13)), 128.0 (C(5)), 126.8 (C(14)), 126.4 (C(4)), 78.2 (C(1)), 63.6 (C(15)), 58.4 (C(10)), 53.7 (C(9)), 41.6 (C(6)), 30.2 (C(7)), 27.7 (C(2)), 23.7 (C(8)), 23.3 (C(3)), 16.3 (C(16)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.46; HRMS (ESI) *m/z* calcd for $C_{27}H_{39}O_4NP$ $[M+H]^+$: 472.26112, found: 472.26042; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 3026.2 (w), 2933.6 (w), 2794.8 (w), 1601.7 (w), 1494.3 (w), 1453.1 (w), 1392.7 (w), 1262.1 (m), 1166.7 (w), 1101.4 (w), 1029.9 (s), 1011.6 (s), 976.5 (m), 817.8 (w), 746.5 (m), 698.9 (m), 624.1 (w); $[\alpha]^{25}_{589}$ = -34.3 (c=1.0 in $CHCl_3$, 86% ee).

(1*R*,2*R*)-2-(3-(dibenzylamino)propyl)cyclohept-3-en-1-yl diethyl phosphate (3n)

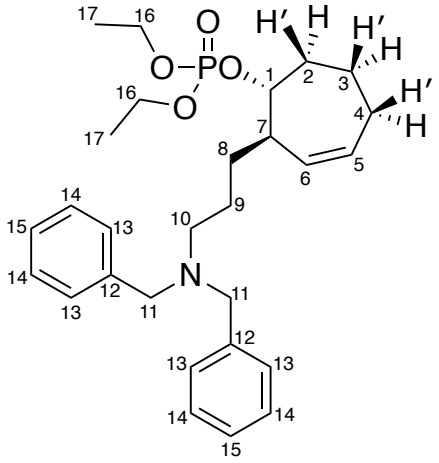


3n

Chemical Formula: $C_{28}H_{40}NO_4P$
Molecular Weight: 485.6048

Synthesised according to general procedure 1b, using *meso*-6-cycloheptene-1,5-bisdiethylphosphate (**4**) and *N*,*N*-dibenzylprop-2-en-1-amine as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (15-40% EtOAc in petroleum ether (with 1% NEt_3)) to give **3n** as a yellow oil (37 mg, 19%).

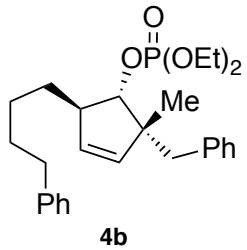
HPLC analysis indicated an enantiomeric excess of 67% [Chiralpak® IA; flow: 0.8 mL/min; hexane/iPrOH: 98:2; λ = 210 nm; major enantiomer, t_R = 34.755 min; minor enantiomer, t_R = 38.765 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.40 – 7.27 (m, 8H, ArH-(13, 14)), 7.25 – 7.19 (m, 2H, ArH-(15)), 5.84 (dtd, *J* = 11.2, 6.3, 1.6 Hz, 1H, CH-(5)), 5.37 (dd, *J* = 11.2, 5.4 Hz, 1H, CH-(6)), 4.23 (qd, *J* = 8.1, 3.1 Hz, 1H, CH-(1)), 4.11 – 3.99 (m, *J* = 7.1 Hz, 4H, $2CH_2$-(18)), 3.54 (q, *J* = 13.6, 7.6 Hz, 2H, CH_2-(11)), 2.53 – 2.44 (m, 1H, CH-(7)), 2.41 (t, *J* = 6.8 Hz, 2H, CH_2-(10)), 2.25 – 2.16 (m, 1H, C***H***H´-(2)), 2.06 (q, *J* = 6.1 Hz, 2H, C***HH´***-(4)), 1.96 – 1.85 (m, 1H,

CH***H´***-(2)), 1.78 – 1.68 (m, 1H, C***H***H´-(3)), 1.74 – 1.26 (m, 5H, CH***H´***- (3), $2CH_2$ (8, 9)), 1.29 (dtd, *J* = 15.3, 7.1, 1.0 Hz, 6H, $2CH_3$-(17)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 140.0 (C(12)), 133.2 (C(5)), 131.4 (C(6)), 128.9 (C(13)), 128.3 (C(14)), 126.9 (C(15)) 79.4 (C(1)), 63.6 (C(16)), 58.6 (C(11)), 53.6 (C(10)), 44.3 (C(7)), 36.5 (C(2)), 29.5 (C8)), 28.0 (C(4)), 24.3 (C(9)), 23.1 (C(3)), 16.3 (C(17)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.74; HRMS (ESI) *m/z* calcd for $C_{28}H_{41}O_4NP$ $[M+H]^+$: 486.27677, found: 486.27567; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2931.0 (w), 2794.6 (w), 1494.2 (w), 1452.7 (w), 1368.3 (w), 1260.5 (m), 1165.8 (w), 1031.2 (s), 997.9 (s), 818.2 (w), 745.8 (w), 699.1 (m); $[\alpha]^{25}_{589}$ = -21.6 (c=1.0 in $CHCl_3$, 67% ee).

(1*S*,2*R*,5*R*)-2-benzyl-2-methyl-5-(4-phenylbutyl)cyclopent-3-en-1-yl diethyl phosphate (4b)

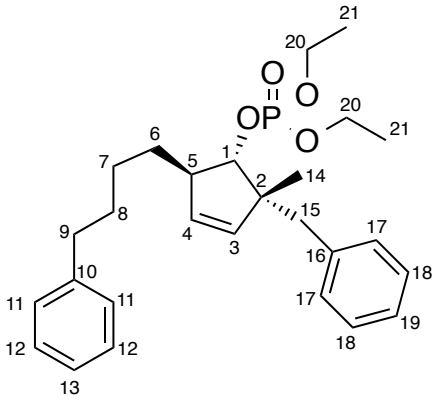


4b

Chemical Formula: $C_{27}H_{37}O_4P$
Molecular Weight: 456.5628

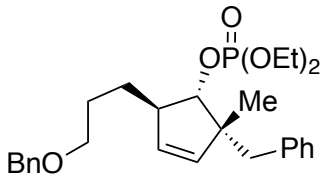
Synthesised according to general procedure 1c, using (1*R*,2*S*,3*S*)-2-benzyl-2-methylcyclopent-4-ene-1,3-bis(diethyl phosphate) (**4a**) and 4-phenyl-1-butene as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (10-20-30% EtOAc in petroleum ether) to give **4b** as a yellow oil (127 mg, 70%).

HPLC analysis indicated an enantiomeric excess of 94% [Chiralpak® IC; flow: 1.0 mL/min; hexane/iPrOH: 95:5; λ = 210 nm; major enantiomer, t_R = 14.330 min; minor enantiomer, t_R = 15.586 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.31 – 7.22 (m, 4H, 4ArH-(12, 17), 7.22 – 7.12 (m, 6H, 6ArH-(11, 13, 18, 19), 5.57 (d, *J* = 6.3 Hz, 1H, CH-(3)), 5.32 (dd, *J* = 6.3, 2.3 Hz, 1H, CH-(4)), 4.33 (dd, *J* = 8.4, 7.4 Hz, 1H, CH-(1)), 4.23 – 4.11 (m, 4H, 2CH_2-(20)), 2.85 (d, *J* = 13.0 Hz, 1H, CHH′-(15)), 2.79 – 2.72 (m, 1H, CH-(5)), 2.66 – 2.60 (m, 2H, CH_2-(9)), 2.65 (d, *J* = 13.0 Hz, 1H, CHH′-(15)), 1.85 – 1.74 (m, 1H, CHH′-(6)), 1.71 – 1.61 (m, 2H, CH_2-(8)), 1.56 – 1.46 (m, 1H, CHH′-(6)), 1.43 – 1.33 (m, 2H, CH_2-(7)), 1.39 (td, *J* = 7.1, 1.1 Hz, 3H, CH_3-(21)), 1.36 (td, *J* = 7.1, 1.1 Hz, 3H, CH_3-(21)), 1.13 (s, 3H, CH_3-(14)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 142.8 (C(10)), 138.8 (C(16)), 137.5 (C(4)), 130.9 (C(17)), 129.8 (C(3)), 128.5 (C(12)), 128.4 (C(11)), 127.7 (C(18)), 126.0 (C(19)), 125.8 (C(13)), 91.2 (C(1)), 63.9 (C(20)), 50.6 (C(2)), 50.1 (C(5)), 41.0 (C(15)), 36.0 (C(9)), 32.2 (C(6)), 31.8 (C(8)), 27.3 (C(7)), 24.5 (C(14)), 16.4 (C(21)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.15; HRMS (ESI) *m/z* calcd for $C_{27}H_{37}O_4NaP$ $[M+Na]^+$: 479.23217, found: 479.23213; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2928.8 (w), 2857.3 (w), 1263.9 (m), 1027.6 (s), 972.6 (m), 745.9 (m), 701.4 (m); $[\alpha]^{25}_{589}$ = -44.3 (c=1.0 in $CHCl_3$, 94% ee).

(1*S*,2*R*,5*R*)-2-Benzyl-5-(3-(benzyloxy)propyl)-2-methylcyclopent-3-en-1-yl diethyl phosphate (4c)

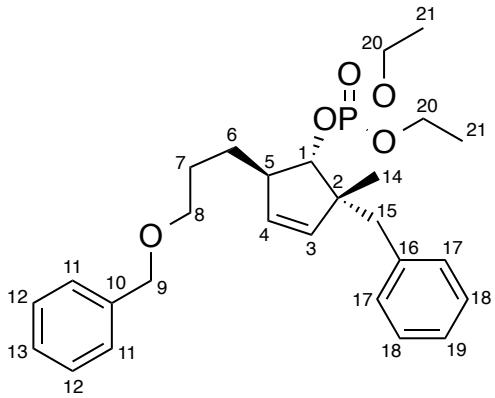


4c

Chemical Formula: $C_{27}H_{37}O_5P$
Molecular Weight: 472.5618

Synthesised according to general procedure 1c, using (1*R*,2*S*,3*S*)-2-benzyl-2-methylcyclopent-4-ene-1,3-bis(diethyl phosphate) (**4a**) and allyl benzyl ether as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (10-30% EtOAc in heptane) to give **4c** as a yellow oil (127 mg, 67%).

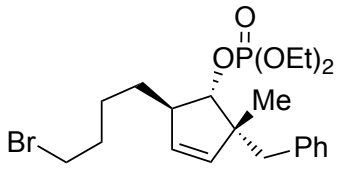
SFC analysis indicated an enantiomeric excess of 89% [Chiralpak® IG; flow: 1.5 mL/min; MeOH/CO_2: 1% to 30%; λ = 210 nm; minor enantiomer, t_R = 3.597 min; major enantiomer, t_R = 3.855 min].



^{1}H NMR (500 MHz, $CDCl_3$) δ_H/ppm: 7.26 (d, *J* = 4.4 Hz, 4H, 4ArH-(11, 12)), 7.23 – 7.19 (m, 1H, ArH-(13)), 7.19 – 7.15 (m, 2H, 2ArH-(18)), 7.14 – 7.10 (m, 1H, ArH-(19)), 7.09 – 7.05 (m, 2H, 2ArH-(17)), 5.51 (d, *J* = 6.3 Hz, 1H, CH-(3)), 5.26 (dd, *J* = 6.3, 2.3 Hz, 1H, CH-(4)), 4.43 (s, 2H, CH_2-(9)), 4.27 (dd, *J* = 8.4, 7.4 Hz, 1H, CH-(1)), 4.14 – 4.04 (m, 4H, 2CH_2-(20)), 3.43 (t, *J* = 6.5 Hz, 2H, CH_2-(8)), 2.78 (d, *J* = 13.0 Hz, 1H, CHH′-(15)), 2.74 – 2.68 (m, 1H,

CH-(5)), 2.59 (d, J = 13.0 Hz, 1H, CHH′-(15)), 1.81 – 1.73 (m, 1H, CHH′-(6)), 1.73 – 1.65 (m, 1H, CHH′-(7)), 1.64 – 1.55 (m, 1H, CHH′-(7)), 1.40 – 1.34 (m, 1H, CHH′-(6)), 1.31 (td, J = 7.1, 1.0 Hz, 3H, CH_3-(21)), 1.27 (td, J = 7.1, 1.0 Hz, 3H, CH_3-(21)), 1.06 (s, 3H, CH_3-(14)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 138.8 (C(16)), 138.7 (C(10)), 137.7 (C(4)), 130.9 (C(17)), 129.7 (C(3)), 128.5 (C(18)), 127.7 (C(12)), 127.7 (C(11)), 127.6 (C(13)), 126.0 (C(19)), 91.1 (C(1)), 73.0 (C(9)), 70.6 (C(8)), 63.9 (C(20)), 50.7 (C(2)), 50.0 (C(5)), 41.1 (C(15)), 28.9 (C(6)), 27.8 (C(7)), 24.5 (C(14)), 16.3 (C(21)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.19; HRMS (ESI) *m/z* calcd for $C_{27}H_{37}O_5NaP$ $[M+Na]^+$: 495.22708, found: 495.22637; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2930.5 (w), 1453.5 (w), 1262.4 (w), 1102.1 (w), 1025.6 (s), 974.3 (w), 742.3 (w), 702.0 (w); $[\alpha]^{25}_{589}$ = -98.6 (c=1.0 in $CHCl_3$, 89% ee).

(1*S*,2*R*,5*R*)-2-Benzyl-5-(4-bromobutyl)-2-methylcyclopent-3-en-1-yl diethyl phosphate (4d)



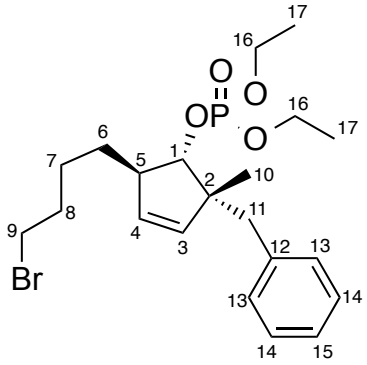
4d

Chemical Formula: $C_{21}H_{32}BrO_4P$
Molecular Weight: 459.3608

Synthesised according to general procedure 1c, using (1*R*,2*S*,3*S*)-2-benzyl-2-methylcyclopent-4-ene-1,3-bis(diethyl phosphate) (**4a**) and 4-bromobut-1-ene as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (10-30% EtOAc in heptane) to give **4d** as a yellow oil (81 mg, 44%).

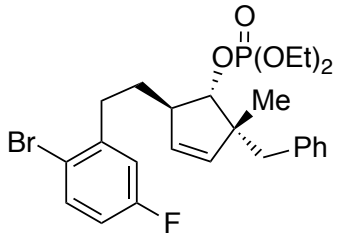
The product was derivatised according to general procedure 2 for HPLC analysis.

HPLC analysis indicated an enantiomeric excess of 90% [Chiralpak® IC; flow: 0.8 mL/min; hexane/iPrOH: 98:2; λ = 210 nm; major enantiomer, t_R = 22.900 min ; minor enantiomer, t_R = 25.200 min].



^{1}H NMR (500 MHz, $CDCl_3$) δ_H/ppm: 7.20 – 7.15 (m, 2H, 2ArH-(14)), 7.14 – 7.10 (m, 1H, ArH-(15)), 7.08 – 7.05 (m, 2H, 2ArH-(13)), 5.50 (d, *J* = 6.3 Hz, 1H, CH-(3)), 5.27 (dd, *J* = 6.3, 2.4 Hz, 1H, CH-(2)), 4.28 – 4.24 (m, 1H, CH-(1)), 4.15 – 4.06 (m, 4H, 2CH_2-(16)), 3.35 (td, *J* = 6.8, 1.2 Hz, 2H, CH_2-(9)), 2.78 (d, *J* = 13.0 Hz, 1H, CHH′-(11)), 2.72 – 2.66 (m, 1H, CH-(5)), 2.58 (d, *J* = 13.0 Hz, 1H, CHH′-(11)), 1.86 – 1.78 (m, 2H, CH_2-(8)), 1.75 – 1.66 (m, 1H, CHH′-(6)), 1.57 – 1.48 (m, 1H, CHH′-(7)), 1.47 – 1.38 (m, 1H, CHH′-(7)), 1.35 – 1.29 (m, 6H, 2CH_3-(17)), 1.33 – 1.26 (m, 1H, CHH′-(6)) 1.06 (s, 3H, CH_3-(10)); ^{13}C NMR (126 MHz, $CDCl_3$) δ_c/ppm: 138.7 (C(12)), 137.8 (C(4)), 130.9 (C(13)), 129.5 (C(3)), 127.8 (C(14)), 126.1 (C(15)), 91.0 (C(1)), 64.0 (C(16)), 50.7 (C(2)), 50.0 (C(5)), 41.1 (C(11)), 33.8 (C(9)), 33.0 (C(8)), 31.5 (C(6)), 26.1 (C(7)), 24.6 (C(10)), 16.4 (C(17)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.13; HRMS (ESI) *m/z* calcd for $C_{21}H_{32}O_4{}^{81}BrNaP$ $[M+Na]^+$: 483.10933, found: 483.10854; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2931.0 (w), 1453.7 (w), 1263.0 (m), 1023.2 (s), 972.0 (m), 746.8 (w), 703.8 (w); $[\alpha]^{25}{}_{589}$ = -75.5 (c=1.0 in $CHCl_3$, 90% ee).

(1*S*,2*R*,5*R*)-2-Benzyl-5-(2-bromo-5-fluorophenethyl)-2-methylcyclopent-3-en-1-yl diethyl phosphate (4e)



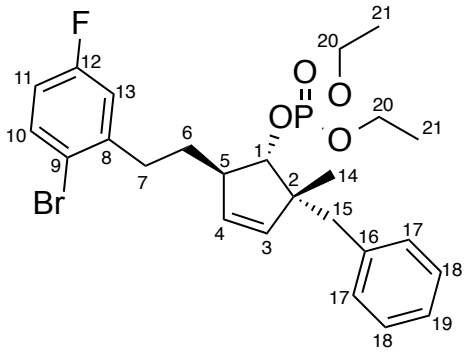
4e

Chemical Formula: $C_{25}H_{31}BrFO_4P$
Molecular Weight: 525.3952

Synthesised according to general procedure 1c, using (1*R*,2*S*,3*S*)-2-benzyl-2-methylcyclopent-4-ene-1,3-bis(diethyl phosphate) (**4a**) and 2-bromo-5-fluorostyene as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (10-30% EtOAc in heptane) to give **4e** as a yellow oil (112 mg, 53%).

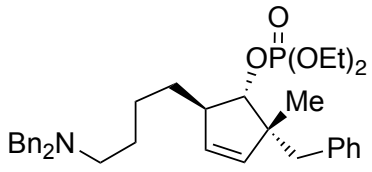
SFC was performed on a Waters SFC 15 system equipped with a Waters 2998 PDA (UV) detector and Waters SQD2 mass spectrometer using a Daicel Chiralpak IA column (10 x 250 mm, 5 μm). Mobile phase was 90% CO_2 and 10% methanol with 20mM NH_3. The flow rate was 10 mL/min, the back pressure was 120 bar, and the column temperature was 40 °C. The PDA detector range was 210 – 400 nm.

SFC analysis indicated an enantiomeric excess of 86; minor enantiomer, t_R = 4.80 min ; major enantiomer, t_R = 5.14 min].



^{1}H NMR (500 MHz, $CDCl_3$) δ_H/ppm: 7.39 (dd, *J* = 8.8, 5.4 Hz, 1H, ArH-(10)), 7.19 – 7.15 (m, 2H, 2ArH-(18)), 7.14 – 7.10 (m, 1H, ArH-(19)), 7.09 – 7.06 (m, 2H, 2ArH-(17)), 6.90 (dd, *J* = 9.4, 3.1 Hz, 1H, ArH-(13)), 6.71 (td, *J* = 8.3, 3.0 Hz, 1H, ArH-(11)), 5.57 (d, *J* = 6.3 Hz, 1H, CH-(3)), 5.32 (dd, *J* = 6.3, 2.3 Hz, 1H, CH-(4)), 4.35 – 4.31 (m, 1H, CH-(1)), 4.15 – 4.04 (m, 4H, 2CH_2-(20)), 2.80 (d, *J* = 13.1 Hz, 1H, CHH′-(15)), 2.78 – 2.66 (m, 3H, CH-(5), CH_2-(7)), 2.59 (d, *J* = 13.0 Hz, 1H, CHH′-(15)), 2.02 – 1.94 (m, 1H, , CHH′-(6)), 1.63 – 1.54 (m, 1H, CHH′-(6)), 1.31 (td, *J* = 7.1, 1.0 Hz, 3H, CH_3-(21)), 1.28 (td, *J* = 7.1, 1.0 Hz, 3H, CH_3-(21)), 1.08 (s, 3H, CH_3-(14)); ^{13}C NMR (126 MHz, $CDCl_3$) δ_c/ppm: 162.1 (C(12)), 143.7 (C(8)), 138.7 (C(16)), 138.1 (C(4)), 133.9 (C(10)), 130.9 (C(17)), 129.3 (C(3)), 127.8 (C(18)), 126.1 (C(19)), 118.5 (C(9)), 117.3 (C(13)), 114.8 (C(11)), 90.8 (C(1)), 64.0 (C(20)), 50.8 (C(2)), 49.8 (C(5)), 41.1 (C(15)), 34.2 (C(7)), 32.3 (C(6)), 24.6 (C(14)), 16.4 (C(21)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.05; HRMS (ESI) *m/z* calcd for $C_{25}H_{32}O_4{}^{79}BrFP$ $[M+H]^+$: 525.12001, found: 525.09136; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2980.6 (m), 1470.0 (w), 1392.1 (w), 1261.6 (w), 1155.3 (w), 1025.2 (s), 964.5 (m), 808.3 (w), 744.6 (w), 703.6 (w); $[\alpha]^{25}_{589}$ = -101.1 (c=1.0 in $CHCl_3$, 86% ee).

(1*S*,2*R*,5*R*)-2-Benzyl-5-(4-(dibenzylamino)butyl)-2-methylcyclopent-3-en-1-yl diethyl phosphate (4f)



4f

Chemical Formula: $C_{35}H_{46}NO_4P$
Molecular Weight: 575.7298

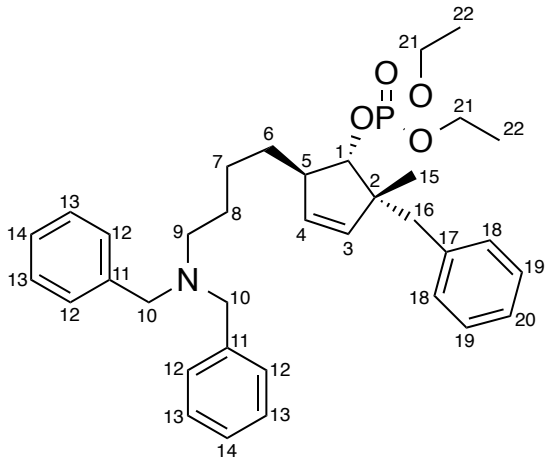
Synthesised according to general procedure 1c, using (1*R*,2*S*,3*S*)-2-benzyl-2-methylcyclopent-4-ene-1,3-bis(diethyl phosphate) (**4a**) and N,N-dibenzylbut-3-en-1-amine as the alkene partner

(hydrozirconation time 20 mins). Purified by flash chromatography (10-30% EtOAc in heptane) to give **4f** as a yellow oil (145 mg, 63%).

SFC was performed on a Waters UPC system equipped with a PDA (UV) detector and QDa (MS) detector using a Daicel Chiralpak IA column (3.0 x 50 mm, 3 μm). Mobile phase A was CO_2 and mobile phase B was methanol with 20mM NH_3. A gradient from 5% to 50% mobile phase B over 3.5 minutes was used, followed by an increase to 60% over 0.05 minutes, a hold at 60% for 0.4 minutes and return to 5%. The total flow was 2 mL/min, the back pressure was 140 bar, and the column temperature was 40 °C. The PDA detector range was 210 – 400 nm.

The product was derivatised according to general procedure 2 (reduction only) for SFC analysis.

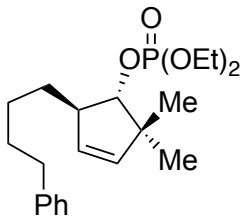
SFC analysis indicated an enantiomeric excess of 86%; minor enantiomer, t_R = 2.03 min ; major enantiomer, t_R = 2.21 min].



^{1}H NMR (500 MHz, $CDCl_3$) δ_H/ppm: 7.30 (d, *J* = 7.2 Hz, 4H, 4ArH-(12)), 7.23 (t, *J* = 7.6 Hz, 4H, 4ArH-(13)), 7.20 – 7.14 (m, 4H, 4ArH, (14, 19)), 7.14 (s, 1H, ArH-(20)), 7.09 – 7.06 (m, 2H, 2ArH-(18)), 5.47 (d, *J* = 6.3 Hz, 1H, CH-(3)), 5.25 (dd, *J* = 6.3, 2.4 Hz, 1H, CH-(4)), 4.21 (dd, *J* = 8.4, 7.4 Hz, 1H, CH-(1)), 4.13 – 4.02 (m, 4H, 2CH_2-(21)), 3.55 – 3.45 (m, 4H, 2CH_2-

(10)), 2.78 (d, J = 13.0 Hz, 1H, CHH′-(15)), 2.66 – 2.61 (m, 1H, CH-(5)), 2.58 (d, J = 13.0 Hz, 1H, CHH′-(15)), 2.37 (t, J = 7.6 Hz, 2H, CH_2-(9)), 1.66 – 1.58 (m, 1H, CHH′-(6)), 1.56 – 1.40 (m, 2H, CH_2-(8)), 1.37 – 1.27 (m, 1H, CHH′-(7)), 1.30 (td, J = 7.1, 1.0 Hz, 3H, CH_3-(22)), 1.26 (td, J = 7.1, 1.0 Hz, 3H, CH_3-(22)), 1.24 – 1.18 (m, 1H, CHH′-(6)), 1.05 (s, 3H, CH_3-(15)); ^{13}C NMR (126 MHz, $CDCl_3$) δ_c/ppm: 138.7 (C(17)), 137.3 (C(4)), 130.8 (C(18)), 129.7 (C(3)), 128.8 (C(12)), 128.2 (C(13)), 127.6 (C(14), 127.6 (C(19)), 126.8 (C(11)), 125.9 (C(20)), 91.1 (C(1)), 63.8 (C(21)), 58.3 (C(10)), 53.4 (C(9)), 50.5 (C(2)), 50.1 (C(5)), 40.9 (C(16)), 32.2 (C(6)), 27.2 (C(8)), 25.2 (C(7)), 24.4 (C(15)), 16.2 (C(22)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.22; HRMS (ESI) *m/z* calcd for $C_{35}H_{47}O_4NP$ $[M+H]^+$: 576.32372, found: 576.32325; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2930.4 (w), 1453.2 (w), 1262.9 (m), 1026.9 (s), 973.3 (m), 745.7 (m), 700.8 (m); $[\alpha]^{25}_{589}$ = -94.0 (c=1.0 in $CHCl_3$, 86% ee).

(1*S*,5*R*)-2,2-Dimethyl-5-(4-phenylbutyl)cyclopent-3-en-1-yl diethyl phosphate (9b)

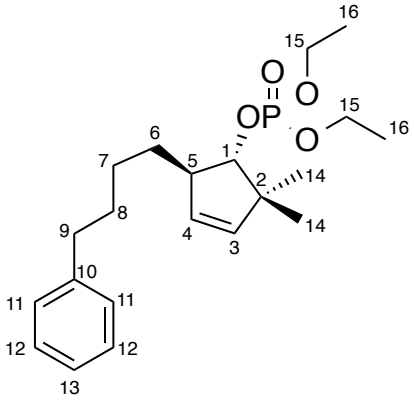


9b

Chemical Formula: $C_{21}H_{33}O_4P$
Molecular Weight: 380.4648

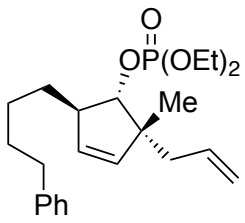
Synthesised according to general procedure 1c, using *cis*-2,2-dimethylcyclopent-4-ene-1,3-bis(diethyl phosphate) (**9a**) and 4-phenyl-1-butene as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (10-20-30% EtOAc in petroleum ether) to give **9b** as a yellow oil (112 mg, 74%).

HPLC analysis indicated an enantiomeric excess of 91% [Chiralpak® ID; flow: 0.8 mL/min; hexane/iPrOH: 96:4; λ = 210 nm; major enantiomer, t_R = 18.136 min; minor enantiomer, t_R = 18.920 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.30 – 7.24 (m, 2H, 2ArH-(12)), 7.20 – 7.14 (m, 3H, 3ArH-(11, 13)), 5.47 (s, 1H, CH-(3/4)), 5.47 (s, 1H, CH-(3/4)), 4.22 (dd, *J* = 8.3, 6.7 Hz, 1H, CH-(1)), 4.12 (h, *J* = 7.1 Hz, 4H, 2CH_2-(15)), 2.79 – 2.71 (m, 1H, CH-(5)), 2.64 – 2.59 (m, 2H, CH_2-(9)), 1.82 – 1.71 (m, 1H, CHH´-(6)), 1.71 – 1.59 (m, 2H, CH_2-(8)), 1.53 – 1.44 (m, 1H, CHH´-(6)), 1.43 – 1.29 (m, 2H, CH_2-(8)), 1.34 (td, *J* = 7.1, 1.0 Hz, 6H, 2CH_3-(16)), 1.16 (s, 3H, CH_3-(14)), 1.02 (s, 3H, CH_3-(14)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 142.7 (C(10)), 139.4 (C(4)), 128.9 (C(3)), 128.5 (C(12)), 128.3 (C(11)), 125.7 (C(13)), 90.5 (C(1)), 63.7 (C(15)), 50.5 (C5)), 47.1 (C(2)), 36.0 (C(9)), 32.5 (C(6)), 31.8 (C(8)), 27.3 (C(7)), 27.3 (C14)), 21.6 (C(14)), 16.3 (C(16)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.20; HRMS (ESI) *m/z* calcd for $C_{21}H_{33}O_4NaP$ $[M+Na]^+$: 403.20087, found: 403.20079; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2980.31 (w), 2929.6 (w), 2858.9 (w), 1263.6 (w), 1027.3 (s), 970.6 (m), 747.1 (w), 700.0 (w); $[\alpha]^{25}_{589}$ = -61.6 (c=1.0 in $CHCl_3$, 91% ee).

(1*S*,2*R*,5*R*)-2-Allyl-2-methyl-5-(4-phenylbutyl)cyclopent-3-en-1-yl diethyl phosphate (10b)

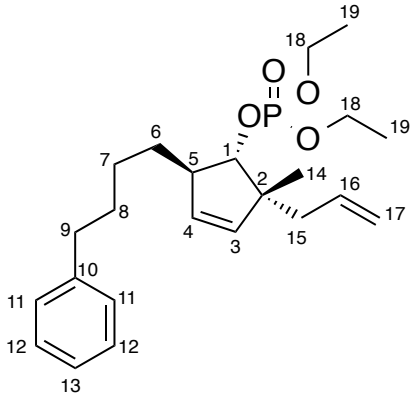


10b

Chemical Formula: $C_{23}H_{35}O_4P$
Molecular Weight: 406.5028

Synthesised according to general procedure 1c, using (1*R*,2*S*,3*S*)-2-allyl-2-methylcyclopent-4-ene-1,3-bis(diethyl phosphate) (**10a**) and 4-phenyl-1-butene as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (10-20-30% EtOAc in petroleum ether) to give **10b** as a yellow oil (143 mg, 88%).

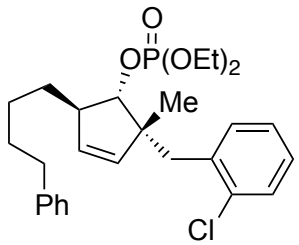
HPLC analysis indicated an enantiomeric excess of 94% [Chiralpak® ID; flow: 1.0 mL/min; hexane/iPrOH: 95:5; λ = 210 nm; major enantiomer, t_R = 12.123 min; minor enantiomer, t_R = 12.992 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.30 – 7.24 (m, 2H, 2ArH-(12)), 7.20 – 7.14 (m, 3H, 3ArH-(11, 13)), 5.87 – 5.74 (m, 1H, CH-(16)), 5.55 (dd, *J* = 6.2, 0.9 Hz, 1H, CH-(3)), 5.48 (dd, *J* = 6.2, 2.2 Hz, 1H, CH-(4)), 5.05 – 5.02 (m, 1H, CHH′-(18)), 5.01 – 4.98 (m, 1H, CHH′-(17)), 4.27 (dd, *J* = 8.4, 7.0 Hz, 1H, CH-(1)), 4.17 – 4.07 (m, 4H, 2CH_2-(18)), 2.78 – 2.71 (m, 1H, CH-(5)), 2.62 (td, *J* = 8.0, 2.1 Hz, 2H, CH_2-(9)), 2.28 (dd, *J* = 13.5, 7.1 Hz, 1H, CHH′-

(15)), 2.12 (dd, *J* = 13.5, 7.8 Hz, 1H, CHH′-(15)), 1.82 – 1.73 (m, 1H, CHH′-(6)), 1.69 – 1.60 (m, 2H, CH_2-(8)), 1.53 – 1.45 (m, 1H, CHH′-(6)), 1.44 – 1.29 (m, 2H, CH_2-(7)), 1.37 – 1.31 (m, 6H, $2CH_3$-(19)), 1.15 (s, 3H, CH_3-(19)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 142.8 (C(10)), 137.3 (C(4)), 135.4 (C(16)), 130.0 (C(3)), 128.5 (C(12)), 128.4 (C(11)), 125.7 (C(13)), 117.3 (C(17)), 91.0 (C(1)), 63.8 (C(18)), 50.8 (C(5)), 50.1 (C2)), 40.1 (C15)), 36.0 (C(9)), 32.6 (C(6)), 31.8 (C(8)), 27.3 (C7)), 25.0 (C(14)), 16.3 (C(19)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.18; HRMS (ESI) *m/z* calcd for $C_{23}H_{35}O_4NaP$ $[M+Na]^+$: 429.21644, found: 429.21652; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2980.0 (w), 2929.2 (w), 2857.9 (w), 1263.3 (m), 1025.9 (s), 963.8 (m), 748.9 (m), 699.8 (w); $[\alpha]^{25}_{589}$ = -83.5 (c=1.0 in $CHCl_3$, 94% ee).

(1*S*,2*R*,5*R*)-2-(2-chlorobenzyl)-2-methyl-5-(4-phenylbutyl)cyclopent-3-en-1-yl diethyl phosphate (11b)

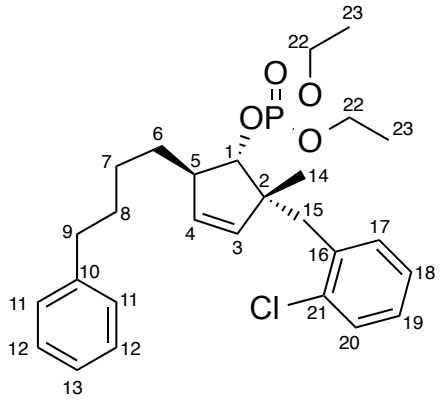


11b

Chemical Formula: $C_{27}H_{36}ClO_4P$
Molecular Weight: 491.0048

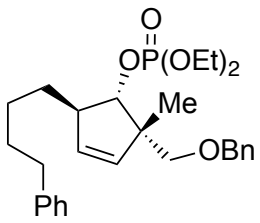
Synthesised according to general procedure 1c, using ((1*R*,2*S*,3*S*)-2-(2-chlorobenzyl)-2-methylcyclopent-4-ene-1,3-bis(diethyl phosphate) (**11a**) and 4-phenyl-1-butene as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (10-20-30% EtOAc in petroleum ether) to give **11b** as a yellow oil (154 mg, 79%).

HPLC analysis indicated an enantiomeric excess of 94% [Chiralpak® ID; flow: 1.0 mL/min; hexane/iPrOH: 95:5; λ = 210 nm; major enantiomer, t_R = 19.110 min; minor enantiomer, t_R = 19.878 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.35 – 7.31 (m, 1H, ArH-(20)), 7.30 – 7.25 (m, 2H, 2ArH-(12)), 7.25 – 7.22 (m, 1H, ArH-(19)), 7.21 – 7.16 (m, 3H, 3ArH-(11, 13), 7.16 – 7.12 (m, 2H, 2ArH-(17, 19)), 5.55 (d, *J* = 6.3 Hz, 1H, CH-(3)), 5.40 (dd, *J* = 6.3, 2.3 Hz, 1H, CH-(4)), 4.34 (dd, *J* = 8.6, 7.5 Hz, 1H, CH-(1)), 4.25 – 4.13 (m, 4H, 2CH_2-(22)), 3.03 (d, *J* = 13.2 Hz, 1H, CHH´-(15)), 2.94 (d, *J* = 13.2 Hz, 1H, CHH´-(15)), 2.87 – 2.78 (m, 1H, CH-(5)), 2.63 (dt, *J* = 7.7, 2.0, 1.7 Hz, 2H, CH_2-(9)), 1.86 – 1.76 (m, 1H, CHH´-(6)), 1.71 – 1.61 (m, 2H, CH_2-(8)), 1.56 – 1.46 (m, 1H, CHH´-(6)), 1.44 – 1.32 (m, 2H, CH_2-(7)), 1.38 (dtd, *J* = 8.2, 7.1, 1.0 Hz, 6H, 2CH_3-(23)), 1.18 (s, 3H, CH_3-(14)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 142.8 (C(10)), 137.2 (C(4)), 137.0 (C(16)), 135.4 (C(21)), 132.8 (C(20)), 130.0 (C(3)), 129.7 (C(19)), 128.5 (C(12)), 128.4 (C(11)), 127.6 (C(17)), 126.1 (C(18)), 125.8 (C(13)), 91.2 (C(1)), 63.9 (C(22)), 51.4 (C(2)), 50.2 (C(5)), 36.9 (C(15)), 36.0 (C(9)), 32.2 (C(6)), 31.8 (C(8)), 27.3 (C(7)), 24.7 (C(14)), 16.4(C(23)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.13; HRMS (ESI) *m/z* calcd for $C_{27}H_{36}O_4{}^{35}ClNaP$ $[M+Na]^+$: 513.19319, found: 513.19327; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2980.7 (w), 2929.7 (w), 2857.6 (w), 1263.9 (m), 1027.3 (s), 971.7 (m), 749.2 (m), 699.7 (w); $[\alpha]^{25}{}_{589}$ = -81.2 (c=1.0 in $CHCl_3$, 94% ee).

(1*S*,2*S*,5*R*)-2-((benzyloxy)methyl)-2-methyl-5-(4-phenylbutyl)cyclopent-3-en-1-yl diethyl phosphate (12b)

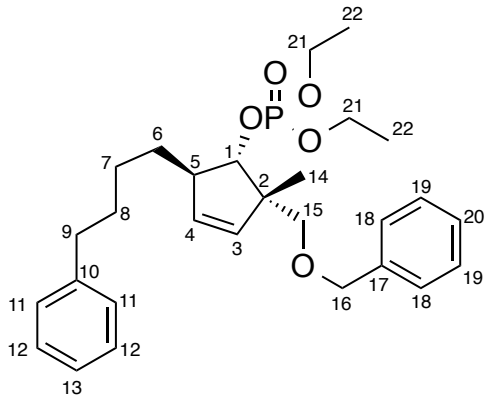


12b

Chemical Formula: $C_{28}H_{39}O_5P$
Molecular Weight: 486.5888

Synthesised according to general procedure 1c, using (1*R*,2*S*,3*S*)-2-((benzyloxy)methyl)-2-methylcyclopent-4-ene-1,3-bis(diethyl phosphate) (**12a**) and 4-phenyl-1-butene as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (10-25-35% EtOAc in petroleum ether) to give **12b** as a yellow oil (128 mg, 66%).

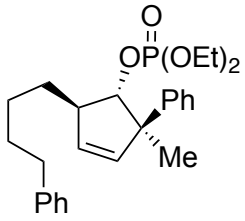
HPLC analysis indicated an enantiomeric excess of 90% [Chiralpak® ID; flow: 1.0 mL/min; hexane/iPrOH: 95:5; λ = 210 nm; major enantiomer, t_R = 18.954 min; minor enantiomer, t_R = 20.164 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.25 – 7.22 (m, 4H, 4ArH-(12, 19)), 7.22 – 7.16 (m, 3H, 3ArH-(11, 13)), 7.12 – 7.07 (m, 3H, 3ArH-(18, 20)), 5.58 – 5.54 (m, 1H, CH-(3)), 5.51 (dd, *J* = 6.1, 2.0 Hz, 1H, CH-(4)), 4.43 (d, *J* = 2.8 Hz, 2H, CH_2-(16)), 4.23 (dd, *J* = 8.5, 6.6 Hz, 1H, CH-(1)), 4.04 – 3.94 (m, 4H, 2CH_2-(21)), 3.45 (d, *J* = 9.0 Hz, 1H, CHH′-(15)), 3.33 (d, *J* = 9.0 Hz, 1H, CHH′-(15)), 2.83 – 2.77 (m, 1H, CH-(5)), 2.58 – 2.51 (m, 2H, CH_2-(9)), 1.74 – 1.64

(m, 1H, CHH′-(6)), 1.62 – 1.51 (m, 2H, CH_2-(8)), 1.45 – 1.36 (m, 1H, CHH′-(6)), 1.36 – 1.25 (m, 2H, CH_2-(7)), 1.21 (qd, J = 6.9, 1.1 Hz, 6H, $2CH_3$-(22)), 1.14 (s, 3H, CH_3-(14)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 142.8 (C(10)), 138.9 (C(17)), 135.9 (C(4)), 131.2 (C(3)), 128.5 (C(12)), 128.4 (C(11)), 128.3 (C(19)), 127.4 (C(18)), 127.4 (C(20)), 125.7 (C(13)), 90.5 (C(1)), 74.2 (C(15)), 73.5 (C(16)), 63.8 (C(21)), 51.5 (C(2)), 51.4 (C(5)), 36.0 (C(9)), 32.8 (C(6)), 31.8 (C(8)), 27.3 (C(7)), 23.0 (C(14)), 16.3 (C(22)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.15; HRMS (ESI) *m/z* calcd for $C_{28}H_{39}O_5NaP$ $[M+Na]^+$: 509.24273, found: 509.24260; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2980.7 (w), 2929.4 (w), 2857.0 (w), 1263.3 (m), 1100.2 (w), 1027.0 (s), 972.9 (m), 748.1 (w), 698.9 (w); $[\alpha]^{25}_{589}$ = -83.4 (c=1.0 in $CHCl_3$, 90% ee).

Diethyl ((1*S*,2*R*,5*R*)-2-methyl-2-phenyl-5-(4-phenylbutyl)cyclopent-3-en-1-yl) phosphate (13b)

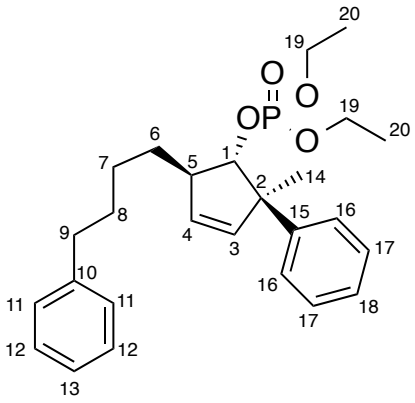


13b

Chemical Formula: $C_{26}H_{35}O_4P$
Molecular Weight: 442.5358

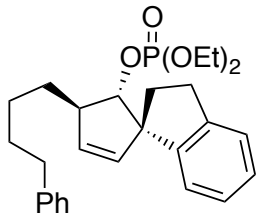
Synthesised according to general procedure 1c, using (1*R*,2*R*,3*S*)-2-methyl-2-phenylcyclopent-4-ene-1,3-bis(diethyl phosphate) (**13a**) and 4-phenyl-1-butene as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (10-20-30% EtOAc in petroleum ether) to give **13b** as a yellow oil (52 mg, 29%).

HPLC analysis indicated an enantiomeric excess of 20% [Chiralpak® IB; flow: 1.0 mL/min; hexane/iPrOH: 95:5; λ = 210 nm; major enantiomer, t_R = 6.241 min; minor enantiomer, t_R = 7.776 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.38 – 7.24 (m, 6H, 6ArH-(11-13, 16-18)), 7.23 – 7.14 (m, 4H, 4ArH-(11-13, 16-18)), 5.76 – 5.70 (m, 2H, 2CH-(3,4)), 4.57 (dd, *J* = 8.3, 6.0 Hz, 1H, CH-(1)), 4.06 – 3.81 (m, 4H, 2CH_2-(19)), 2.87 – 2.80 (m, 1H, CH-(5)), 2.60 (dd, *J* = 8.0, 2.1 Hz, 2H, CH_2-(9)), 1.80 – 1.70 (m, 1H, CHH´-(6)), 1.67 – 1.57 (m, 2H, CH_2-(8)), 1.53 – 1.28 (m, 3H, CHH´-(6), CH_2-(7)), 1.46 (s, 3H, CH_3-(14)), 1.23 (td, *J* = 7.1, 1.0 Hz, 3H, CH_3-(20)), 1.19 (td, *J* = 7.1, 1.0 Hz, 3H, CH_3-(20)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 147.5 (C(15)), 142.8 (C(10)), 137.9 (C(3)), 130.8 (C(4)), 128.5 (C(12)), 128.4 (C(11)), 128.3 (C(17)), 126.6 (C(16)), 126.4 (C(18)), 125.7 (C(13)), 91.5 (C(1)), 63.7 (C(19)), 54.8 (C(2)), 51.1 (C(5)), 35.9 (C(9)), 32.2 (C(6)), 31.7 (C(8)), 27.3 (C(7)), 20.3 (C(14)), 16.2 (C(20)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.67; HRMS (ESI, EI) Not found; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2981.3 (w), 2929.7 (w), 2857.0 (w), 1264.3 (w), 1260.1 (w), 1030.2 (s), 970.1 (m), 773.5 (w), 748.6 (w), 699.8 (w); $[\alpha]^{25}_{589}$ = -1.7 (c=1.0 in $CHCl_3$, 20% ee).

Diethyl ((1*S*,4*R*,5*S*)-4-(4-phenylbutyl)-2',3'-dihydrospiro[cyclopentane-1,1'-inden]-2-en-5-yl) phosphate (14b)

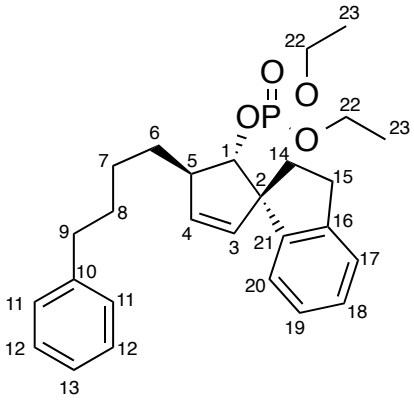


14b

Chemical Formula: $C_{27}H_{35}O_4P$
Molecular Weight: 454.5468

Synthesised according to general procedure 1c, using (1*S*,2*R*,5*S*)-2',3'-dihydrospiro[cyclopentane-1,1'-inden]-3-ene-2,5-bis(diethyl phosphate) (**14a**) and 4-phenyl-1-butene as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (10-20-30% EtOAc in petroleum ether) to give **14b** as a yellow oil (112 mg, 61%).

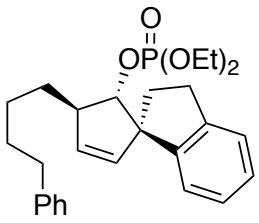
HPLC analysis indicated an enantiomeric excess of 90% [Chiralpak® ID; flow: 1.0 mL/min; hexane/iPrOH: 95:5; λ = 210 nm; major enantiomer, t_R = 21.376 min; minor enantiomer, t_R = 23.910 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.32 – 7.27 (m, 2H, 2ArH-(12), 7.23 – 7.18 (m, 4H, 4ArH-(11, 13, 17), 7.18 – 7.14 (m, 3H, 3ArH-(18, 19, 20), 5.81 (dd, *J* = 6.0, 2.0 Hz, 1H, CH-(3)), 5.63 (dd, *J* = 6.0, 1.7 Hz, 1H, CH-(4)), 4.59 (dd, *J* = 8.6, 4.7 Hz, 1H, CH-(1)), 3.87 – 3.74 (m, 2H, CH_2-(22)), 3.50 – 3.36 (m, 2H, CH_2-(22)), 3.17 – 3.07 (m, 1H, CHH′-(15)), 2.99 –

2.93 (m, 1H, CH-(5)), 2.92 – 2.83 (m, 1H, CHH′-(15)), 2.66 (t, *J* = 7.7 Hz, 2H, CH_2-(9)), 2.24 – 2.17 (m, 2H, CH_2-(14)), 1.85 – 1.74 (m, 1H, CHH′-(6)), 1.73 – 1.64 (m, 2H, CH_2-(8)), 1.60 – 1.40 (m, 3H, CH_2-(7), CHH′-(6)), 1.19 (td, *J* = 7.1, 1.1 Hz, 3H, CH_3-(23)), 1.02 (td, *J* = 7.1, 1.1 Hz, 3H, CH_3-(23)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 144.6 (C(21)), 143.8 (C(16)), 142.7 (C(10)), 136.6 (C(4)), 132.0 (C(3)), 128.5 (C(12)), 128.4 (C(11)), 127.1 (C(17)), 126.0 (C(20)), 125.9 (C(18)), 125.7 (C(13)), 124.4 (C(19)), 88.7 (C(1)), 64.5 (C(2)), 63.5 (C(22)), 63.2 (C(22)), 52.7 (C(5)), 39.1 (C(14)), 36.0 (C(9)), 33.7 (C(15)), 31.8 (C(8)), 31.0 (C(6)), 27.5 (C(7)), 16.0 (C(23)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.97; HRMS (ESI) *m/z* calcd for $C_{27}H_{36}O_4P$ $[M+H]^+$: 455.23457, found: 455.23463; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2980.8 (w), 2929.9 (w), 2856.9 (w), 1275.1 (w), 1262.7 (w), 1029.1 (s), 971.2 (m), 772.1 (w), 748.6 (w), 700.0 (w); $[\alpha]^{25}_{589}$ = -111.9 (c=1.0 in $CHCl_3$, 90% ee).

Diethyl ((1*R*,4*R*,5*S*)-4-(4-phenylbutyl)-2',3'-dihydrospiro[cyclopentane-1,1'-inden]-2-en-5-yl) phosphate (15b)

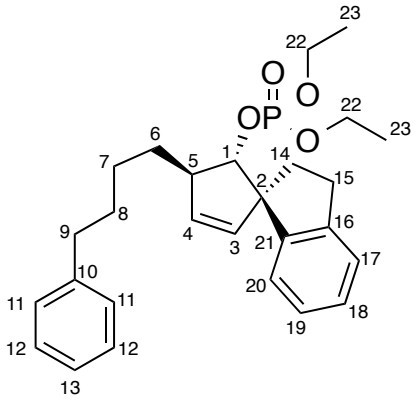


15b

Chemical Formula: $C_{27}H_{35}O_4P$
Molecular Weight: 454.5468

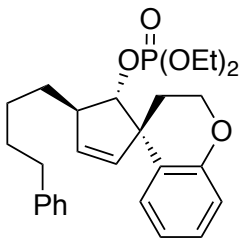
Synthesised according to general procedure 1c, using (1*R*,2*R*,5*S*)-2',3'-dihydrospiro[cyclopentane-1,1'-inden]-3-ene-2,5-bis(diethyl phosphate) (**15a**) and 4-phenyl-1-butene as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (10-20-30% EtOAc in petroleum ether) to give **15b** as a yellow oil (35 mg, 19%).

HPLC analysis indicated an enantiomeric excess of 91% [Chiralpak® ID; flow: 1.0 mL/min; hexane/iPrOH: 95:5; λ = 210 nm; minor enantiomer, t_R = 22.804 min; major enantiomer, t_R = 26.682 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.31 – 7.25 (m, 2H, 2ArH-(12)), 7.21 – 7.15 (m, 6H, ArH-(11, 13, 17, 18, 20)), 7.12 – 7.08 (m, 1H, ArH-(19)), 5.91 (dd, *J* = 6.1, 2.6 Hz, 1H, CH-(3)), 5.65 (d, *J* = 6.1 Hz, 1H, CH-(4)), 4.84 (dd, *J* = 9.0, 7.3 Hz, 1H, CH-(1)), 3.94 (dp, *J* = 10.0, 7.1 Hz, 1H, CHH′-(22)), 3.77 – 3.67 (m, 3H, CHH′, CH_2-(22)), 3.05 (dt, *J* = 16.5, 8.5 Hz, 1H, CHH′-(15)), 2.90 – 2.83 (m, 2H, CHH′-(15), CH-(5)), 2.66 – 2.62 (m, 2H, CH_2-(9)), 2.62 – 2.58 (m, 1H, CHH′-(14)), 1.95 (dt, *J* = 13.1, 8.8 Hz, 1H, CHH′-(14)), 1.90 – 1.84 (m, 1H, CHH′-(6)), 1.74 – 1.60 (m, 2H, CH_2-(8)), 1.56 – 1.45 (m, 1H, CHH′-(7)), 1.44 – 1.29 (m, 2H, CHH′-(6, 7)), 1.14 (td, *J* = 7.1, 1.1 Hz, 3H, CH_3-(23)), 1.07 (td, *J* = 7.1, 1.1 Hz, 3H, CH_3-(23)); ^{13}C NMR (125 MHz, $CDCl_3$) δ_c/ppm: 147.5 (C(21)), 144.6 (C(16)), 142.8 (C(10)), 136.8 (C(4)), 132.8 (C(3)), 128.5 (C(12)), 128.4 (C(11)), 127.4 (C(17)), 126.8 (C(20)), 125.8 (C(13)), 124.5 (C(18)), 123.3 (C(19)), 87.2 (C(1)), 63.6 (C(22)), 62.9 (C(2)), 47.7 (C(5)), 36.0 (C(9)), 33.5 (C(14)), 31.9 (C(8)), 31.5 (C(15)), 30.7 (C(6)), 27.6 (C(7)), 16.1 (C(23)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.69; HRMS (ESI) *m/z* calcd for $C_{27}H_{35}O_4NaP$ $[M+H]^+$: 477.21652, found: 477.21661; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2971.1 (w), 2930.7 (w), 2856.3 (w), 1275.1 (w), 1264.7 (w), 1231.7 (w), 1029.6 (s), 962.3 (m), 771.7 (w), 751.4 (w), 699.1 (w); $[\alpha]^{25}_{589}$ = -106.4 (c=1.0 in $CHCl_3$, 91% ee).

Diethyl ((4S,4'R,5'S)-4'-(4-phenylbutyl)spiro[chromane-4,1'-cyclopentan]-2'-en-5'-yl) phosphate (16b)

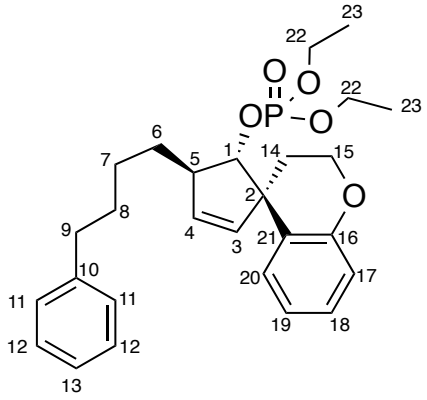


16b

Chemical Formula: $C_{27}H_{35}O_5P$
Molecular Weight: 470.5458

Synthesised according to general procedure 1c, using (2'*R*,4*S*,5'*S*)-spiro[chromane-4,1'-cyclopentan]-3'-ene-2',5'-bis(diethyl phosphate) (**16a**) and 4-phenyl-1-butene as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (10-20-30% EtOAc in petroleum ether) to give **16b** as a yellow oil (107 mg, 57%).

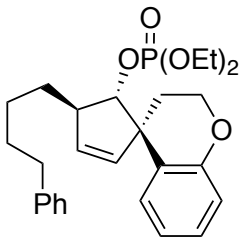
HPLC analysis indicated an enantiomeric excess of 91% [Chiralpak® ID; flow: 1.0 mL/min; hexane/iPrOH: 95:5; λ = 210 nm; major enantiomer, t_R = 30.321 min; minor enantiomer, t_R = 41.961 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.30 – 7.26 (m, 2H, 2ArH-(12)), 7.21 – 7.16 (m, 3H, 3ArH-(11, 13)), 7.11 – 7.06 (m, 2H, 2ArH-(18,20), 6.82 (td, *J* = 7.5, 1.3 Hz, 1H, ArH-(19)), 6.78 (dd, *J* = 8.7, 1.4 Hz, 1H, ArH-(17)), 5.87 (dd, *J* = 6.0, 2.1 Hz, 1H, CH-(3)), 5.54 (dd, *J* = 6.0, 1.9 Hz, 1H, CH-(4)), 4.46 (dd, *J* = 8.8, 4.1 Hz, 1H, CH-(1)), 4.42 (td, *J* = 11.6, 2.2 Hz, 1H,

CHH′-(15)), 4.27 (dt, *J* = 11.3, 3.7 Hz, 1H, CHH′-(15)), 3.83 (p, *J* = 7.2 Hz, 2H, CH_2-(22)), 3.53 (dp, *J* = 10.1, 7.1 Hz, 1H, CHH′-(22)), 3.43 (dp, *J* = 10.1, 7.1 Hz, 1H, CHH′-(22)), 2.97 – 2.92 (m, 1H, CH-(5)), 2.64 (t, *J* = 7.7 Hz, 2H, CH_2-(9)), 2.19 – 2.11 (m, 1H, CHH′-(14)), 1.85 – 1.77 (m, 2H, CHH′-(14), CHH′-(6)), 1.72 – 1.63 (m, 2H, CH_2-(8)), 1.54 – 1.43 (m, 3H, CHH′-(6), CH_2-(7)), 1.19 (td, *J* = 7.1, 1.0 Hz, 3H, CH_3-(23)), 1.03 (td, *J* = 7.1, 1.0 Hz, 3H, CH_3-(23)); ^{13}C NMR (125 MHz, $CDCl_3$) δ_c/ppm: 154.7 (C(16)), 142.7 (C(10)), 136.7 (C(4)), 133.0 (C(3)), 130.7 (C(20)), 128.5 (C(12)), 128.4 (C(11)), 128.3 (C(18)), 125.8 (C(13)), 122.0 (C(21)), 119.8 (C(19)), 116.8 (C(17)), 89.9 (C(1)), 63.7 (C(22)), 63.4 (C(22)), 62.9 (C(15)), 53.8 (C(5)), 52.7 (C(2)), 36.0 (C(9)), 35.3 (C(14)), 34.3 (C(6)), 31.7 (C(8)), 27.6 (C(7)), 16.1 (C(23)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -2.29; HRMS (ESI) *m/z* calcd for $C_{27}H_{35}O_5NaP$ $[M+H]^+$: 493.21143, found: 493.21134; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2980.7 (w), 2929.6 (w), 2857.1 (w), 1488.3 (w), 1452.0 (w), 1261.4 (w), 1224.3 (w), 1027.8 (s), 975.3 (m), 755.0 (w), 700.2 (w); $[\alpha]^{25}_{589}$ = -62.9 (c=1.0 in $CHCl_3$, 91% ee).

Diethyl ((4R,4'R,5'S)-4'-(4-phenylbutyl)spiro[chromane-4,1'-cyclopentan]-2'-en-5'-yl) phosphate (17b)

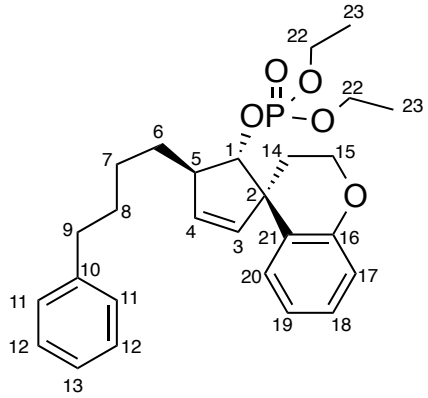


17b

Chemical Formula: $C_{27}H_{35}O_5P$
Molecular Weight: 470.5458

Synthesised according to general procedure 1c, using (2′*R*,4*R*,5′*S*)-spiro[chromane-4,1'-cyclopentan]-3'-ene-2',5'-bis(diethyl phosphate) (**17a**) and 4-phenyl-1-butene as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (10-20-30% EtOAc in petroleum ether) to give **17b** as a yellow oil (8 mg, 4%).

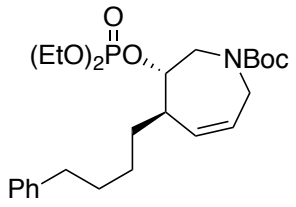
HPLC analysis indicated an enantiomeric excess of 13% [Chiralpak® ID; flow: 1.0 mL/min; hexane/iPrOH: 95:5; λ = 210 nm; major enantiomer, t_R = 15.313 min; minor enantiomer, t_R = 21.816 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.30 – 7.26 (m, 2H, 2ArH-(12)), 7.21 – 7.16 (m, 3H, 3ArH-(11, 13)), 7.14 (dd, *J* = 7.8, 1.7 Hz, 1H, ArH-(20)), 7.14 – 7.07 (m, 1H, ArH-(18)), 6.90 (td, *J* = 7.5, 1.3 Hz, 1H, ArH-(19)), 6.80 (dd, *J* = 8.2, 1.3 Hz, 1H, ArH-(17)), 5.73 (dd, *J* = 6.1, 1.1 Hz, 1H, CH-(3)), 5.51 (dd, *J* = 6.1, 2.3 Hz, 1H, CH-(4)), 4.73 (dd, *J* = 9.0, 7.3 Hz, 1H, CH-(1)), 4.32 (td, *J* = 10.8, 2.6 Hz, 1H, CHH′-(15)), 4.17 (dt, *J* = 10.8, 4.5 Hz, 1H, CHH′-(15)), 3.98 (dp, *J* = 10.1, 7.2 Hz, 1H, CHH′-(22)), 3.91 – 3.83 (m, 1H, CHH′-(22)), 3.79 (dp, *J* = 10.1, 7.2 Hz, 1H, CHH′-(22)), 3.66 – 3.57 (m, 1H, CHH′-(22)), 2.91 – 2.86 (m, 1H, CH-(5)), 2.71 – 2.61 (m, 2H, CH_2-(9)), 2.35 (ddd, *J* = 14.2, 5.0, 2.5 Hz, 1H, CHH′-(14)), 1.96 – 1.89 (m, 1H, CHH′-(6)), 1.83 (ddd, *J* = 14.2, 10.4, 3.9 Hz, 1H, CHH′-(14)), 1.74 – 1.64 (m, 2H, CH_2-(8)), 1.60 – 1.41 (m, 3H, CHH′-(6), CH_2-(7)), 1.18 (td, *J* = 7.1, 1.1 Hz, 3H, CH_3-(23)), 1.05 (td, *J* = 7.1, 1.1 Hz, 3H, CH_3-(23)); ^{13}C NMR (125 MHz, $CDCl_3$) δ_c/ppm: 155.2 (C(16)), 142.7 (C(10)), 138.0 (C(4)), 131.1 (C(3)), 128.6 (C(20)), 128.5 (C(12)), 128.4 (C(11)), 128.1 (C(18)), 127.0 (C(21)), 125.8 (C(13)), 121.0 (C(19)), 117.1 (C(17)), 91.3 (C(1)), 64.0 (C(15)), 63.8 (C(22)), 49.4 (C(5)), 49.4 (C(2)), 36.0 (C(9)), 31.8 (C(8)), 31.7 (C(6)), 28.4 (C(14)), 27.2 (C(7)), 16.1 (C(23)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.49; HRMS (ESI) *m/z* calcd for $C_{27}H_{35}O_5NaP$ $[M+H]^+$: 493.21143, found: 493.21150; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 3025.3 (w), 2929.8 (w), 2857.4 (w), 1452.0 (w), 1395.7 (w), 1263.2 (w), 1223.7 (w), 1029.8

(s), 983.0 (m), 962.7 (m), 771.1 (w), 753.1 (m), 700.2 (w); $[\alpha]^{25}_{589}$ = +15.3 (c=0.58 in $CHCl_3$, 13% ee).

tert-Butyl (3*S*,4*R*)-3-((diethoxyphosphoryl)oxy)-4-(4-phenylbutyl)-2,3,4,7-tetrahydro-1*H*-azepine-1-carboxylate (23b)



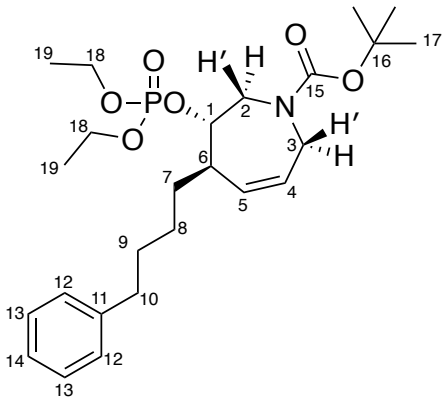
23b

Chemical Formula: $C_{25}H_{40}NO_6P$
Molecular Weight: 481.56976

Synthesised according to general procedure 1c, using *tert*-butyl (3*R*,6*S*)-3,6-bis((diethoxyphosphoryl)oxy)-2,3,6,7-tetrahydro-1*H*-azepine-1-carboxylate (**23a**) and 4-phenyl-1-butene as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (10-30-40% EtOAc in petroleum ether) to give **23b** as a yellow oil (140 mg, 73%). Obtained as a mixture of rotamers.

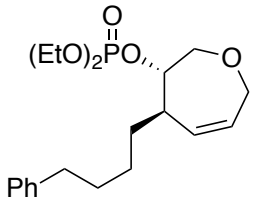
SFC was performed on a Waters UPC system equipped with a PDA (UV) detector and QDa (MS) detector using a Lux Cellulose 2 column (3.0 x 50 mm, 3 μm). Mobile phase A was CO_2 and mobile phase B was IPA with 20mM NH_3. A gradient from 5% to 50% mobile phase B over 3.5 minutes was used, followed by an increase to 60% over 0.05 minutes, a hold at 60% for 0.4 minutes and return to 5%. The total flow was 2 mL/min, the back pressure was 140 bar, and the column temperature was 40 °C. The PDA detector range was 210 – 400 nm.

SFC analysis indicated an enantiomeric excess of 93%, major enantiomer, t_R = 2.27min; minor enantiomer, t_R = 2.77 min].



^{1}H NMR (500 MHz, DMSO-d_6, 338K) δ_H/ppm: 7.26 (t, J = 7.6 Hz, 2H, 2ArH- (13)), 7.19 – 7.13 (m, 3H, 3ArH-(12, 14)), 5.71 – 5.66 (m, 1H, CH-(4)), 5.52 – 5.46 (m, 1H, CH-(5)), 4.37 – 4.29 (m, 1H, CH-(1)), 4.08 – 4.00 (m, 2H, 2CH_2-(18)), 3.98 – 3.89 (m, 2H, CH_2-(3)), 3.89 – 3.83 (m, 1H, CHH′-(2)), 3.56 (dd, J = 14.7, 5.2 Hz, 1H, CHH′-(2)), 2.59 (t, J = 7.6 Hz, 2H, CH_2-(10)), 2.62 – 2.54 (m, 1H, CH-(6)), 1.64 – 1.57 (m, 3H, CH_2-(9), CHH′-(7)), 1.42 (s, 9H, 3CH_3-(17)), 1.46 – 1.31 (m, 3H, CH_2-(8), CHH′-(7)), 1.27 (td, J = 7.2, 5.9 Hz, 6H, 2CH_3-(19)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 155.3, 142.6, 131.0, 130.3, 128.9, 128.6, 128.5, 128.4, 125.8, 80.3, 79.9, 79.0, 63.9, 50.6, 46.8, 46.6, 42.3, 36.0, 32.5, 32.1, 31.7, 28.5, 26.9, 16.3; ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: –1.60; HRMS (ESI) *m/z* calcd for $C_{25}H_{41}O_6NP$ $[M+H]^+$: 482.26660, found: 482.26662; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2928.9 (w), 2856.8 (w), 1694.3 (s), 1248.3 (m), 1166.8 (m), 1131.0 (w), 1008.6 (s), 749.4 (w), 699.9 (w); $[\alpha]^{25}_{589}$ = -94.1 (c=1.0 in $CHCl_3$, 93% ee).

Diethyl ((3*S*,4*R*)-4-(4-phenylbutyl)-2,3,4,7-tetrahydrooxepin-3-yl) phosphate (24b)

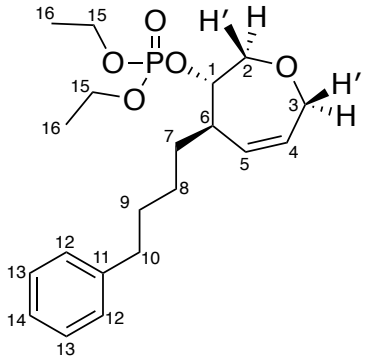


24b

Chemical Formula: $C_{20}H_{31}O_5P$
Molecular Weight: 382.43676

Synthesised according to general procedure 1c, using tetraethyl ((3*R*,6*S*)-2,3,6,7-tetrahydrooxepine-3,6-diyl) bis(phosphate) (**24a**) and 4-phenyl-1-butene as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (10-30-40% EtOAc in petroleum ether) to give **24b** as a yellow oil (109 mg, 71%).

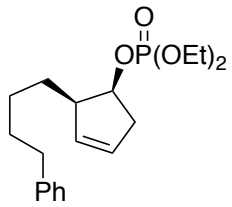
SFC analysis indicated an enantiomeric excess of 92% [Chiralpak® IG; flow: 1.5 mL/min; MeOH/CO_2: 1% to 30%; λ = 210 nm; minor enantiomer, t_R = 2.584 min; major enantiomer, t_R = 2.680 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.30 – 7.24 (m, 2H, 2ArH-(13)), 7.19 – 7.14 (m, 3H, 3ArH-(12, 14)), 5.61 – 5.55 (m, 1H, CH-(4)), 5.50 – 5.44 (m, 1H, CH-(5)), 4.40 (tt, *J* = 7.9, 3.6 Hz, 1H, CH-(1)), 4.33 (dq, *J* = 16.7, 2.4 Hz, 1H, CHH′-(3)), 4.16 (dt, *J* = 4.0, 1.6 Hz, 1H, CHH′-(3)), 4.13 – 4.04 (m, 4H, 2CH_2-(15)), 3.97 (dd, *J* = 4.9, 3.6 Hz, 2H, CH_2-(2)), 2.89 – 2.80 (m, 1H, CH-(6)), 2.61 (t, *J* = 7.6 Hz, 2H, CH_2-(10)), 1.74 – 1.60 (m, 3H, CH_2-(9), CHH′-(8)), 1.57 – 1.43 (m, 2H, CHH′-(7, 8)), 1.41 – 1.35 (m, 1H, CHH′-(7)), 1.32 (tdd, *J* = 7.1, 3.6,

1.0 Hz, 6H, $2CH_3$-(16)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 142.7 (C(11)), 130.1 (C(5)), 129.7 (C(4)), 128.5 (C(12)), 128.4 (C(13)), 125.8 (C(14)), 81.0 (C(1)), 73.2 (C(2)), 70.9 (C(3)), 63.9 (C(15)), 41.9 (C(6)), 36.0 (C(10)), 32.1 (C(8)), 31.7 (C(9)), 26.8 (C(7)), 16.3 (C(16)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: –1.58; HRMS (ESI) *m/z* calcd for $C_{20}H_{32}O_5P$ $[M+H]^+$: 383.19819, found: 383.19822; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 3025.9 (w), 2926.1 (w), 2855.6 (w), 1496.7 (w), 1274.1 (w), 1103.1 (w), 1029.9 (s), 748.7 (w), 699.7 (w); $[\alpha]^{25}_{589}$ = -46.0 (c=1.0 in $CHCl_3$, 92% ee).

Diethyl ((1*S*,2*R*)-2-(4-phenylbutyl)cyclopent-3-en-1-yl) phosphate (33)

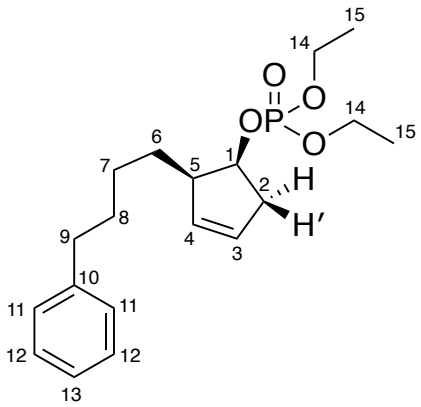


33

Chemical Formula: $C_{19}H_{29}O_4P$
Molecular Weight: 352.4108

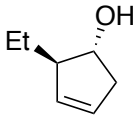
Synthesised according to general procedure 1b, using (1*S*,3*S*)-cyclopent-4-ene-1,3-diyl tetraethyl bis(phosphate) (**31**) and 4-phenyl-1-butene as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (20-40% EtOAc in petroleum ether) to give **33** as a yellow oil (91 mg, 65%).

HPLC analysis indicated an enantiomeric excess of >99% [Chiralpak® IA; flow: 1.0 mL/min; hexane/iPrOH: 95:5; λ = 210 nm; minor enantiomer, t_R = 9.663 min; major enantiomer, t_R = 10.616 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.30 – 7.24 (m, 2H, ArH-(12)), 7.20 – 7.15 (m, 3H, ArH-(11, 13)), 5.72 – 5.67 (m, 2H, 2CH-(3, 4)), 4.99 (dtd, *J* = 6.8, 5.7, 3.7 Hz, 1H, CH-(1)), 4.14 – 4.03 (m, 4H, $2CH_2$-(14)), 2.74 – 2.66 (m, 1H, CH-(5)), 2.65 – 2.58 (m, 4H, $2CH_2$-(2, 9)), 1.71 – 1.59 (m, 3H, CH_2-(8), CHH′-(6)), 1.50 – 1.40 (m, 3H, CH_2-(7), CHH′-(6)), 1.32 (td, *J* = 7.1, 1.0 Hz, 6H, $2CH_3$-(15)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 142.8 (C(10)), 133.2 (C(4)), 128.5 (C(11)), 128.4 (C(12)), 127.4 (C(3)), 125.8 (C(13)), 79.8 (C(1)), 63.7 (C(14)), 49.1 (C(5)), 39.9 (C(2)), 36.1 (C(9)), 32.0 (C(6)), 28.1 (C(8)), 27.8 (C(7)), 16.3 (C(15)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: 7.26; HRMS (ESI) *m/z* calcd for $C_{19}H_{29}O_4NaP$ $[M+Na]^+$: 375.16957, found: 375.16960; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2981.3 (w), 2932.2 (w), 2857.9 (w), 1603.9 (w), 1454.2 (w), 1393.0 (w), 1262.5 (m), 1165.6 (w), 1029.5 (s), 973.5 (m), 819.8 (w), 746.5 (w), 700.2 (w); $[\alpha]^{25}_{589}$ = -36.1 (c=1.0 in $CHCl_3$, >99% ee).

(1*R*,2*R*)-2-ethylcyclopent-3-en-1-ol (27)



27

Chemical Formula: $C_7H_{12}O$
Molecular Weight: 112.1720

To a solution of **1c** (98 μL, 0.4 mmol, 1.0 eq) in Et_2O was added $LiAlH_4$ (1.0 M in Et_2O, 0.89 mL, 0.89 mmol, 2.2 eq) at 0 ˚C. The mixture was left to stir at room temperature for 90 mins before quenching with dropwise addition of H_2O, until effervescence stopped. The resulting

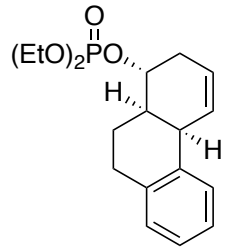
residue was suspended in CH_2Cl_2 and filtered through celite, washing the filter pad with CH_2Cl_2. The filtrate was evaporated *in vacuo* and purified on silica (40% Et_2O in pentane) to give **27** as a colourless oil (43 mg, 96%; **NOTE**: Product is volatile and should not be dried by high vacuum. Rotary evaporator at 35 ˚C, 150 mbar was sufficient).

The product was derivatised according to general procedure 2 (esterification process only) for HPLC analysis.

HPLC analysis indicated an enantiomeric excess of 90% [Chiralpak® ID; flow: 0.7 mL/min; hexane/iPrOH: 99:1; λ = 210 nm; minor enantiomer, t_R = 14.157 min; major enantiomer, t_R = 14.785 min].

^{1}H NMR (500 MHz, $CDCl_3$) δ_H/ppm: 5.68 – 5.65 (m, 1H, CH-(4)), 5.64 – 5.61 (m, 1H, CH-(3)), 4.66 (tt, *J* = 6.6, 3.1 Hz, 1H, CH-(1)), 4.08 (dtd, *J* = 14.6, 7.1, 3.2 Hz, 4H, 2CH_2-(8)), 2.77 – 2.72 (m, 1H, C***H***H´-(2)), 2.73 – 2.67 (m, 1H, CH-(5)), 2.51 – 2.44 (m, 1H, CH***H´***-(2)), 1.52 – 1.39 (m, 1H, CHH´-(6)), 1.39 – 1.33 (m, 1H, CHH´-(6)), 1.31 (tdd, *J* = 7.1, 2.3, 1.0 Hz, 6H, CH_3-(9)), 0.93 (t, *J* = 7.5 Hz, 3H, 2CH_3-(7)); ^{13}C NMR (126 MHz, $CDCl_3$) δ_c/ppm: 132.5 (C(4)), 127.3 (C(3)), 82.9 (C(1), 63.7 (C(8)), 54.6 (C(5)), 40.0 (C(2)), 25.6 (C(6)), 16.3 (C(9)), 11.8 (C(7)). Consistent with data found in the literature.[226]

Diethyl ((1*R*,4a*R*,10a*R*)-1,4,4a,9,10,10a-hexahydrophenanthren-1-yl) phosphate (28)

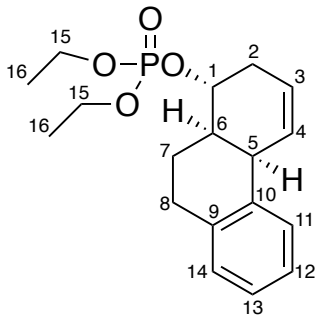


28

Chemical Formula: $C_{18}H_{25}O_4P$
Molecular Weight: 336.3678

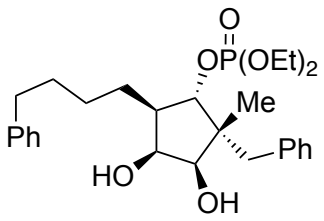
A 10 mL round bottomed flask was charged with $Pd(OAc)_2$ (12 mg, 0.054 mmol, 0.15 eq), 1,3-bis(diphenylphosphino)propane (45 mg, 0.108 mmol, 0.30 eq) and K_2CO_3 (199 mg, 1.44 mmol, 4.0 eq). The flask was purged with Ar 3 times and capped with a rubber septum. The mixture was suspended in toluene (4 mL), before adding **2m** (119 µL, 0.36 mmol, 1.0 eq). The flask was wrapped in parafilm to prevent loss of solvent, and stirred at 110 ˚C (dark brown mixture forms) for 21 hours. The reaction mixture was cooled to room temperature, poured over H_2O (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The organic layers were combined, washed with brine (50 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a brown oil. The oil was purified on silica (20-30-40% EtOAc in petroleum ether) to give **28** as a yellow oil (97 mg, 80%).

HPLC analysis indicated an enantiomeric excess of 91% [Chiralpak® IA; flow: 1.0 mL/min; hexane/iPrOH: 95:5; λ = 210 nm; major enantiomer, t_R = 8.687 min; minor enantiomer, t_R = 11.302 min].



^{1}H NMR (500 MHz, $CDCl_3$) δ_H/ppm: 7.25 (d, *J* = 7.6 Hz, 1H, ArH-(11)), 7.18 (td, *J* = 7.4, 1.5 Hz, 1H, ArH-(13)), 7.13 (td, *J* = 7.4, 1.5 Hz, 1H, ArH-(12)), 7.08 (d, *J* = 7.3 Hz, 1H, ArH-(14)), 5.78 – 5.71 (m, 1H, CH-(4)), 5.55 – 5.48 (m, 1H, CH-(3)), 4.70 (dq, *J* = 7.6, 3.8 Hz, 1H, CH-(1)), 4.16 – 4.06 (m, 4H, CH_2-(15)), 3.69 (m, 1H, CH-(5)), 2.88 – 2.74 (m, 2H, CH_2-(8)), 2.44 – 2.38 (m, 1H, CH-(6)), 2.36 (m, 2H, CH_2-(2)), 1.75 – 1.56 (m, 2H, CH_2-(7)), 1.33 (dtd, *J* = 11.1, 7.1, 1.0 Hz, 6H, CH_3-(16)); ^{13}C NMR (126 MHz, $CDCl_3$) δ_c/ppm: 138.8 (C(10)), 136.6 (C(9)), 131.5 (C(4)), 129.3 (C(11)), 129.1 (C(14)), 126.4 (C(13)), 126.1 (C(12)), 120.8 (C(3)), 76.3 (C(1)), 63.8 (C(15)), 37.6 (C(6)), 35.7 (C(5)), 28.9 (C(8)), 28.6 (C(2)), 22.6 (C(7)), 16.3 (C(16)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.21; HRMS (ESI) *m/z* calcd for $C_{18}H_{26}O_4P$ $[M+H]^+$: 337.15632, found: 337.15604; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2982.2 (w), 2929.8 (w), 1488.9 (w), 1448.1 (w), 1392.8 (w), 1261.4 (m), 1165.4 (w), 1028.8 (s), 1009.0 (s), 818.7 (w), 775.1 (w), 744.9 (m), 679.0 (w); $[\alpha]^{25}_{589}$ = -80.3 (c=1.0 in $CHCl_3$, 91% ee).

(1*S*,2*R*,3*R*,4*S*,5*R*)-2-benzyl-3,4-dihydroxy-2-methyl-5-(4-phenylbutyl)cyclopentyl diethyl phosphate (29)



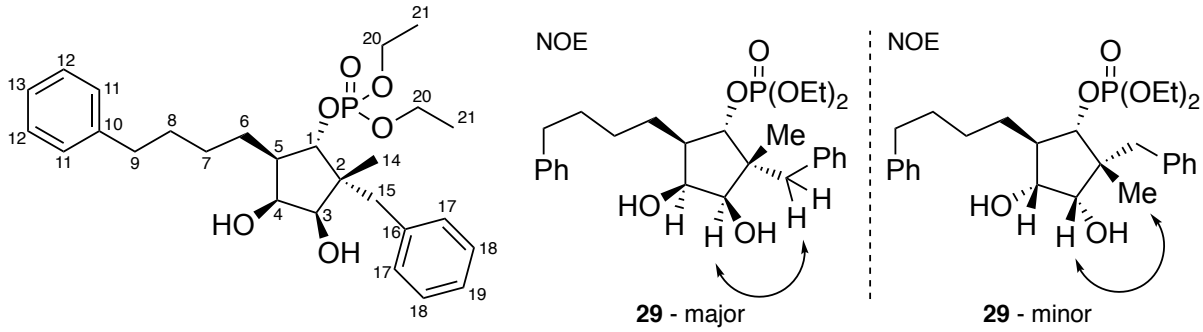
29

Chemical Formula: $C_{27}H_{39}O_6P$
Molecular Weight: 490.57676

To a solution of **4b** (100 mg, 0.22 mmol, 1.0 eq, 94% ee) in acetone (350 µL) and H_2O (90 µL) was added NMO (39 mg, 0.33 mmol, 1.50 eq) and $K_2OsO_4 \cdot H_2O$ (3 mg, 0.008 mmol, 4 mol%) at rt. The resulting heterogeneous mixture was stirred for 21 hours at rt. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ (1 mL) and stirred for a further 20 minutes. The mixture was extracted with EtOAc (3 x 2 mL). The organic layers were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. The yellow oil was purified on silica (30-70% EtOAc in heptane) to give **17** as a yellow oil (107 mg, 75%, 94% ee). Other diastereomer observed in crude NMR at a 4:1 ratio in favour of the isolated product.

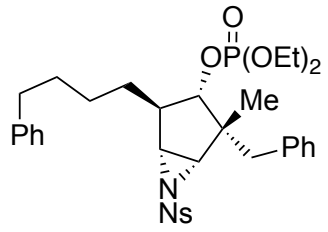
SFC was performed on a Waters UPC system equipped with a PDA (UV) detector and QDa (MS) detector using a Daicel Chiralpak IC column (3.0 x 50 mm, 3 µm). Mobile phase A was CO_2 and mobile phase B was methanol with 20mM NH_3. A gradient from 5% to 50% mobile phase B over 3.5 minutes was used, followed by an increase to 60% over 0.05 minutes, a hold at 60% for 0.4 minutes and return to 5%. The total flow was 2 mL/min, the back pressure was 140 bar, and the column temperature was 40 °C. The PDA detector range was 210 – 400 nm.

SFC analysis indicated an enantiomeric excess of 94%; major enantiomer, t_R = 1.65 min ; minor enantiomer, t_R = 2.20 min].



^{1}H NMR (500 MHz, $CDCl_3$) δ_H/ppm: 7.31 – 7.26 (m, 4H, 4ArH-(12, 18), 7.25 – 7.20 (m, 3H, 3ArH-(17, 19)), 7.20 – 7.15 (m, 3H, 3ArH-(11, 13)), 4.46 (t, *J* = 9.0 Hz, 1H, CH-(1)), 4.18 – 4.09 (m, 5H, CH-(4)), $2CH_2$-(20)), 4.03 (d, *J* = 4.5 Hz, 1H, CH-(3)), 2.77 (d, *J* = 13.5 Hz, 1H, CHH´-(15)), 2.70 – 2.57 (m, 2H), 2.65 (d, *J* = 12.1 Hz, 1H, CHH´-(15)), 1.97 – 1.89 (m, 1H, CH-(5)), 1.75 – 1.62 (m, 4H, $2CH_2$-(6, 8)), 1.60 – 1.50 (m, 1H, CHH´-(7)), 1.42 – 1.30 (m, 1H, CHH´-(7)), 1.36 (m, 6H, $2CH_3$-(21)), 1.14 (s, 3H, CH_3-(14)); ^{13}C NMR (126 MHz, $CDCl_3$) δ_c/ppm: 142.8 (C(10)), 138.4 (C(16)), 130.6 (C(17)), 128.5 (C(12)), 128.3 (C(11)), 128.3 (C(18)), 126.5 (C(19)), 125.7 (C(13)), 91.0 (C(1)), 76.9 (C(3)), 71.4 (C(4)), 64.0 (C(20)), 46.3 (C(5)), 46.2 (C(2)), 41.8 (C(15)), 36.0 (C(9)), 31.8 (C(8)), 27.8 (C(7)), 26.6 (C(6)), 21.2 (C(14)), 16.3 (C(21)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: 1.23; HRMS (ESI) *m/z* calcd for $C_{27}H_{39}O_6NaP$ $[M+Na]^+$: 513.23765, found: 513.23778; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 3360.5 (br. w), 3026.6 (w), 2933.1 (w), 1248.7 (w), 1024.2 (s), 981.0 (w), 754.9 (w), 701.2 (w); $[\alpha]^{25}_{589}$ = -42.9 (c=1.0 in $CHCl_3$, 94% ee).

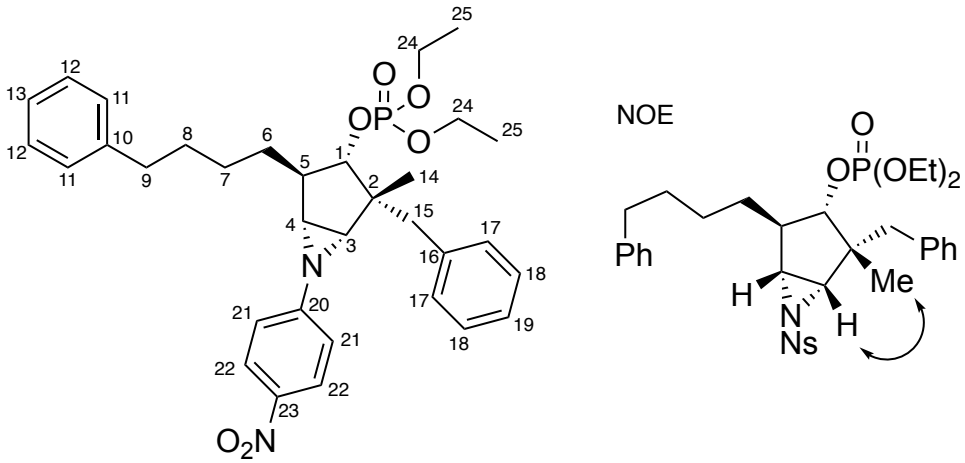
(1*S*,2*R*,3*S*,4*R*,5*R*)-2-benzyl-2-methyl-6-((4-nitrophenyl)sulfonyl)-4-(4-phenylbutyl)-6-azabicyclo[3.1.0]hexan-3-yl diethyl phosphate (30)



30

Chemical Formula: $C_{33}H_{41}N_2O_8PS$
Molecular Weight: 656.73076

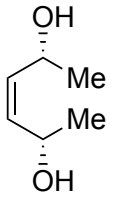
To a solution of **4b** (50 mg, 0.11 mmol, 1.0 eq, 94% ee) in MeCN (2.5 mL) under a N_2 atmosphere was added 4-nitro-*N*-(phenyl-λ^3-iodaneylidene)benzenesulfonamide (prepared according to literature procedure) (66 mg, 0.16 mmol, 1.5 eq) and $Cu(OTf)_2$ (6.0 mg, 0.017 mmol, 0.15 eq). The resulting mixture was left to stir at rt for 16 hours. The mixture was loaded onto silica and purified on silica (20-40% EtOAc in heptane) to give **30** as a yellow oil (24.5 mg, 34%).



^{1}H NMR (500 MHz, $CDCl_3$) δ_H/ppm: (d, *J* = 8.8 Hz, 2H, 2ArH-(22)), 8.02 (d, *J* = 8.8 Hz, 2H, 2ArH-(21)), 7.34 – 7.27 (m, 4H, 5ArH-(12, 18, 19)), 7.23 – 7.19 (m, 1H, ArH-(13)), 7.20 – 7.16 (m, 2H, 2ArH-(17)), 7.14 – 7.10 (m, 2H, 2ArH-(11)), 4.21 – 4.03 (m, 4H, $2CH_2$-(24)), 3.81 (dd, *J* = 9.2, 7.9 Hz, 1H, CH-(1)), 3.33 (s, 2H, 2CH-(3, 4)), 2.75 (d, *J* = 13.8 Hz, 1H, CHH′-(15)), 2.65 (d, *J* = 13.8 Hz, 1H, CHH′-(15)), 2.56 – 2.45 (m, 2H, CH_2-(9)), 2.01 – 1.95 (m, 1H, CH-(5)), 1.73 – 1.65 (m, 1H, CHH′-(6)), 1.53 – 1.43 (m, 1H, CHH′-(8)), 1.41 – 1.35

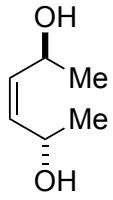
(m, 1H, CHH′-(8)), 1.36 (td, J = 7.1, 0.9 Hz, 3H, CH_3-(25)), 1.32 (td, J = 7.1, 0.9 Hz, 3H, CH_3-(25)), 1.29 – 1.18 (m, 2H, CH_2-(7)), 1.17 – 1.11 (m, 1H, CHH′-(6)), 1.09 (s, 3H, CH_3-(14)); ^{13}C NMR (126 MHz, $CDCl_3$) δ_c/ppm: 150.7 (C(23)), 144.0 (C(20)), 142.3 (C(10)), 136.6 (C(16)), 130.9 (C(17)), 129.2 (C(21)), 128.5 (C(11)), 128.5 (C(12)), 127.0 (C(19)), 126.0 (C(13)), 124.3 (C(22)), 87.1 (C(1)), 64.2 (C(24)), 52.2 (C(3)), 47.3 (C(4)), 45.3 (C(2)), 44.7 (C(5)), 39.1 (C(15)), 35.9 (C(9)), 31.5 (C(8)), 28.9 (C(6)), 27.4 (C(7)), 20.7 (C(14)), 16.3 (C(25)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: –1.57; HRMS (ESI) *m/z* calcd for $C_{33}H_{41}N_2O_8PS$ $[M+H]^+$: 657.73076, found: 657.73081; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 3103.7 (w), 3029.5 (w), 2936.0 (w), 1528.3 (s), 1402.4 (s), 1329.1 (s), 1247.7 (w), 1151.4 (s), 1023.1 (s), 981.2 (w), 752.3 (w), 700.3 (w); $[\alpha]^{25}_{589}$ = -51.2 (c=1.0 in $CHCl_3$, 94% ee).

***cis*-Hex-3-ene-2,5-diol (34) and *trans*-hex-3-ene-2,5-diol (35)**



34

Chemical Formula: $C_6H_{12}O_2$
Molecular Weight: 116.16000



35

Chemical Formula: $C_6H_{12}O_2$
Molecular Weight: 116.16000

To a solution of 3-hexyn-2,5-diol (mixture of diastereomers) (22.62 mL, 200.0 mmol, 1 eq) in EtOAc (500 mL) was added Lindlar's catalyst (560 mg) and quinoline (0.1 mL). The resulting mixture was sparged with H_2 for 10 minutes before stirring under a H_2 atmosphere for 18 hours. The reaction mixture was filtered over celite, rinsing the pad with EtOAc. The filtrate was evaporated *in vacuo* and the residue was dissolved in 50 mL of 2:1 $CHCl_3$:hexane. The solution was stored in a freezer overnight to give colourless crystals. The mixture was filtered and the crystals were washed with cold hexane to give *trans*-diol **35** as colourless crystals (7.63 g, 33%). The filtrate was again concentrated and the residue was dissolved in 25 mL of 2:1 $CHCl_3$:hexane. The solution was again stored in a freezer overnight to precipitate more **35** (1.95 g, 8%, 41% overall). The filtrate was evaporated *in vacuo* to give a yellow oil. The yellow oil was purified on silica (100% Et_2O) to give *cis*-diol **34** as a colourless oil (more polar spot R_f = 0.41 in 100% EtOAc 4.51 g, 19%).

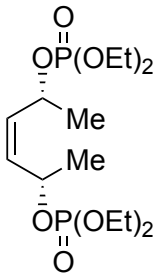
Analytical data for *cis*-hex-3-ene-2,5-diol (34)

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 5.45 (dd, J = 5.6, 1.8 Hz, 2H), 4.70 – 4.59 (m, 2H), 3.58 (s, 2H), 1.23 (d, J = 6.3 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 134.8, 63.5, 23.5. Consistent with data in the literature.[227]

Analytical data for *trans*-hex-3-ene-2,5-diol (35)

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 5.47 (dd, J = 4.9, 1.7 Hz, 2H), 4.73 – 4.63 (m, 2H), 1.94 (s, 2H), 1.30 (d, J = 6.3 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 134.7, 64.6, 24.1. Consistent with data in the literature.[228]

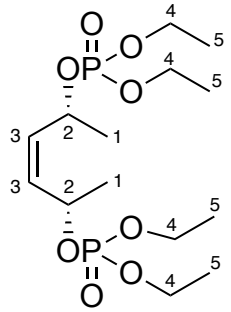
Tetraethyl (*cis*-hex-3-ene-2,5-diyl) bis(phosphate) (36)



36

Chemical Formula: $C_{14}H_{30}O_8P_2$
Molecular Weight: 388.33352

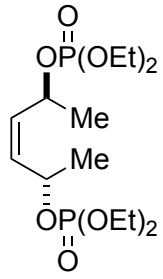
Synthesised according to general procedure 6 using **34** on a 3.53 mmol scale. Purified by flash chromatography (0-4% MeOH in EtOAc) to give Tetraethyl (*cis*-hex-3-ene-2,5-diyl) bis(phosphate) (**36**) as a colourless oil (841 mg, 61%).



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 5.55 (dd, J = 5.3, 1.8 Hz, 2H, 2CH-(3)), 5.25 – 5.16 (m, 2H, 2CH-(2)), 4.15 – 4.03 (m, 8H, 4CH_2-(4)), 1.38 (d, J = 6.4 Hz, 6H, 2CH_3-(1)), 1.32 (td, J = 7.1, 3.2 Hz, 6H, 2CH_3-(5)), 1.30 (td, J = 7.1, 3.2 Hz, 6H, 2CH_3-(5)); ^{13}C NMR (101 MHz,

$CDCl_3$) δ_c/ppm: 131.3 (C(3)), 71.2 (C(2)), 63.8 (C(4)), 23.0 (C(1)), 16.2 (C(5)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_p/ppm: –2.07; HRMS (ESI) *m/z* calcd for $C_{14}H_{30}O_8NaP_2$ $[M+Na]^+$: 411.13081, found: 411.13043; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2984.5 (w), 1446.0 (w), 1377.8 (w), 1260.1 (m), 1165.6 (w), 1018.7 (s), 976.5 (s), 868.6 (w), 819.8 (w), 758.4 (w).

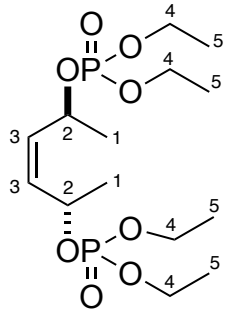
Tetraethyl (*trans*-hex-3-ene-2,5-diyl) bis(phosphate) (37)



37

Chemical Formula: $C_{14}H_{30}O_8P_2$
Molecular Weight: 388.33352

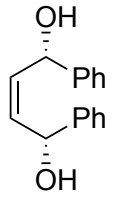
Synthesised according to general procedure 6 using **35** on a 4.91 mmol scale. Purified by flash chromatography (0-4% MeOH in EtOAc) to give Tetraethyl (*trans*-hex-3-ene-2,5-diyl) bis(phosphate) (**37**) as a colourless oil (1.21 g, 63%).



^1H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 5.49 (dd, *J* = 6.2, 2.1 Hz, 2H, 2CH-(3)), 5.30 – 5.25 (m, 2H, 2CH-(2)), 4.10 – 3.98 (m, 8H, $4CH_2$-(4)), 1.41 (d, *J* = 6.4 Hz, 3H, CH_3-(1)), 1.40 (d, *J* = 6.3 Hz, 3H, CH_3-(1)), 1.29 (td, *J* = 7.1, 4.8 Hz, 6H, $2CH_3$-(5)), 1.28 (td, *J* = 7.1, 4.8 Hz, 6H, $2CH_3$-(5)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 131.8 (C(3)), 71.1 (C(2)), 63.7 (C(4)), 22.5

(C(1)), 16.2 (C(5)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_p/ppm: –1.85; HRMS (ESI) *m/z* calcd for $C_{14}H_{30}O_8NaP_2$ $[M+Na]^+$: 411.13081, found: 411.13056; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2986.0 (w), 1446.4 (w), 1374.4 (w), 1259.9 (m), 1165.9 (w), 1027.3 (s), 977.1 (s), 820.4 (w).

(*cis*)-1,4-Diphenylbut-2-ene-1,4-diol (38)



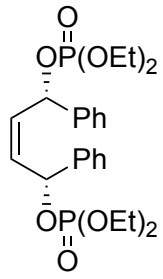
38

Chemical Formula: $C_{16}H_{16}O_2$
Molecular Weight: 240.30200

To a solution of 1,4-diphenylbut-2-yne-1,4-diol (mixture of diastereomers) (4.10 g, 17.22 mmol, 1 eq) in EtOAc (250 mL) was added Lindlar's catalyst (260 mg) and quinoline (0.05 mL). The resulting mixture was sparged with H_2 for 10 minutes before stirring under a H_2 atmosphere for 18 hours. The reaction mixture was filtered over celite, rinsing the pad with EtOAc. The filtrate was evaporated *in vacuo* to give a yellow oil. The yellow oil was purified on silica (20-30-40-50-60-80% EtOAc in petroleum ether) to give *cis*-diol **38** as a colourless oil (more polar spot R_f = 0.22 in 55% EtOAc in petroleum ether, 692 mg, 17%).

^{1}H NMR (400 MHz, d_4-MeOD) δ_H/ppm: 7.17 – 7.14 (m, 5H), 7.15 – 7.08 (m, 2H), 5.64 – 5.52 (m, 2H); ^{13}C NMR (101 MHz, d_4-MeOD) δ_c/ppm: 143.5, 132.5, 128.0, 126.0, 69.3. Consistent with data in the literature.[229]

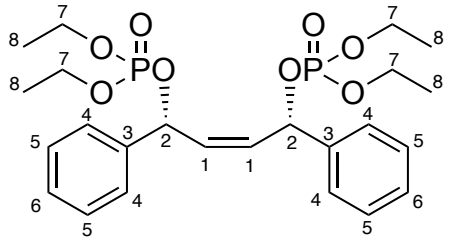
Tetraethyl (*cis*-hex-3-ene-2,5-diyl) bis(phosphate) (36)



39

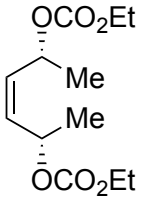
Chemical Formula: $C_{24}H_{34}O_8P_2$
Molecular Weight: 512.47552

Synthesised according to general procedure 6 using **38** on a 2.25 mmol scale. Purified by flash chromatography (0-1-3% MeOH in EtOAc) to give Tetraethyl (*cis*-hex-3-ene-2,5-diyl) bis(phosphate) (**39**) as a colourless oil (910 mg, 79%). **NOTE**: Unstable on silica, columned as fast as possible.



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.27 – 7.23 (m, 3H, 3ArH-(4,6)), 7.21 – 7.17 (m, 2H, 2ArH-(5)), 6.14 (ddd, *J* = 7.3, 5.2, 1.6 Hz, 2H, CH-(2)), 5.93 (dd, *J* = 5.2, 1.7 Hz, 2H, 2CH-(1)), 4.14 – 3.90 (m, 8H, 4CH_2-(7)), 1.28 – 1.24 (dd, *J* = 7.1, 1.0 Hz, 3H, CH_3-(8)), 1.24 – 1.19 (dd, *J* = 7.1, 1.0 Hz, 3H, CH_3-(8)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 139.4 (C(3)), 130.9 (C(1)), 128.7 (C(5)), 128.6 (C(6)), 127.2 (C(4)), 76.1 (C(2)), 63.8 (C(7)), 16.1 (C(8)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_p/ppm: –1.94; HRMS (ESI) *m/z* calcd for $C_{24}H_{34}O_8NaP_2$ $[M+Na]^+$: 535.16448, found: 535.16205; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2987.5 (w), 1455.7 (w), 1394.6 (w), 1261.5 (m), 1165.8 (w), 1020.1 (s), 976.2 (s), 859.3 (w), 802.4 (w), 748.5 (w), 699.3 (w).

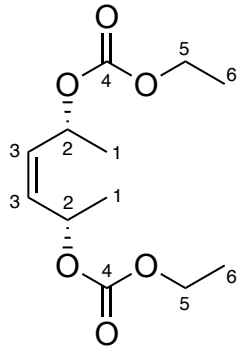
Diethyl (*cis*-hex-3-ene-2,5-diyl) bis(carbonate) (40)



40

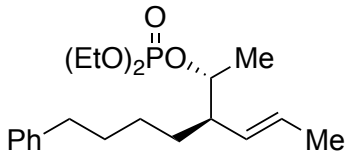
Chemical Formula: $C_{12}H_{20}O_6$
Molecular Weight: 260.28600

Synthesised according to general procedure 6 using ethyl chloroformate and **34** on a 9.90 mmol scale. Purified by flash chromatography (100% CH_2Cl_2) to give Diethyl (*cis*-hex-3-ene-2,5-diyl) bis(carbonate) (**40**) as a colourless oil (2.028 g, 79%).



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 5.57 – 5.51 (m, 4H, 4CH-(2, 3)), 4.17 (q, J = 7.1 Hz, 4H, $2CH_2$-(5)), 1.34 (d, J = 5.9 Hz, 6H, $2CH_3$-(1)), 1.28 (t, J = 7.1 Hz, 6H, $2CH_3$-(6)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 154.4 (C(4)), 131.3 (C(3)), 70.6 (C(2)), 63.89 (C(5)), 21.0 (C(1)), 14.4 (C(6)); HRMS (ESI) *m/z* calcd for $C_{12}H_{20}O_6Na$ $[M+Na]^+$: 283.11631, found: 283.11499; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2986.3 (w), 1739.4 (s), 1448.4 (w), 1371.5 (w), 1247.2 (s), 1072.5 (w), 1027.4 (w), 1007.1 (w), 882.8 (w), 853.6 (w), 836.0 (w), 790.6 (w).

Diethyl ((2*R*,3*R*)-7-phenyl-3-((*E*)-prop-1-en-1-yl)heptan-2-yl) phosphate (38)

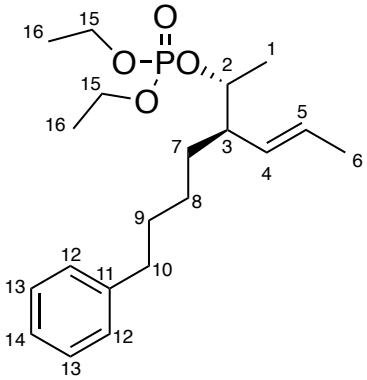


38

Chemical Formula: $C_{20}H_{33}O_4P$
Molecular Weight: 368.45376

Synthesised according to general procedure 1b, using **L14**, Tetraethyl (*cis*-hex-3-ene-2,5-diyl) bis(phosphate) (**36**) and 4-phenyl-1-butene as the alkene partner (hydrozirconation time 20 mins). Purified by flash chromatography (20-40% EtOAc in petroleum ether) to give **38** as a yellow oil (27 mg, 18%).

SFC analysis indicated an enantiomeric excess of 75% [Chiralpak® IA; flow: 1.5 mL/min; MeOH/CO_2: 1% to 50%; λ = 210 nm; major enantiomer, t_R = 3.633 min; minor enantiomer, t_R = 3.787 min].

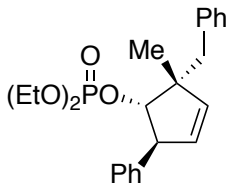


^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.29 – 7.22 (m, 2H, ArH-(13), 7.19 – 7.14 (m, 3H, ArH-(12, 14)), 5.49 – 5.39 (m, 1H, CH-(5)), 5.20 (ddd, *J* = 15.3, 9.2, 1.7 Hz, 1H, CH-(4)), 4.49 – 4.40 (m, 1H, CH-(2)), 4.14 – 4.03 (m, 4H, 2CH_2-(15)), 2.66 – 2.52 (m, 2H, CH_2-(10)), 2.11 – 2.02 (m, 1H, CH-(3)), 1.67 (dd, *J* = 6.4, 1.6 Hz, 3H, CH_3-(6)), 1.65 – 1.56 (m, 2H, CH_2-(9)), 1.55 – 1.48 (m, 1H, CHH′-(7)), 1.45 – 1.36 (m, 1H, CHH′-(8)), 1.32 (tdd, *J* = 7.1, 1.8, 1.0 Hz, 6H, 2CH_3-(16)), 1.29 – 1.27 (m, 2H, 2CHH′-(7, 8)), 1.26 (d, *J* = 6.4 Hz, 3H, CH_3-(1)); ^{13}C

NMR (101 MHz, $CDCl_3$) δ_c/ppm: 142.9 (C(11)), 130.3 (C(4)), 128.5 (C(13)), 128.4 (C(12)), 128.3 (C(5)), 125.7 (C(14)), 78.5 (C(2)), 63.6 (C(15)), 49.0 (C(3)), 36.0 (C(10)), 31.6 (C(9)), 30.4 (C(7)), 27.1 (C(8)), 19.1 (C(1)), 18.2 (C(6)), 16.3 (C(16)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: –1.46; HRMS (ESI) *m/z* calcd for $C_{22}H_{33}O_4NaP$ $[M+Na]^+$: 391.20326, found: 391.20367; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2932.7 (w), 2856.9 (w), 1453.4 (w), 1262.1 (m), 1032.5 (s), 1002.6 (s), 819.9 (w), 748.8 (w), 699.8 (w); $[\alpha]^{25}_{589}$ = +7.0 (c=1.0 in $CHCl_3$, 75% ee).

4.5 Experimental Procedures for Chapter 3

(1*S*,2*R*,5*S*)-2-Benzyl-2-methyl-5-phenylcyclopent-3-en-1-yl diethyl phosphate (4g)

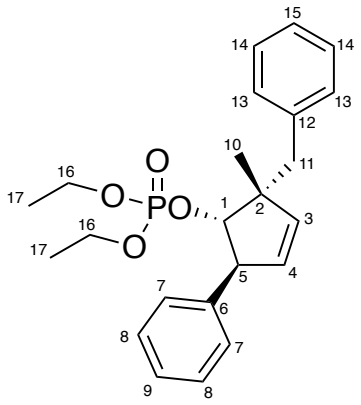


4g

Chemical Formula: $C_{23}H_{29}O_4P$
Molecular Weight: 400.45476

Synthesised according to general procedure 2b using (1*R*,2*S*,3*S*)-2-Benzyl-2-methylcyclopent-4-ene-1,3-bis(diethyl phosphate) (**4a**) on a 0.4 mmol scale. Purified by flash chromatography (10-30-40% EtOAc in petroleum ether) to give (1*S*,2*R*,5*S*)-2-benzyl-2-methyl-5-phenylcyclopent-3-en-1-yl diethyl phosphate (**4g**) as a yellow oil (138 mg, 86%).

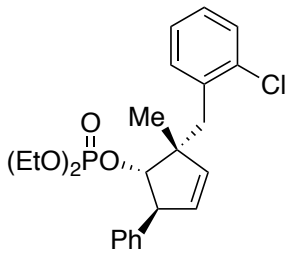
SFC analysis indicated an enantiomeric excess of >99% [Chiralpak® IA; flow: 1.5 mL/min; MeOH/CO_2: 1% to 30%; λ = 210 nm; minor enantiomer, t_R = 2.443 min; major enantiomer, t_R = 2.591 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.34 – 7.18 (m, 10H, 10ArH-(7-9, 12-15)), 5.61 (ddd, *J* = 6.2, 1.6, 1.1 Hz, 1H, CH-(3)), 5.53 (dd, *J* = 6.2, 2.5 Hz, 1H, CH-(4)), 4.56 (dd, *J* = 8.6, 7.8 Hz, 1H, CH-(1)), 4.08 – 3.99 (m, 1H, CH_2-(16)), 3.97 (dt, *J* = 7.8, 2.2 Hz, 1H, CH-(5)), 3.91 – 3.70 (m, 3H, CH_2-(3)), 2.99 (d, *J* = 13.0 Hz, 1H, CHH′-(11)), 2.75 (d, *J* = 13.0 Hz, 1H, CHH′-

(11)), 1.22 (td, J = 7.1, 1.1 Hz, 3H, CH_3-(17)), 1.21 (s, 3H, CH_3-(10)), 1.11 (td, J = 7.1, 1.1 Hz, 3H, CH_3-(17)); ^{13}C NMR (126 MHz, $CDCl_3$) δ_c/ppm: 142.0 (C(6)), 139.0 (C(4)), 138.7 (C(12)), 131.0 (C(13)), 130.0 (C(3)), 129.6 (C(7)), 128.2 (C(8)), 127.8 (C(14)), 127.1 (C(9)), 126.1 (C(15)), 93.7 (C(1)), 63.7 (C(16)), 56.2 (C5)), 50.9 (C(2)), 41.0 (C(11)), 24.2 (C(10)), 16.1 (C(17)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.84; HRMS (ESI) *m/z* calcd for $C_{23}H_{39}O_4NaP$ $[M+Na]^+$: 423.16957, found: 423.16941; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2981.0 (w), 1494.7 (w), 1453.9 (w), 1264.3 (w), 1025.9 (s), 974.1 (m), 750.4 (w), 701.7 (w); $[\alpha]^{25}_{589}$ = -169.4 (c=1.0 in $CHCl_3$, >99% ee).

(1*S*,2*R*,5*S*)-2-(2-Chlorobenzyl)-2-methyl-5-phenylcyclopent-3-en-1-yl diethyl phosphate (11c)

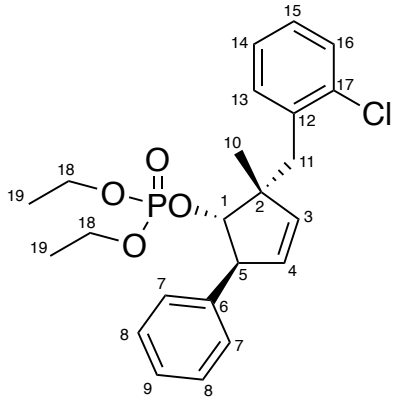


11c

Chemical Formula: $C_{23}H_{28}ClO_4P$
Molecular Weight: 434.89676

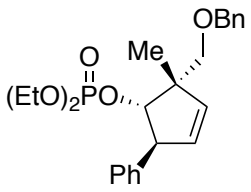
Synthesised according to general procedure 2b using (1*R*,2*S*,3*S*)-2-(2-chlorobenzyl)-2-methylcyclopent-4-ene-1,3-bis(diethyl phosphate) (**11a**) on a 0.4 mmol scale. Purified by flash chromatography (10-30-40% EtOAc in petroleum ether) to give 1*S*,2*R*,5*S*)-2-(2-chlorobenzyl)-2-methyl-5-phenylcyclopent-3-en-1-yl diethyl phosphate (**11c**) as a yellow oil (158 mg, 91%).

SFC analysis indicated an enantiomeric excess of >99% [Chiralpak® IA; flow: 1.5 mL/min; MeOH/CO_2: 1% to 30%; λ = 210 nm; minor enantiomer, t_R = 2.755 min; major enantiomer, t_R = 2.936 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.36 – 7.33 (m, 1H, ArH-(15)), 7.33 – 7.28 (m, 3H, 3ArH-(8, 16)), 7.27 – 7.22 (m, 3H, 3ArH-(7, 9)), 7.20 – 7.11 (m, 2H, 2ArH-(13, 14)), 5.58 (s, 2H, 2CH-(3, 4)), 4.56 (dd, *J* = 8.8, 7.8 Hz, 1H, CH-(1)), 4.06 – 3.97 (m, 2H, CH-(5), CH_2-(18)), 3.90 – 3.69 (m, 3H, CH_2-(18)), 3.09 (s, 2H, CH_2-(11)), 1.25 (s, 3H, CH_3-(10)), 1.20 (td, *J* = 7.1, 1.1 Hz, 3H, CH_3-(19)), 1.11 (td, *J* = 7.1, 1.1 Hz, 3H, CH_3-(19)); ^{13}C NMR (126 MHz, $CDCl_3$) δ_c/ppm: 141.9 (C(6)), 138.6 (C(4)), 136.8 (C(12)), 135.4 (C(17)), 132.9 (C(16)), 130.1 (C(3)), 129.8 (C(7)), 128.6 (C(15)), 128.2 (C(8)), 127.7 (C(13)), 127.1 (C(9)), 126.2 (C(14)), 93.7 (C(1)), 63.7 (C(18)), 56.2 (C(5)), 51.7 (C(2)), 36.9 (C(11)), 24.6 (C(10)), 16.2 (C(19)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.78; HRMS (ESI) *m/z* calcd for $C_{23}H_{29}O_4{}^{35}ClP$ $[M+H]^+$: 435.14865, found: 435.14863; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2980.8 (w), 1442.1 (w), 1265.0 (w), 1024.3 (s), 973.1 (m), 754.0 (w), 700.7 (w); $[\alpha]^{25}_{589}$ = -153.0 (c=1.0 in $CHCl_3$, >99% ee).

(1*S*,2*S*,5*S*)-2-((Benzyloxy)methyl)-2-methyl-5-phenylcyclopent-3-en-1-yl diethyl phosphate (12c)

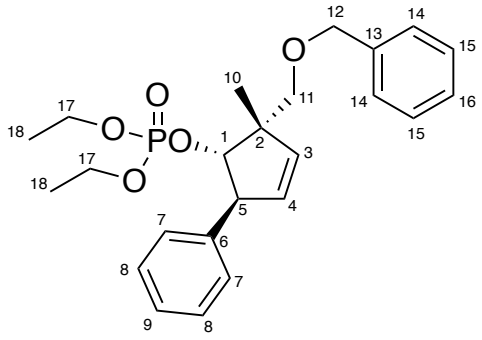


12c

Chemical Formula: $C_{24}H_{31}O_5P$
Molecular Weight: 430.48076

Synthesised according to general procedure 2b using (1*R*,2*S*,3*S*)-2-((benzyloxy)methyl)-2-methylcyclopent-4-ene-1,3-bis(diethyl phosphate) (**12a**) on a 0.4 mmol scale. Purified by flash chromatography (10-30-40% EtOAc in petroleum ether) to give (1*S*,2*S*,5*S*)-2-((Benzyloxy)methyl)-2-methyl-5-phenylcyclopent-3-en-1-yl diethyl phosphate (**12c**) as a yellow oil (97 mg, 56%).

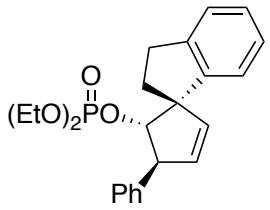
SFC analysis indicated an enantiomeric excess of >99% [Chiralpak® IA; flow: 1.5 mL/min; MeOH/CO_2: 1% to 30%; λ = 210 nm; minor enantiomer, t_R = 3.090 min; major enantiomer, t_R = 3.179 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.27 – 7.24 (m, 2H, 2ArH-(8)), 7.24 – 7.10 (m, 7H, 7ArH-(7, 9, 14-16)), 5.69 (dd, *J* = 6.1, 2.3 Hz, 1H, CH-(4)), 5.63 – 5.55 (m, 1H, CH-(3)), 4.47 (d, *J* = 5.6 Hz, 2H, CH_2-(12)), 4.43 (dd, *J* = 8.7, 7.2 Hz, 1H, CH-(1)), 4.06 – 4.02 (m, 1H, CH-(5)), 3.84 (m, 1H, CH_2-(17)), 3.72 – 3.59 (m, 3H, CH_2-(17)), 3.56 (d, *J* = 9.0 Hz, 1H, CHH′-(11)), 3.38 (d, *J* = 9.0 Hz, 1H, CHH′-(11)), 1.18 (s, 3H, CH_3-(10)), 1.04 (td, *J* = 7.1, 1.1 Hz,

3H, CH_3-(18)), 0.98 (td, *J* = 7.1, 1.1 Hz, 3H, CH_3-(18)); ^{13}C NMR (126 MHz, $CDCl_3$) δ_c/ppm: 142.3 (C(6)), 138.9 (C(13)), 137.4 (C(4)), 131.2 (C(3)), 128.6 (C(7)), 128.4 (C(15)), 128.1 (C(8)), 127.5 (C(14)), 127.5 (C(16)), 127.0 (C(9)), 92.9 (C(1)), 74.1 (C(11)), 73.6 (C(12)), 63.7 (C(17), 57.3 (C(5)), 51.7 (C(2)), 22.7 (C(10)), 16.1 (C(18)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -1.76; HRMS (ESI) *m/z* calcd for $C_{24}H_{32}O_5P$ $[M+H]^+$: 431.19819, found: 431.19799; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2980.6 (w), 1453.9 (w), 1264.0 (w), 1100.0 (w), 1029.7 (s), 974.2 (m), 746.8 (w), 699.9 (w); $[\alpha]^{25}_{589}$ = -115.2 (c=1.0 in $CHCl_3$, >99% ee).

Diethyl ((1*S*,4*S*,5*S*)-4-phenyl-2',3'-dihydrospiro[cyclopentane-1,1'-inden]-2-en-5-yl) phosphate (14c)

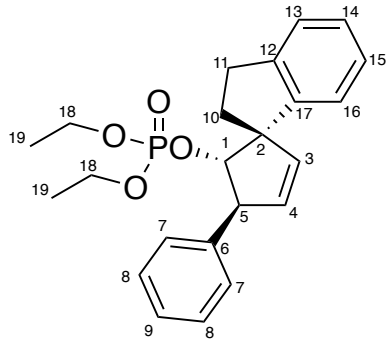


14c

Chemical Formula: $C_{23}H_{27}O_4P$
Molecular Weight: 398.43876

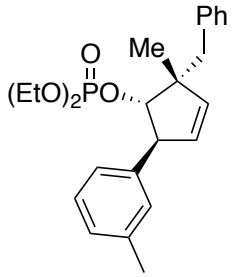
Synthesised according to general procedure 2b using (1*S*,2*R*,5*S*)-2',3'-dihydrospiro[cyclopentane-1,1'-inden]-3-ene-2,5-bis(diethyl phosphate) (**14a**) on a 0.4 mmol scale. Purified by flash chromatography (10-30-40% EtOAc in petroleum ether) to give Diethyl ((1*S*,4*S*,5*S*)-4-phenyl-2',3'-dihydrospiro[cyclopentane-1,1'-inden]-2-en-5-yl) phosphate (**14c**) as a yellow oil (51 mg, 32%).

SFC analysis indicated an enantiomeric excess of >99% [Chiralpak® IG; flow: 1.5 mL/min; MeOH/CO_2: 1% to 30%; λ = 210 nm; minor enantiomer, t_R = 3.300 min; major enantiomer, t_R = 3.517 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.29 – 7.23 (m, 4H, 4ArH-(7, 8)), 7.21 – 7.16 (m, 2H, 2ArH-(9, 13)), 7.15 – 7.08 (m, 3H, 3ArH-(14-16)), 5.80 (s, 2H, 2CH-(3, 4)), 4.70 (dd, *J* = 8.7, 4.8 Hz, 1H, CH-(1)), 4.18 (d, *J* = 4.8 Hz, 1H, CH-(5)), 3.59 (m, 1H, CH_2-(18)), 3.48 – 3.37 (m, 1H, CH_2-(18)), 3.36 – 3.21 (m, 2H, CH_2-(18)), 3.05 – 2.94 (m, 1H, CHH´-(11)), 2.76 (ddd, *J* = 15.9, 7.9, 3.9 Hz, 1H, CHH´-(11)), 2.18 – 2.09 (m, 2H, CH_2-(10)), 0.95 (td, *J* = 7.1, 1.1 Hz, 3H, CH_3-(19)), 0.88 (td, *J* = 7.1, 1.1 Hz, 3H, CH_3-(19)); ^{13}C NMR (126 MHz, $CDCl_3$) δ_c/ppm: 144.9 (C(17)), 143.5 (C(12)), 141.9 (C(6)), 138.5 (C(4)), 131.1 (C(3)), 128.6 (C(7)), 128.1 (C(8)), 127.3 (C(13)), 127.1 (C(9)), 126.0 (C(16)) 126.0 (C(14)), 124.5 (C(15)), 90.7 (C(1)), 64.7 (C(2)), 63.3 (C(18)), 58.2 (C(5)), 38.5 (C(10)), 31.0 (C(11)), 15.9 (C(19)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: -2.12; HRMS (ESI) *m/z* calcd for $C_{23}H_{28}O_4P$ $[M+H]^+$: 399.17197, found: 399.17191; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2981.0 (w), 1477.3 (w), 1455.3 (w), 1257.2 (m), 1029.8 (s), 969.9 (m), 757.7 (w), 701.3 (w); $[\alpha]^{25}_{589}$ = -269.8 (c=1.0 in $CHCl_3$, >99% ee).

(1*S*,2*R*,5*S*)-2-benzyl-2-methyl-5-(m-tolyl)cyclopent-3-en-1-yl diethyl phosphate (4h)

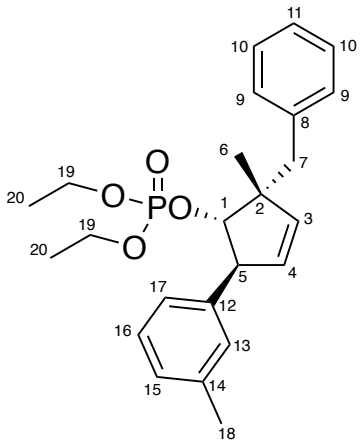


4h

Chemical Formula: $C_{24}H_{31}O_4P$
Molecular Weight: 414.48176

Synthesised according to general procedure 2b, using (1*R*,2*S*,3*S*)-2-benzyl-2-methylcyclopent-4-ene-1,3-bis(diethyl phosphate) (**4a**) and 3-methylphenylboronic acid on a 0.4 mmol scale. Purified by flash chromatography (10-30-40% EtOAc in petroleum ether) to give the product (**4h**) as a yellow oil (128.4 mg, 77%).

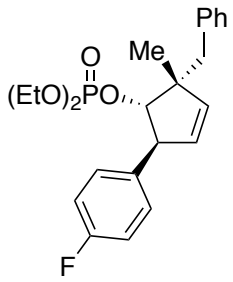
SFC analysis indicated an enantiomeric excess of >99% [Chiralpak® IF; flow: 1.5 mL/min; MeOH/CO_2: 1% to 30 %; λ = 210 nm; minor enantiomer, t_R = 3.064 min, major enantiomer, t_R = 3.162 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.31 – 7.26 (m, 2H, 2ArH-(9)), 7.25 – 7.17 (m, 4H, 4ArH-(10, 13, 16)), 7.07 – 7.02 (m, 3H, 3ArH-(11, 15, 17)), 5.61 (dt, *J* = 6.2, 1.4 Hz, 1H, CH-(4)), 5.52 (dd, *J* = 6.2, 2.5 Hz, 1H, CH-(3)), 4.55 (dd, *J* = 8.6, 7.8 Hz, 1H, CH-(2)), 4.11 – 3.98

(m, 1H, CH_2-(19)), 3.93 (dt, *J* = 7.8, 2.1 Hz, 1H, CH-(5)), 3.90 – 3.70 (m, 3H, CH_2-(19)), 2.99 (d, *J* = 13.0 Hz, 1H, CHH′-(7)), 2.74 (d, *J* = 13.0 Hz, 1H, CHH′-(7)), 2.33 (s, 3H, CH_3-(18)), 1.26 – 1.22 (m, 3H, CH_3-(20)), 1.21 (s, 3H, CH_3-(6)), 1.12 (td, *J* = 7.1, 1.1 Hz, 3H, CH_3-(20)); ^{13}C NMR (126 MHz, $CDCl_3$) δ_c/ppm: 141.9 (C(12)), 138.9 (C(3)), 138.8 (C(8)), 138.1 (C(12)), 131.0 (C(10)), 130.1 (C(4)), 128.9 (C(15)), 128.5 (C(16)), 127.9 (C(9)), 127.8 (C(11)), 126.1 (C(13)), 125.3 (C(17)), 93.7 (C(1)), 63.7 (C(19)) , 56.1 (C(5)), 50.9 (C(2)), 41.0 (C(7)), 24.4 (C(6)), 21.5 (C(18)), 16.1 (C(20)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: –1.85; HRMS (ESI) *m/z* calcd for $C_{24}H_{32}O_4P$ $[M+H]^+$: 415.20437, found: 415.20340; IR (ATR) *v* (cm^{-1}) thin film, $CHCl_3$: 2980.3 (w), 1606.1 (w), 1494.0 (w), 1453.6 (w), 1369.2 (w), 1264.5 (m), 1165.5 (w), 1025.3 (s), 973.8 (m), 901.3 (w), 786.0 (w), 749.6 (m), 702.7 (m); $[\alpha]^{25}_{589}$ = –159.5 (c=1.0 in $CHCl_3$, >99% ee).

(1*S*,2*R*,5*S*)-2-benzyl-5-(4-fluorophenyl)-2-methylcyclopent-3-en-1-yl diethyl phosphate (4i)

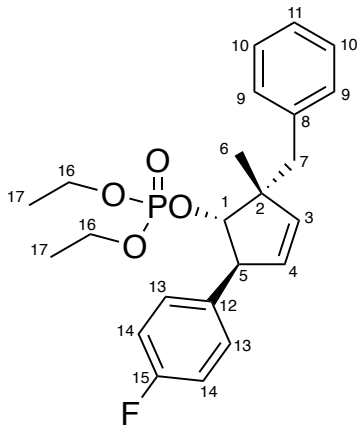


4i

Chemical Formula: $C_{23}H_{28}FO_4P$
Molecular Weight: 418.44517

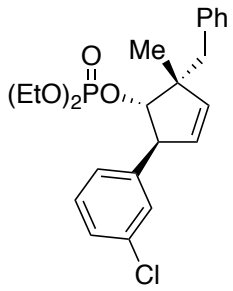
Synthesised according to general procedure 2b, using (1*R*,2*S*,3*S*)-2-benzyl-2-methylcyclopent-4-ene-1,3-bis(diethyl phosphate) (**4a**) and 4-fluorophenylboronic acid on a 0.4 mmol scale. Purified by flash chromatography (10-30-40% EtOAc in petroleum ether) to give the product (**4i**) as colourless crystals (101.2 mg, 61%).

SFC analysis indicated an enantiomeric excess of >99% [Chiralpak® IG; flow: 1.0 mL/min; MeOH/CO_2: 0% isocratic for 3min, 0% to 10% over 5 min, 10% to 50% over 1 min; λ = 210 nm; minor enantiomer, t_R = 8.675 min, major enantiomer, t_R = 8.911 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.31 – 7.17 (m, 7H, 7ArH-(9-11, 13)), 7.04 – 6.97 (m, 2H, 2ArH-(14)), 5.58 (dt, *J* = 6.4, 1.2 Hz, 1H, CH-(4)), 5.54 (dd, *J* = 6.3, 2.5 Hz, 1H, CH-(3)), 4.50 (dd, *J* = 8.7, 7.7 Hz, 1H, CH-(1)), 4.11 – 4.00 (m, 1H, CH_2-(18)), 3.98 – 3.75 (m, 4H, CH-(1), CH_2-(18)), 2.98 (d, *J* = 13.0 Hz, 1H, CHH′-(7)), 2.73 (d, *J* = 13.0 Hz, 1H, CHH′-(7)), 1.26 (td, *J* = 7.0, 1.1 Hz, 3H, CH_3-(19)), 1.20 (s, 3H, CH_3-(6)), 1.15 (td, *J* = 7.1, 1.1 Hz, 3H, CH_3-(19)); ^{13}C NMR (126 MHz, $CDCl_3$) δ_c/ppm: 148.0 (C(15)), 139.3 (C(3)), 138.6 (C(12)), 131.0 (C(10)), 129.7 (C(8)), 129.6 (C(13)), 127.9 (C(9)), 126.2 (C(11)), 115.3 (C(14)), 93.6 (C(1)), 63.7 (C(16)), 55.5 (C(5)), 51.0 (C(2)), 41.0 (C(7)), 24.4 (C(6)), 16.2 (C(17)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: –1.72; ^{19}F NMR (376 MHz, $CDCl_3$) δ_F/ppm: –116.22; HRMS (ESI) *m/z* calcd for $C_{23}H_{29}O_4FP$ $[M+H]^+$: 419.17820, found: 419.17913; IR (ATR) *v* (cm^{-1}) thin film, $CHCl_3$: 2981.5 (w), 1603.8 (w), 1509.7 (m), 1454.1 (w), 1369.7 (w), 1265.0 (m), 1223.9 (m), 1159.2 (w), 1025.3 (s), 973.5 (m), 903.7 (w), 863.0 (w), 831.4 (w), 750.1 (m), 704.1 (m), 626.2 (w); $[\alpha]^{25}_{589}$ = –139.1 (c=1.0 in $CHCl_3$, >99% ee); Melting Point: 74.9 °C.

(1*S*,2*R*,5*S*)-2-benzyl-5-(3-chlorophenyl)-2-methylcyclopent-3-en-1-yl diethyl phosphate (4j)

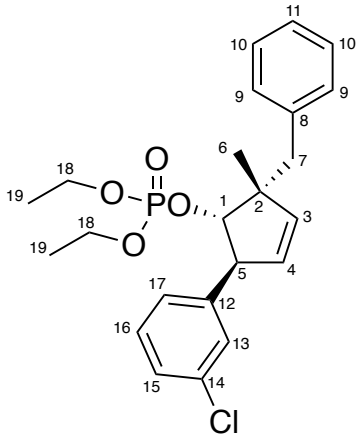


4j

Chemical Formula: $C_{23}H_{28}ClO_4P$
Molecular Weight: 434.89676

Synthesised according to general procedure 2b, using (1*R*,2*S*,3*S*)-2-benzyl-2-methylcyclopent-4-ene-1,3-bis(diethyl phosphate) (**4a**) and 3-chlorophenylboronic acid on a 0.4 mmol scale. Purified by flash chromatography (10-30-40% EtOAc in petroleum ether) to give the product (**4j**) as a dark yellow oil (110.7 mg, 64%).

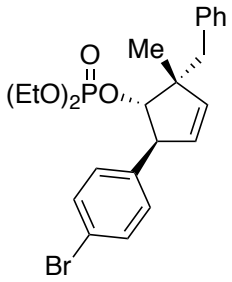
SFC analysis indicated an enantiomeric excess of >99% [Chiralpak® IG; flow: 1.5 mL/min; MeOH/CO_2: 1% to 30 %; λ = 210 nm; minor enantiomer, t_R = 3.204 min, major enantiomer, t_R = 3.397 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.31 – 7.11 (m, 9H, 9ArH-(9-11, 12-13, 15-17)), 5.63 – 5.54 (m, 2H, CH-(3, 4)), 4.51 (dd, *J* = 8.7, 7.8 Hz, 1H, CH-(1)), 4.13 – 4.00 (m, 1H, CH_2-(18)), 4.00 – 3.77 (m, 4H, CH-(5), CH_2-(18)), 2.97 (d, *J* = 13.0 Hz, 1H, CHH′-(7)), 2.74 (d, *J* = 13.0

Hz, 1H, CHH′-(7)), 1.26 (td, J = 7.1, 1.1 Hz, 3H, CH_3-(19)), 1.21 (s, 3H, CH_3-(6)), 1.16 (td, J = 7.1, 1.1 Hz, 3H, CH_3-(19)); ^{13}C NMR (126 MHz, $CDCl_3$) δ_c/ppm: 144.2 (C(12)), 139.7 (C(3)), 138.5 (C(8)), 134.4 (C(14)), 131.0 (C(10)), 129.9 (C(16)), 129.2 (C(4)), 128.4 (C(15)), 127.9 (C(9)), 127.2 (C(11)), 126.3 (C(13)), 126.2 (C(17)), 93.33 (C(1)), 63.8 (C(18)), 55.9 (C(5)), 51.1 (C(2)), 41.0(C(7)), 24.4 (C(6)), 16.2 (C(19)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: –1.75; HRMS (ESI) *m/z* calcd for $C_{23}H_{29}O_4{}^{35}ClP$ $[M+H]^+$: 435.14865, found: 435.14816; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2980.9 (w), 1597.7 (w), 1454.0 (w), 1393.3 (w), 1265.0 (m), 1165.1 (w), 1026.4 (s), 972.7 (m), 785.9 (w), 750.3 (m), 722.1 (w), 703.4 (w); $[\alpha]^{25}{}_{589}$ = –84.2 (c=1.0 in $CHCl_3$, >99% ee).

(1*S*,2*R*,5*S*)-2-benzyl-5-(4-bromophenyl)-2-methylcyclopent-3-en-1-yl diethyl phosphate (4k)

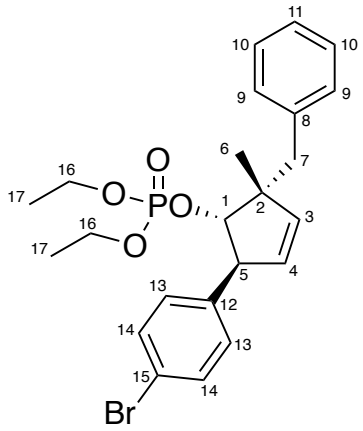


4k

Chemical Formula: $C_{23}H_{28}BrO_4P$
Molecular Weight: 479.35076

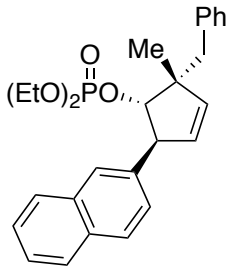
Synthesised according to general procedure 2b, using (1*R*,2*S*,3*S*)-2-benzyl-2-methylcyclopent-4-ene-1,3-bis(diethyl phosphate) (**4a**) and 4-bromophenylboronic acid on a 0.4 mmol scale. Purified by flash chromatography (10-30-40% EtOAc in petroleum ether) to give the product (**4k**) as yellow crystals (113.8 mg, 59%).

SFC analysis indicated an enantiomeric excess of >99% [Chiralpak® IG; flow: 0.5 mL/min; MeOH/CO_2: 1% to 30 %; λ = 210 nm; minor enantiomer, t_R = 9.411 min, major enantiomer, t_R = 9.664 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.47 – 7.40 (m, 2H, 2ArH-(14)), 7.31 – 7.11 (m, 7H, 7ArH-(9-11, 13)), 5.60 – 5.53 (m, 2H, CH-(3, 4)), 4.50 (dd, *J* = 8.7, 7.7 Hz, 1H, CH-(1), 4.11 – 4.00 (m, 1H, CH_2-(16)), 3.98 – 3.75 (m, 4H, CH-(5), CH_2-(16)), 2.97 (d, *J* = 13.0 Hz, 1H, CHH′-(7)), 2.73 (d, *J* = 13.1 Hz, 1H, CHH′-(7)), 1.25 (td, *J* = 7.1, 1.1 Hz, 3H, CH_3-(17)), 1.20 (s, 3H, CH_3-(6)), 1.15 (td, *J* = 7.1, 1.1 Hz, 3H, CH_3-(17)); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C/ppm: 141.1 (C(12)), 139.6 (C(3)), 138.5 (C(8)), 131.6 (C(14)), 131.0 (C(10)), 129.9 (C(9)), 129.4 (C(4)), 127.9 (C(13)), 126.2 (C(11)), 120.9 (C(15)), 93.34 (C(1)), 63.8 (C(16)), 55.7 (C(5)), 51.1 (C(2)), 41.0 (C(7)), 24.40 (C(6)), 16.2 (C(17)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: –1.74; HRMS (ESI) *m/z* calcd for $C_{23}H_{29}O_4{}^{79}BrP$ $[M+H]^+$:479.09813, found: 479.09805; IR (ATR) *v* (cm^{-1}) thin film, $CHCl_3$: 2980.7 (w), 1489.2 (w), 1453.8 (w), 1393.2 (w), 1264.6 (m), 1165.3 (w), 1025.2 (s), 973.2 (m), 903.4 (w), 817.7 (m), 749.8 (m), 704.0 (m); $[\alpha]^{25}{}_{589}$ = –146.6 (c=1.0 in $CHCl_3$, >99% ee); Melting Point: 78.6 °C.

(1*S*,2*R*,5*S*)-2-benzyl-2-methyl-5-(naphthalen-2-yl)cyclopent-3-en-1-yl diethyl phosphate (4l)

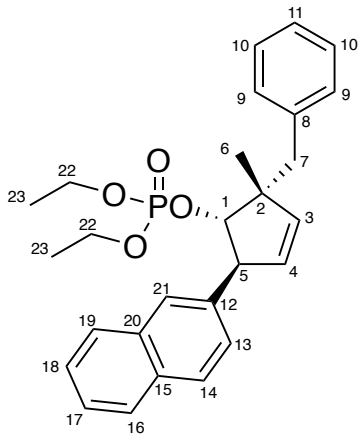


4l

Chemical Formula: $C_{27}H_{31}O_4P$
Molecular Weight: 450.51476

Synthesised according to general procedure 2b, using (1*R*,2*S*,3*S*)-2-benzyl-2-methylcyclopent-4-ene-1,3-bis(diethyl phosphate) (**4a**) and naphthalen-2-ylboronic acid on a 0.4 mmol scale. Purified by flash chromatography (10-30-40% EtOAc in petroleum ether) to give the product (**4l**) as colourless crystals (119.7 mg, 66%).

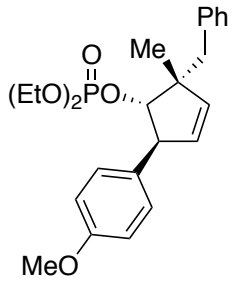
SFC analysis indicated an enantiomeric excess of >99% [Chiralpak® IA; flow: 1.5 mL/min; MeOH/CO_2: 1% to 30 %; λ = 210 nm; minor enantiomer, t_R = 3.161 min, major enantiomer, t_R = 3.321 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.87 – 7.74 (m, 3H, 3ArH-(14, 16, 19)), 7.70 (s, 1H, 1ArH-(14)), 7.51 – 7.36 (m, 3H, 3ArH-(9, 17-18)), 7.32 – 7.27 (m, 2H, 2Ar-(9)), 7.26 – 7.20 (m, 3H, 3ArH-(10)), 5.70 (dt, *J* = 6.2, 1.3 Hz, 1H, CH-(4)), 5.60 (dd, *J* = 6.3, 2.5 Hz, 1H, CH-

(3)), 4.67 (dd, J = 8.7, 7.7 Hz, 1H, CH-(1)), 4.14 (dt, J = 7.7, 2.1 Hz, 1H, CH-(5)), 4.07 – 3.92 (m, 1H, CH_2-(22)), 3.89 – 3.78 (m, 1H, CH_2-(22)), 3.78 – 3.60 (m, 2H, CH_2-(22)), 3.04 (d, J = 13.0 Hz, 1H, CHH′-(7)), 2.78 (d, J = 13.0 Hz, 1H, CHH′-(7)), 1.25 (s, 3H, CH_3-(6)), 1.13 (td, J = 7.1, 1.1 Hz, 3H, CH_3-(23)), 0.95 (td, J = 7.1, 1.1 Hz, 3H, CH_3-(23)); ^{13}C NMR (126 MHz, $CDCl_3$) δ_c/ppm: 139.3 (C(12)), 139.2 (C(8)), 138.7 (C(3)), 133.6 (C(20)), 132.8 (C(15)), 131.0 (C(10)), 129.9 (C(4)), 128.4 (C(16)), 127.9 (C(9)), 127.8 (C(19)), 127.7 (C(14)), 126.9 (C(21)), 126.2 (C(13)), 126.2 (C(18)), 126.2 (C(11)), 125.7 (C(17)), 93.4 (C(1)), 63.7 (C(22)), 56.4 (C(5)), 51.1 (C(2)), 41.0 (C(7)), 24.4 (C(6)), 16.0 (C(23)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: –1.79; HRMS (ESI) *m/z* calcd for $C_{27}H_{31}O_4{}^{23}NaP$ $[M+Na]^+$: 473.18631, found: 473.18524; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2980.7 (w), 1602.1 (w), 1495.1 (w), 1453.7 (w), 1370.0 (w), 1264.3 (m), 1165.3 (w), 1025.7 (s), 974.3 (m), 900.6 (w), 818.9 (m), 748.7 (m), 704.0 (m); $[\alpha]^{25}_{589}$ = –201.0 (c=1.0 in $CHCl_3$, >99% ee); Melting Point: 79.5 °C.

(1*S*,2*R*,5*S*)-2-benzyl-5-(4-methoxyphenyl)-2-methylcyclopent-3-en-1-yl diethyl phosphate (4m)

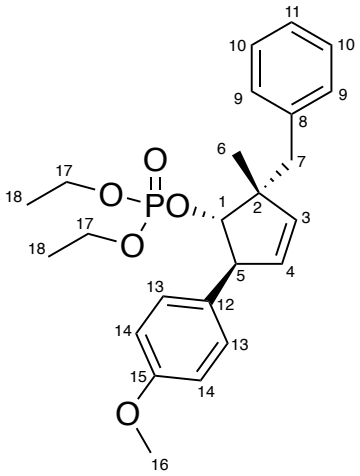


4m

Chemical Formula: $C_{24}H_{31}O_5P$
Molecular Weight: 430.48076

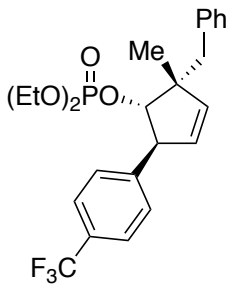
Synthesised according to general procedure 2b, using (1*R*,2*S*,3*S*)-2-benzyl-2-methylcyclopent-4-ene-1,3-bis(diethyl phosphate) (**4a**) and (4-methoxyphenyl)boronic acid on a 0.4 mmol scale. Purified by flash chromatography (10-30-40% EtOAc in petroleum ether) to give the product (**4m**) as a yellow oil (109.1 mg, 63%).

SFC analysis indicated an enantiomeric excess of >99% [Chiralpak® IG; flow: 1.5 mL/min; MeOH/CO_2: 1% to 30 %; λ = 210 nm; minor enantiomer, t_R = 3.542 min, major enantiomer, t_R = 3.708 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.30 – 7.12 (m, 7H, 7ArH-(9-11, 13)), 6.88 – 6.82 (m, 2H, 2ArH-(14)), 5.59 (dt, *J* = 6.3, 1.3 Hz, 1H, CH-(4)), 5.51 (dd, *J* = 6.2, 2.5 Hz, 1H, CH-(3)), 4.52 (dd, *J* = 8.6, 7.7 Hz, 1H, CH-(1)), 4.08 – 3.99 (m, 1H, CH_2-(17)), 3.93 (dt, *J* = 7.3, 2.4, 1.7 Hz, 1H, CH-(5)), 3.91 – 3.80 (m, 2H, CH_2-(17)), 3.79 (s, 3H, CH_3-(16)), 3.78 – 3.74 (m, 1H, CH_2-(17)), 2.98 (d, *J* = 13.0 Hz, 1H, CHH′-(7)), 2.74 (d, *J* = 13.0 Hz, 1H, CHH′-(7)), 1.27 – 1.22 (m, 3H, CH_3-(18)), 1.20 (s, 3H, CH_3-(6)), 1.14 (td, *J* = 7.1, 1.1 Hz, 3H, CH_3-(18)); ^{13}C NMR (126 MHz, $CDCl_3$) δ_c/ppm: 158.8 (C(15)), 138.8 (C(3)), 134.1 (C(12)), 131.0 (C(10)), 130.26 (C(4)), 129.1 (C(13)), 127.8 (C(9)), 126.14 (C(11)), 114.0 (C(14)), 93.78 (C(1)), 63.7 (C(17)), 55.5 (C(5)), 55.4 (C(16)), 50.8 (C(2)), 41.0 (C(7)), 24.4 (C(6)), 16.2 (C(18)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: –1.78; HRMS (ESI) *m/z* calcd for $C_{24}H_{32}O_5P$ $[M+H]^+$: 431.19819, found: 431.19830; IR (ATR) *v* (cm^{-1}) thin film, $CHCl_3$: 3281.6 (w), 2982.8 (w), 2849.9 (w), 2360.3 (w), 1587.9 (m), 1513.2 (m), 1492.0 (m), 1479.1 (m), 1371.7 (w), 1257.7 (s), 1140.5 (m), 1082.3 (m), 1026.8 (s), 976.7 (m), 840.7 (m), 741.5 (m), 715.8 (m), 645.9 (w); $[\alpha]^{25}_{589}$ = –133.0 (c=1.0 in $CHCl_3$, >99% ee).

(1*S*,2*R*,5*S*)-2-benzyl-2-methyl-5-(4-(trifluoromethyl)phenyl)cyclopent-3-en-1-yl diethyl phosphate (4n)

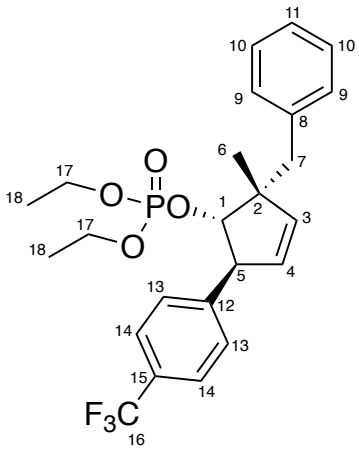


4n

Chemical Formula: $C_{24}H_{28}F_3O_4P$
Molecular Weight: 468.45297

Synthesised according to general procedure 2b, using (1*R*,2*S*,3*S*)-2-benzyl-2-methylcyclopent-4-ene-1,3-bis(diethyl phosphate) (**4a**) and (4-(trifluoromethyl)phenyl)boronic acid on a 0.4 mmol scale. Purified by flash chromatography (10-30-40% EtOAc in petroleum ether) to give the product (**4n**) as a dark red crystals (103.7 mg, 55%).

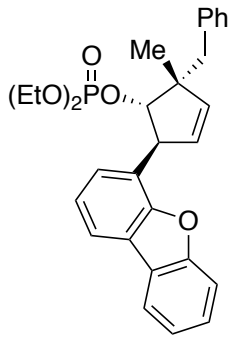
SFC analysis indicated an enantiomeric excess of >99% [Chiralpak® IC; flow: 0.5 mL/min; MeOH/CO_2: 1% isocratic for 4 min, 1% to 5% in 1 min, 5% isocratic for 8 min, then 5% to 30% in 5 min; λ = 210 nm; minor enantiomer, t_R = 10.704 min, major enantiomer, t_R = 11.062 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.58 (d, *J* = 8.0 Hz, 2H, 2ArH-(14)), 7.38 (d, *J* = 8.0 Hz, 2H, 2ArH-(13)), 7.32 –7.17 (m, 5H, 5ArH-(9-11)), 5.60 (d, *J* = 0.9 Hz, 2H, CH-(3, 4)), 4.54

(dd, J = 8.7, 7.8 Hz, 1H, CH-(1)), 4.10 – 3.99 (m, 2H, CH_2-(17), CH-(1)), 3.96 – 3.72 (m, 3H, CH_2-(17)), 2.99 (d, J = 13.0 Hz, 1H, CHH′-(7)), 2.74 (d, J = 13.0 Hz, 1H, CHH′-(7)), 1.28 – 1.20 (m, 6H, CH_3-(6), CH_3-(18)), 1.11 (td, J = 7.1, 1.1 Hz, 3H, CH_3-(18)); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C/ppm: 146.2 (C(12)), 139.9 (C(3)), 138.4 (C(8)), 131.0 (C(10)) 129.6 (C(15)), 129.0 (C(4)), 128.6 (C(13)), 127.9 (C(9)), 126.3 (C(11)), 125.5 (C(14)), 125.5 (C(16)), 93.2 (C(1)), 63.8 (C(17)), 56.0 (C(5)), 51.1 (C(2)), 41.0 (C(7)), 24.4 (C(6)), 16.1 (C(18)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: –1.74; ^{19}F NMR (376 MHz, $CDCl_3$) δ_F/ppm: –62.47; HRMS (ESI) *m/z* calcd for $C_{24}H_{29}O_4F_3P$ $[M+H]^+$: 469.17501, found: 469.17484; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 2981.4 (w), 1619.3 (w), 1454.2 (w), 1421.2 (w), 1325.7 (s), 1266.0 (m), 1164.7 (m), 1124.4 (m), 1068.2 (m), 1026.2 (s), 973.2 (m), 904.7 (w), 832.0 (w), 750.5 (m), 704.1 (m); $[\alpha]^{25}_{589}$ = –113.8 (c=1.0 in $CHCl_3$, >99% ee); Melting Point: 58.2 °C.

(1*S*,2*R*,5*S*)-2-benzyl-5-(dibenzo[b,d]furan-4-yl)-2-methylcyclopent-3-en-1-yl diethyl phosphate (4o)

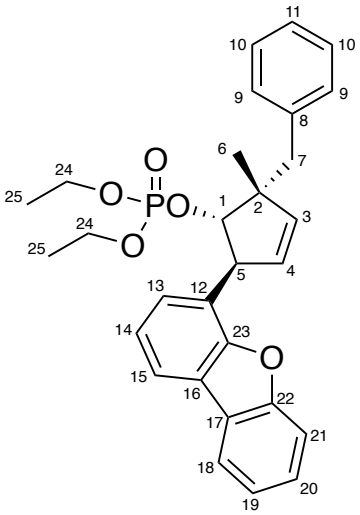


4o

Chemical Formula: $C_{29}H_{31}O_5P$
Molecular Weight: 490.53576

Synthesised according to general procedure 2b, using (1*R*,2*S*,3*S*)-2-benzyl-2-methylcyclopent-4-ene-1,3-bis(diethyl phosphate) (**4a**) and dibenzo[*b*,*d*]furan-4-ylboronic acid on a 0.4 mmol scale. Purified by flash chromatography (10-30-40% EtOAc in petroleum ether) to give the product (**4o**) as an orange oil (56.7 mg, 29%).

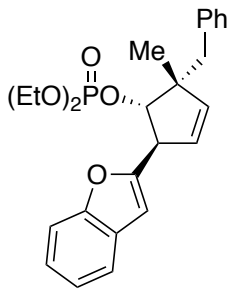
SFC analysis indicated an enantiomeric excess of 94% [Chiralpak® ID; flow: 1.5 mL/min; MeOH/CO_2: 1% to 30 %; λ = 210 nm; minor enantiomer, t_R = 4.325 min, major enantiomer, t_R = 3.995 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.95 (ddd, *J* = 7.7, 1.4, 0.7 Hz, 1H, 1ArH-(18)), 7.85 (dd, *J* = 7.0, 2.0 Hz, 1H, 1ArH-(15)), 7.58 (dt, *J* = 8.2, 0.9 Hz, 1H, 1ArH-(21)), 7.46 (ddd, *J* = 8.4, 7.3, 1.4 Hz, 1H, 1ArH-(11)), 7.39 – 7.22 (m, 8H, 8 ArH-(9-10, 13, 14, 19, 20), 5.71 (dt, *J* = 6.1, 1.6 Hz, 1H, CH-(4)), 5.59 (dt, *J* = 6.2, 2.6 Hz, 1H, CH-(3)), 4.90 (dd, *J* = 8.8, 8.1 Hz, 1H, CH-(1)), 4.72 (dt, *J* = 8.1, 2.6, 1.7 Hz, 1H, CH-(5)), 4.04 – 3.92 (m, 1H, CH_2-(24)), 3.87 – 3.76 (m, 1H, CH_2-(24)), 3.63 – 3.45 (m, 2H, CH_2-(24)), 3.12 (d, *J* = 12.9 Hz, 1H, CHH′-(7)), 2.83 (d, *J* = 12.9 Hz, 1H, CHH′-(7)), 1.30 (s, 3H, CH_3-(6)), 1.15 (td, *J* = 7.1, 1.1 Hz, 3H, CH_3-(25)), 0.79 (td, *J* = 7.1, 1.1 Hz, 3H, CH_3-(25)); ^{13}C NMR (126 MHz, $CDCl_3$) δ_c/ppm: 156.2 (C(22)), 155.0 (C(23)), 139.2 (C(3)), 138.8 (C(8)), 131.0 (C(10)), 129.5 (C(4)), 127.9 (C(9)), 127.3 (C(11)), 126.2 (C(20)), 126.2 (C(19)), 126.1 (C(12)), 124.5 (C(17)), 124.2 (C(16)), 123.3 (C(13)), 122.8 (C(14)), 120.9 (C(18)), 119.2 (C(15)), 111.8 (C(21)), 92.4 (C(1)), 63.6 (C(24)), 50.9 (C(2)), 50.0 (C(5)), 41.0 (C(7)), 24.2 (C(6)), 15.8 (C(25)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: –1.86; HRMS (ESI) *m/z* calcd for $C_{29}H_{32}O_5P$ $[M+H]^+$: 491.19819, found: 491.19809; IR (ATR) *v* (cm^{-1}) thin film, $CHCl_3$: 2979.1 (w), 1494.9 (w), 1451.8 (m), 1425.0 (w), 1268.5

(m), 1186.3 (m), 1025.3 (s), 973.4 (m), 899.3 (w), 845.3 (w), 754.2 (m), 703.9 (m); $[\alpha]^{25}_{589}$ = –114.9 (c=1.0 in $CHCl_3$, 94% ee).

(1,2*R*,5*R*)-5-(benzofuran-2-yl)-2-benzyl-2-methylcyclopent-3-en-1-yl diethyl phosphate (4p)

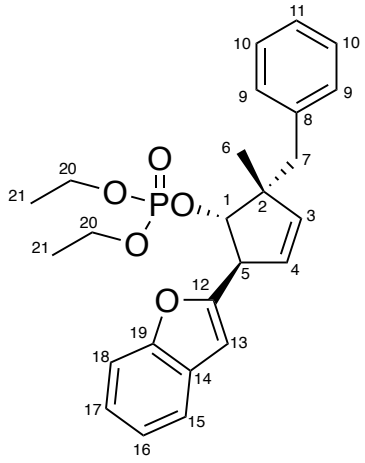


4p

Chemical Formula: $C_{25}H_{29}O_5P$
Molecular Weight: 440.47576

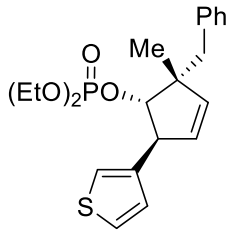
Synthesised according to general procedure 2b, using (1*R*,2*S*,3*S*)-2-benzyl-2-methylcyclopent-4-ene-1,3-bis(diethyl phosphate) (**4a**) and benzofuran-2-ylboronic acid on a 0.4 mmol scale. Purified by flash chromatography (10-30-40% EtOAc in petroleum ether) to give the product (**4p**) as colourless crystals (73.3 mg, 42%).

SFC analysis indicated an enantiomeric excess of >99% [Chiralpak® IG; flow: 1.5 mL/min; MeOH/CO_2: 1% to 30 %; λ = 210 nm; minor enantiomer, t_R = 3.606 min, major enantiomer, t_R = 3.913 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.55 – 7.50 (m, 1H, 1ArH-(15)), 7.46 – 7.41 (m, 1H, 1ArH-(18)), 7.34 – 7.18 (m, 7H, 7ArH-(9-11, 16, 17)), 6.62 (s, 1H, 1ArH-(13)), 5.72 (dt, *J* = 6.3, 1.3 Hz, 1H, CH-(4)), 5.61 (dd, *J* = 6.2, 2.6 Hz, 1H, CH-(3)), 4.94 (dd, *J* = 8.8, 7.6 Hz, 1H, CH-(1)), 4.21 – 4.16 (m, 1H, CH_2- (20)), 4.15 – 3.91 (m, 4H, CH-(5), CH_2-(20)), 3.01 (d, *J* = 13.1 Hz, 1H, CHH′-(7)), 2.79 (d, *J* = 13.1 Hz, 1H-CHH′-(7)), 1.30 – 1.23 (m, 6H, CH_3-(6), CH_3-(21)), 1.14 (td, *J* = 7.1, 1.1 Hz, 3H, CH_3-(21)); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C/ppm: 157.7 (C(12)), 155.1 (C(19)), 139.5 (C(3)), 138.4 (C(8)), 131.0 (C(10)), 128.8 (C(14)), 127.9 (C(9)), 127.0 (C(4)), 126.3 (C(11)), 123.8 (C(17)), 122.8 (C(16)), 120.8 (C(15)), 111.1 (C(18)), 103.3 (C(13)), 89.4 (C(1)), 63.9 (C(20)), 51.0 (C(2)), 50.4 (C(5)), 41.0 (C(7)), 24.4 (C(6)), 16.1 (C(21)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: –1.73; HRMS (ESI) *m/z* calcd for $C_{25}H_{30}O_5P$ $[M+H]^+$: 441.18254, found: 441.18256; IR (ATR) *v* (cm^{-1}) thin film, $CHCl_3$: 2980.7 (w), 1601.8 (w), 1454.7 (m), 1256.4 (m), 1166.3 (w), 1025.2 (s), 972.8 (m), 901.0 (w), 803.1 (w), 749.5 (m), 703.9 (m); $[\alpha]^{25}_{589}$ = –214.8 (c=1.0 in $CHCl_3$, >99% ee); Melting Point: 81.3 °C.

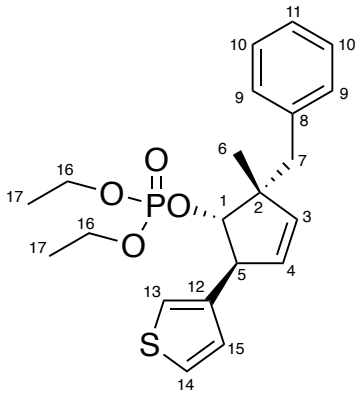
(1*S*,2*R*,5*S*)-2-benzyl-2-methyl-5-(thiophen-3-yl)cyclopent-3-en-1-yl diethyl phosphate (4q)



Chemical Formula: $C_{21}H_{27}O_4PS$
Molecular Weight: 406.4768

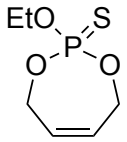
Synthesised according to general procedure 2b, using (1*R*,2*S*,3*S*)-2-benzyl-2-methylcyclopent-4-ene-1,3-bis(diethyl phosphate) (**4a**) and thiophen-3-ylboronic acid on a 0.4 mmol scale. Purified by flash chromatography (10-30-40% EtOAc in petroleum ether) to give the product (**4q**) as an orange oil (19.6 mg, 12%).

SFC analysis indicated an enantiomeric excess of 98% [Chiralpak® IF; flow: 1.5 mL/min; MeOH/CO_2: 1% to 30 %; λ = 210 nm; minor enantiomer, t_R = 3.399 min, major enantiomer, t_R = 3.648 min].



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.31 – 7.15 (m, 6H, 6ArH-(9-11, 13)), 7.11 (dd, *J* = 3.0, 1.2 Hz, 1H, 1ArH-(14)), 7.03 (dd, *J* = 5.0, 1.3 Hz, 1H, 1ArH-(15)), 5.64 (dt, *J* = 6.2, 1.3 Hz, 1H, CH-(4)), 5.50 (dd, *J* = 6.2, 2.5 Hz, 1H, CH-(3)), 4.61 (dd, *J* = 8.5, 7.5 Hz, 1H, CH-(1)), 4.15 – 4.03 (m, 2H, CH_2-(16), CH-(5)), 4.02 – 3.83 (m, 3H, CH_2-(16)), 2.97 (d, *J* = 13.0 Hz, 1H, CHH′-(7)), 2.73 (d, *J* = 13.0 Hz, 1H, CHH′-(7)), 1.29 (td, *J* = 7.1, 1.1 Hz, 3H, CH_3-(17)), 1.24 – 1.16 (m, 6H, CH_3-(16), CH_3-(6)); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C/ppm: 142.7 (C(12)), 138.63 (C(8)), 138.57 (C(3)), 131.0 (C(10)), 129.6 (C(4)), 127.9 (C(9)), 127.4 (C(15)), 126.2 (C(14)), 125.9 (C(11)), 121.4 (C(13)), 92.6 (C(1)), 63.8 (C(16)), 51.5 (C(5)), 50.9 (C(2)), 40.9 (C(7)), 24.5 (C(6)), 16.2 (C(17)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: –1.71; HRMS (ESI) *m/z* calcd for $C_{21}H_{27}O_4{}^{23}NaP^{32}S$ $[M+Na]^+$: 429.12599, found: 429.12607; IR (ATR) *v* (cm^{-1}) thin film, $CHCl_3$: 2980.6 (w), 1495.6 (w), 1454.0 (w), 1392.4 (w), 1259.7 (m), 1165.5 (w), 1030.7 (s), 987.3 (s), 777.4 (w), 753.3 (w), 704.4 (m); $[\alpha]^{25}{}_{589}$ = –36.3 (c=1.0 in $CHCl_3$, 98% ee).

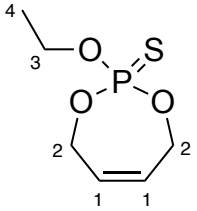
2-Ethoxy-4,7-dihydro-1,3,2-dioxaphosphepine 2-sulfide (42)



42

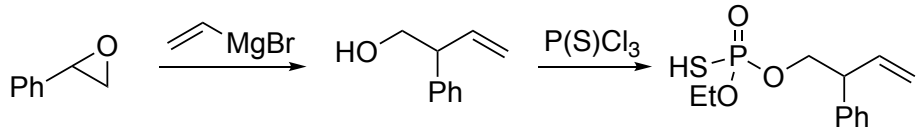
Chemical Formula: $C_6H_{11}O_3PS$
Molecular Weight: 194.18476

To a solution of diethyl chlorophosphite (1.14 mL, 10.0 mmol, 1.0 eq) in THF (100 mL) was slowly added NEt_3 (11.2 mL, 80.0 mmol, 8.0 eq). The resulting solution was cooled to 0 ºC and a solution of *cis*-buten-1,4-diol (0.93 mL, 11.3, 1.13 eq) in THF (10 mL) was added via syringe pump over 4 hours at 0 ºC. The mixture was warmed to room temperature and S_8 (2.00g, excess) in diisopropylamine (10 mL) was added. The resulting mixture was left to stir at room temperature for 2 hours before putting the reaction mixture in the freezer overnight to precipitate NEt_3HCl. The mixture was filtered over celite and rinsed with THF. The filtrate was evaporated *in vacuo* and the residue was purified on silica (5-10% Et_2O in pentane) to give 2-ethoxy-4,7-dihydro-1,3,2-dioxaphosphepine 2-sulfide (**42**) (1.18 g, 61%) as a colourless oil.



^1H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 5.75 (dd, J = 1.6, 1.8 Hz, 2H, 2CH-(1)), 4.72 – 4.66 (m, 2H, 2CH-(2)), 4.27 (dq, J = 10.5, 7.1 Hz, 2H, CH_2-(3)), 1.37 (td, J = 7.1, 0.8 Hz, 3H, CH_3-(4)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 127.4 (C(1)), 65.2 (C(2)), 64.4 (C(3)), 16.0 (C(4)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: 73.49; HRMS (ESI) *m/z* calcd for $C_6H_{12}O_3PS$ $[M+H]^+$: 195.0239, found: 195.0241; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 1456.1 (w), 1394.1 (w), 1262.6 (w), 1163.5 (w), 1021.0 (s), 996.2 (s), 950.5 (s), 880.6 (m), 862.8 (m), 816.6 (s), 744.5 (m), 627.3 (m).

***O*-Ethyl *O*-(2-phenylbut-3-en-1-yl) *S*-hydrogen phosphorothioate (43)**

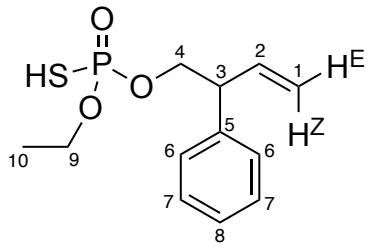


43

Chemical Formula: $C_{12}H_{17}O_3PS$
Molecular Weight: 272.29876

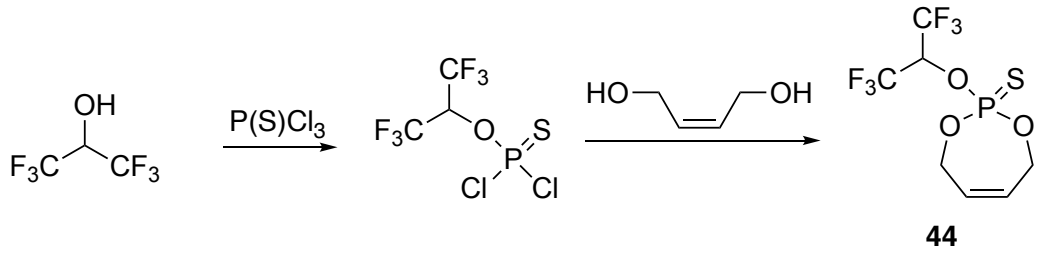
Styrene oxide (1.14 mL, 10.0 mmol, 1.0 eq) was dissolved in THF (7.5 mL) before slow addition of vinylmagnesium bromide (1.0 M in THF, 11 mL, 11.0 mmol, 1.1 eq) at room temperature. The resulting mixture was heated to 70 ºC for 2 hours before cooling to room temperature and quenching with H_2O (10 mL). The mixture was extracted with Et_2O (3 x 10 mL). The organic extracts were combined, washed with brine (10 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. The yellow oil was purified by flash chromatography (10-20% Et_2O in pentane) to give 2-phenyl-but-3-en-1-ol (502 mg, 34%) as a colourless oil.

2-phenyl-but-3-en-1-ol (502 mg, 3.38 mmol, 1.0 eq) was added to a solution of thiophosphoryl chloride (0.343 mL, 3.38 mmol, 1.0 eq) in CH_2Cl_2 (10 mL) at 0 ºC followed by NEt_3 (0.47 mL, 3.38 mmol, 1.0 eq). The resulting mixture was warmed to room temperature and left to stir overnight. The reaction mixture was cooled to 0 ºC before addition of EtOH (0.20 mL, 3.38 mmol, 1.0 eq) followed by NEt_3 (0.47 mL, 3.38 mmol, 1.0 eq). The resulting mixture was warmed to room temperature and left to stir for 2 hours before quenching with 1M HCl (10 mL). The mixture was extracted with Et_2O (3 x 10 mL). The organic extracts were combined, washed with brine (10 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. The yellow oil was purified by flash chromatography (0-1-2% Et_2O in pentane) to give *O*-Ethyl *O*-(2-phenylbut-3-en-1-yl) *S*-hydrogen phosphorothioate (**43**) as a colourless oil (228 mg, 24%).



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 7.37 – 7.32 (m, 2H, 2ArH-(7)), 7.30 – 7.24 (m, 3H, 3ArH-(6, 8)), 6.03 (dddd, *J* = 17.3, 10.5, 7.1, 1.1 Hz, 1H, CH-(2)), 5.24 (dt, *J* = 10.5, 1.3 Hz, 1H, CH^Z-(1)), 5.20 (dq, *J* = 17.3, 1.3 Hz, 1H, CH^E-(1)), 4.51 – 4.43 (m, 1H, CHH′-(4)), 4.42 – 4.34 (m, 1H, CHH′-(4)), 4.28 – 4.16 (m, 2H, CH_2-(9)), 3.83 – 3.75 (m, 1H, CH-(3)), 1.36 (td, *J* = 7.1, 1.0 Hz, 3H, CH_3-(10)), 1.35 (td, *J* = 7.1, 1.0 Hz, 3H, CH_3-(10)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 139.3 (C(5)), 136.9 (C(2)), 128.8 (C(7)), 128.2 (C(6)), 127.4 (C(8)), 117.8 (C(1)), 71.7 (C(4)), 66.4 (C(9)), 49.4 (C(3)), 15.7 (C(10)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: 68.61; HRMS (ESI) *m/z* calcd for $C_{12}H_{16}O_3PS$ $[M–H]^-$: 271.0563, found: 271.0563; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 1494.1 (w), 1453.9 (w), 1000.3 (s), 922.9 (w), 858.9 (w), 793.2 (m), 756.1(w), 699.5 (w), 662.0 (w). Obtained as a mixture of diastereomers.

2-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-4,7-dihydro-1,3,2-dioxaphosphepine 2-sulfide (44)

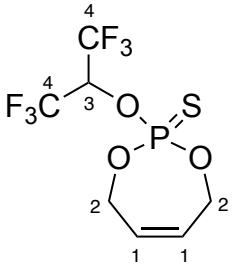


44

Chemical Formula: $C_7H_7F_6O_3PS$
Molecular Weight: 316.15418

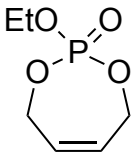
To a solution of thiophosphoryl chloride (2.0 mL, 19.69 mmol, 1.0 eq) in CH_2Cl_2 (50 mL) at 0 ºC was added HFIP (2.07 mL, 19.69 mmol, 1.0 eq) followed by NEt_3 (2.74 mL, 19.69 mmol, 1.0 eq). The reaction mixture was allowed to warm up to room temperature and stir for 18 hours. The reaction mixture was concentrated *in vacuo* and suspended in TBME (5 mL). The supernatant was decanted and the process was repeated. The supernatant was concentrated *in vacuo* to give *O*-(1,1,1,3,3,3-hexafluoropropan-2-yl) phosphorodichloridothioate which was used immediately in the next step.

To a solution of *O*-(1,1,1,3,3,3-hexafluoropropan-2-yl) phosphorodichloridothioate (19.69 mmol, 1.0 eq) in THF (200 mL) was slowly added NEt_3 (22.2 mL, 157.5 mmol, 8.0 eq). The resulting solution was cooled to 0 ºC and a solution of *cis*-buten-1,4-diol (1.62 mL, 19.69 mmol, 1.0 eq) in THF (20 mL) was added via syringe pump over 4 hours at 0 ºC. The mixture was warmed to room temperature left to stir for 1 hour before putting the reaction mixture in the freezer overnight to precipitate NEt_3HCl. The mixture was filtered over celite and rinsed with THF. The filtrate was evaporated *in vacuo* and the residue was purified on silica (10% Et_2O in pentane) to give 2-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-4,7-dihydro-1,3,2-dioxaphosphepine 2-sulfide (**44**) (351 mg, 6% over 2 steps) as a colourless oil.



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 5.79 (dd, *J* = 1.8, 1.9 Hz, 2H, 2CH-(1)), 5.46 (dh, *J* = 15.7, 5.8 Hz, 1H, CH-(3)), 4.83 – 4.78 (m, 2H, CHH′-(2)), 4.78 – 4.74 (m, 2H, CHH′-(2)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 127.0 (C(1)), 120.2 (C(4)), 72.3 (C(3)), 65.5 (C(2)); ^{19}F NMR (162 MHz, $CDCl_3$) δ_P/ppm: –73.92; ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: 75.29; HRMS (ESI) *m/z* calcd for $C_7H_6O_3F_6PS$ $[M–H]^-$: 314.9685, found: 314.9681; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 1380.6 (w), 1292.8 (w), 1235.2 (m), 1199.3 (s), 1133.9 (m), 1111.4 (m), 1037.9 (s), 999.8 (m), 962.7 (w), 885.2 (m), 823.7 (w), 749.7 (s), 686.5 (m), 663.1 (m).

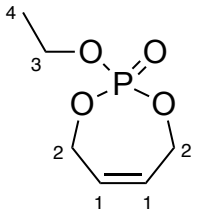
2-Ethoxy-4,7-dihydro-1,3,2-dioxaphosphepine 2-oxide (45)



45

Chemical Formula: $C_6H_{11}O_4P$
Molecular Weight: 178.12376

To a solution of ethyl dichlorophosphate (6.53 mL, 55.0 mmol, 1.0 eq) in THF (500 mL) was slowly added NEt_3 (61.0 mL, 440 mmol, 8.0 eq). The resulting solution was cooled to 0 ºC and a solution of *cis*-buten-1,4-diol (5.10 mL, 62.0 mmol, 1.13 eq) in THF (40 mL) was added via syringe pump over 4 hours at 0 ºC. The mixture was warmed to room temperature left to stir for 1 hour before putting the reaction mixture in the freezer overnight to precipitate NEt_3HCl. The mixture was filtered over celite and rinsed with THF. The filtrate was evaporated *in vacuo* and the residue was purified on silica (50-75% EtOAc in petroleum ether) to give 2-ethoxy-4,7-dihydro-1,3,2-dioxaphosphepine 2-oxide (**45**) (5.58 g, 57%) as a colourless oil.



^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm: 5.74 (dd, J = 1.8, 2.0 Hz, 2H, 2CH-(1)), 4.74 – 4.55 (m, 4H, 2CH_2-(3)), 4.21 (dq, J = 8.6, 7.1 Hz, 2H, 2CH_2-(2)), 1.35 (dt, J = 7.1, 1.0 Hz, 3H, CH_3-(4)); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c/ppm: 127.1 (C(1)), 64.6 (C(2)), 64.2 (C(3)), 16.3 (C(4)); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: 3.64; HRMS (ESI) *m/z* calcd for $C_6H_{12}O_4P$ $[M+H]^+$: 179.04677, found: 179.04691; IR (ATR) ν (cm^{-1}) thin film, $CHCl_3$: 1460.7 (w), 1397.3 (w), 1370.3 (w), 1262.1 (m), 1166.3 (w), 1026.6 (s), 1004.7 (s), 961.8 (s), 871.7 (m), 814.9 (w), 766.4 (m).

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