New Routes to 2,5-Disubstituted Tetrahydropyrans and *P*-Stereogenic Heterocycles *via* Ring-Closing Metathesis

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Abstract

New methodologies have been developed for the synthesis of 2,5-disubstituted tetrahydropyrans and for the asymmetric synthesis of *P*-stereogenic phospholene boranes.

Synthesis of 2,5-disubstituted tetrahydropyrans in a racemic fashion was achieved *via* Grignard addition, *O*-alkylation, ring-closing metathesis and hydrogenation. Using this route, seven potential perfumery compounds were produced in good overall yield. Olfactory evaluation of the potential perfumery molecules accessed the majority of products as having a predominant characteristic of citrus note and others having a floral note. In addition, asymmetric synthesis of two saturated cyclic ethers was achieved using an asymmetric deprotonation approach. An alternative route to an enantioenriched alcohol using catalytic asymmetric deprotonation and trapping with Andersen's sulfinate was briefly studied and proved successful.

The asymmetric synthesis of *P*-stereogenic phospholene boranes was investigated. First, three chiral diamines were synthesised and their asymmetric induction was tested in the asymmetric lithiation of *t*-butyl phosphine boranes. Subsequently, the asymmetric synthesis of *P*-stereogenic vinylic phospholene boranes was carried out. Using *s*-BuLi/(−)-sparteine as a base, alkylated phosphine boranes were isolated with good yield and high enantioselectivity. A telescoped regioselective deprotonation/trapping of paraformaldehyde and elimination reaction was developed to gain access to the dienes. Finally, ring-closing metathesis afforded the desired vinylic phospholene boranes. The application represents the first example of asymmetric synthesis of *P*-stereogenic vinylic phospholene boranes.

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Finally, I would like to thank my family for all of their love and support, especially my mum. Without her, I would not have come this far.

Author's Declaration

The research presented in this thesis is, to the best of my knowledge, original except where due references has been made to other authors and/or co-workers.

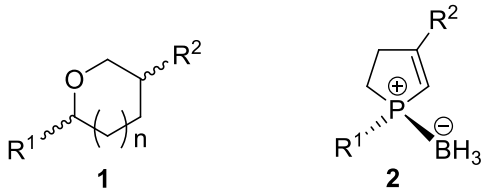
Xiao Wu

Chapter 1. Introduction

1.1 Project Overview

This thesis contains the results of two projects aimed at developing new methodologies for the synthesis of 2,5-disubstituted tetrahydropyrans (THPs) **1** and the asymmetric synthesis of *P*-stereogenic phospholene boranes **2** (Figure 1.1). In both projects, ring-closing metathesis featured as the key step for ring formation.

Figure 1.1: Structure of 2,5-disubstituted tetrahydropyrans (THPs) 1 and *P*-stereogenic phospholene boranes 2



We identified 2,5-disubstituted THPs **1** as an attractive synthetic target because they are potential fragrance molecules. For example, they could be used as a fragrance ingredient for the preparation of perfumery compositions as well as perfumery goods. From a synthetic point of view, there are not many routes for the synthesis of 2,5-disubstituted THPs **1**. Therefore, it was important to develop general synthetic methodology to access the 2,5-disubstituted THP framework, including diastereo- and enantioselective aspects. The results are described in Chapter 2.

In a separate project, we were interested in developing a route for the asymmetric synthesis of *P*-stereogenic phospholene heterocycles **2**. There are limited general routes to access phosphine heterocycles and the asymmetric synthesis of **2** was unknown. Furthermore, phosphine heterocycles **2** may have application as

precursors to chiral phosphine catalysts. Chapter 3 describes our results on this topic.

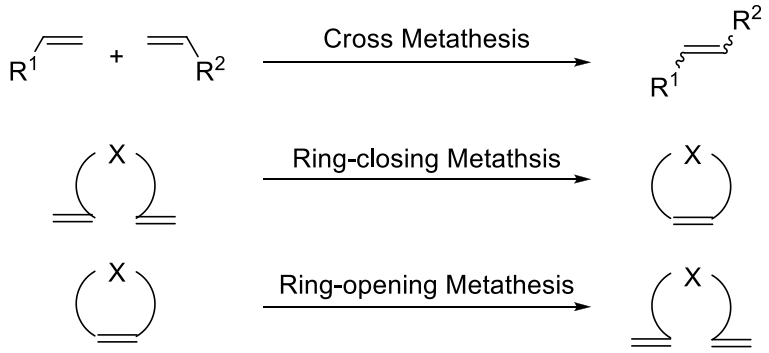
1.2 Ring-Closing Metathesis in Organic Synthesis

The synthesis of 2,5-disubstituted THPs **1** and phospholene boranes **2** relied on key ring-closing metathesis reactions. Hence, a brief overview of ring-closing metathesis is provided in this section.

1.2.1 Background on Ring-Closing Metathesis

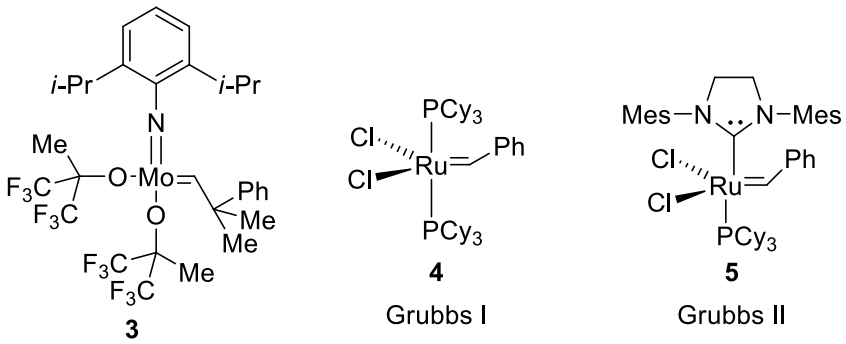
Olefin (or alkene) metathesis has had a profound impact on the formation of carbon-carbon bonds, and is one of the truly significant reactions in modern organic chemistry. In 2005, the Nobel Prize in Chemistry was awarded jointly to Chauvin, Grubbs and Schrock for the development of alkene metathesis in organic synthesis.[1] The first report of double-bond formation using alkene metathesis was actually in 1955[2] N. G. (Du Pont de Nemours & Co.) U.S. Patent 2,721,189.1955 [#155]but Calderon and co-workers introduced the term 'olefin metathesis' thirteen years later.[3] There are several different alkene metathesis reactions: ring-closing metathesis (RCM), ring-opening metathesis polymerization (ROMP), cross-metathesis (CM), ring-opening metathesis (ROM) and acyclic diene metathesis polymerization (ADMET). A selection of the most common types of alkene metathesis reactions is shown in Scheme 1.1. These various alkene metathesis reactions allow access to molecules and polymers that would be difficult to obtain by other means.

Scheme 1.1: Selection of alkene metathesis reactions



Three commonly used alkene metathesis catalysts are shown in Figure 1.2. In 1990, Schrock and co-workers introduced the molybdenum-based catalyst **3**.[4] Catalyst **3** displayed superb metathesis reactivity but its pronounced sensitivity to oxygen, moisture and certain functional groups means that it is not often used in synthesis. Grubbs and co-workers subsequently introduced the ruthenium-based catalysts **4** and **5**, and they are more widely used due to their increased tolerance to most functional groups and their greater stability to atmospheric oxygen and moisture.[5-7]

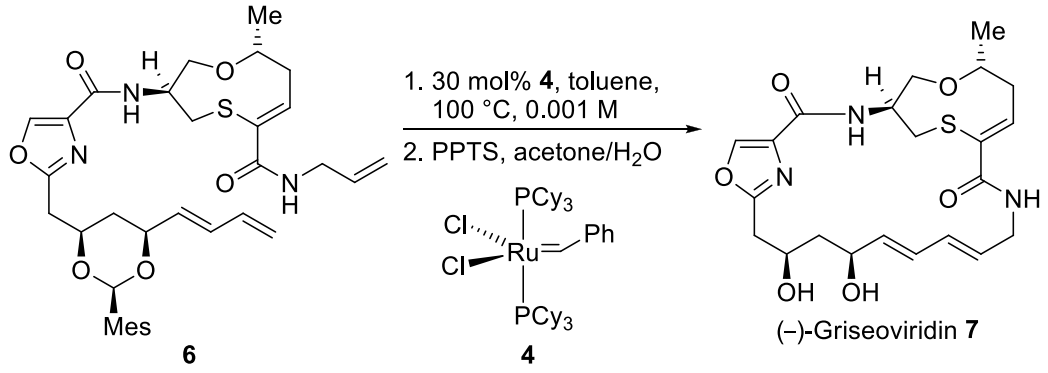
Figure 1.2: Structures of alkene metathesis catalysts



1.2.2 Ring-Closing Metathesis in Modern Natural Product Synthesis

Two examples of natural product syntheses *via* ring-closing metathesis are presented in Schemes 1.2 and 1.3. The first example is the synthesis of (−)-griseoviridin **7**, a streptogramin antibiotic, featuring a 23-membered unsaturated ring.[8] Here, ring-closing metathesis was utilized for the macrocyclic ring formation. Thus, ring-closing metathesis using 30 mol% of Grubbs 1st generation catalyst **4** was carried out on **6** to furnish the cyclized product in 42% yield (Scheme 1.2). Acidic removal of the diol protecting group gave (−)-griseoviridin **7** as a single diastereoisomer in 68% yield.

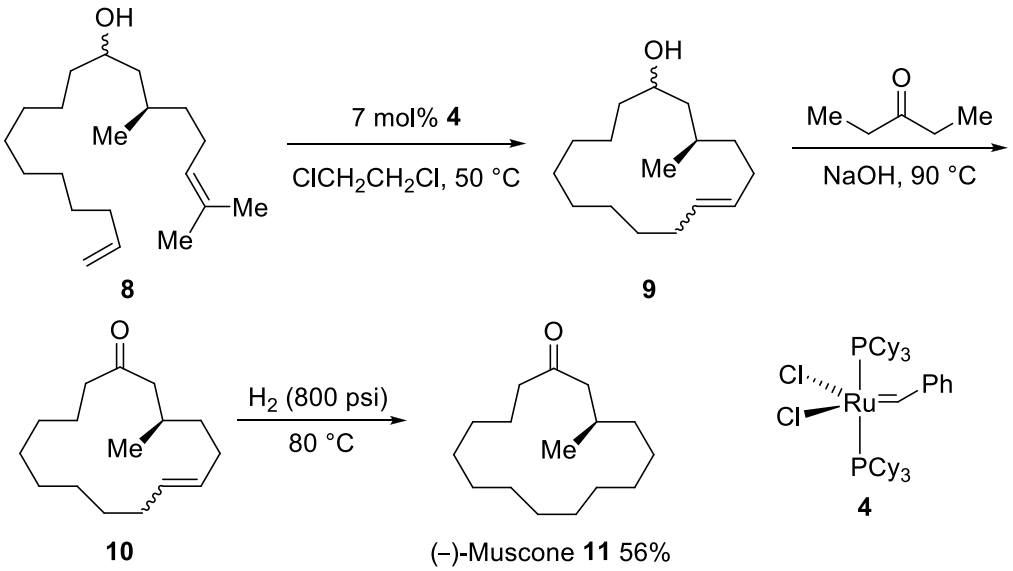
Scheme 1.2: Synthesis of (−)-griseoviridine 7



Musk odorants are of central importance for the fragrance industry and (−)-muscone **11** is the main odorous principle from the animal kingdom.[9] The synthesis of (−)-muscone **11** was achieved by Grubbs and co-workers using ruthenium-based Grubbs 1st generation catalyst **4**, where sequential alkene ring-closing metathesis, hydrogen transfer and hydrogenation reactions were mediated in a tandem process (Scheme 1.3).[10] Diene **8** bearing an alcohol functionality was treated with 7 mol% of Grubbs catalyst **4** in 1,2-dichloroethane at 50 ºC to afford the desired macrocyclic alkene **9** as a mixture of geometrical isomers. Subsequent *in situ* treatment with 3-pentanone and sodium hydroxide

then initiated ruthenium-catalysed transfer of hydrogen to furnish ketone **10**. Under hydrogenation conditions, the still-present ruthenium complex was converted into a ruthenium hydride species, which chemoselectively reduced the alkene in the presence of the ketone group. (−)-Muscone **11** was thus obtained in 56% yield from this one-pot protocol.

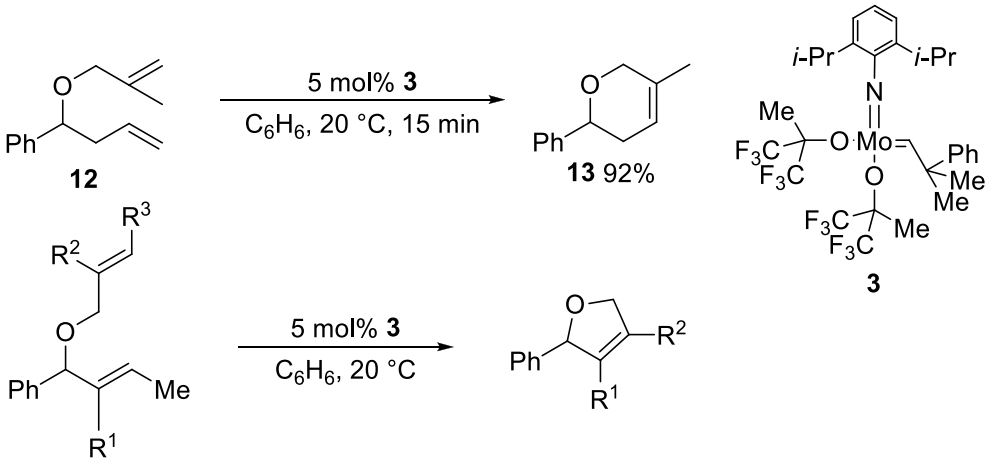
Scheme 1.3: A three-step synthesis of (−)-Muscone



1.2.3 Synthesis of Oxygen Heterocycles *via* Ring-Closing Metathesis

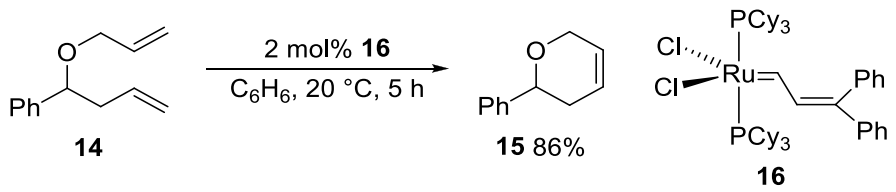
One part of our project (Chapter 2) is concerned with the synthesis of cyclic ethers using ring-closing metathesis. The use of such an approach to 5- and 6-membered cyclic ethers is well-known. In 1992, Grubbs and co-workers reported the first application of catalytic ring-closing metathesis to the synthesis of oxygen heterocycles using molybdenum-based catalyst **3** (Scheme 1.4).[11] As an example, cyclic ether **13** was synthesised in high yield from diene **12** using 5 mol% of molybdenum-based catalyst **3**. It is worth noting that trisubstituted and tetrasubstituted double bonds could be formed efficiently with prolonged reaction times.

Scheme 1.4: Formation of 5- and 6-membered cyclic ethers *via* ring-closing metathesis



Later, the Grubbs group also investigated the ring-closing metathesis reaction employing ruthenium-based catalyst **16** (Scheme 1.5).[12] For example, using 2 mol% of catalyst **16**, monosubstituted cyclic ether **15** was formed from diene **14** in 86% yield. Ruthenium-based catalyst **16** is much more convenient to handle as it is not oxygen and moisture sensitive.

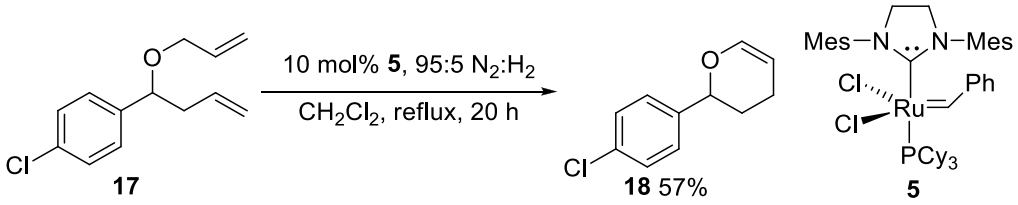
Scheme 1.5: Synthesis of a 2-substituted dihydropyran



Ring-closing metathesis of vinyl ethers is known to be problematic.[13, 14] Therefore, the synthesis of cyclic enol ethers using this approach could not be achieved easily. To solve this problem, Snapper and co-workers reported the synthesis of cyclic enol ethers *via* a tandem ring-closing metathesis-alkene isomerization sequence.[15] As an example, treatment of diene **17** with 10 mol% of

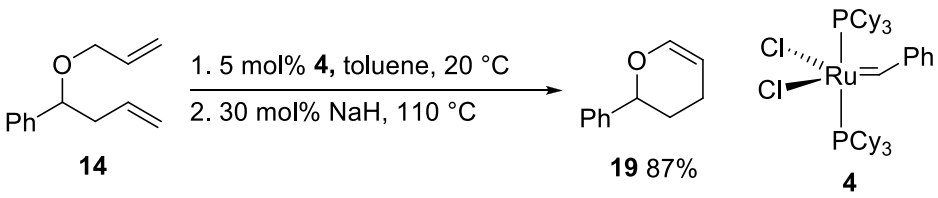
Grubbs 2nd generation catalyst **5** in a 95:5 mixture of nitrogen and hydrogen gas afforded 6-membered ring enol ether **18** in 57% yield (Scheme 1.6). The metathesis catalyst was activated by treatment with diluted hydrogen to allow the isomerization step, presumably *via* a ruthenium hydride intermediate. The reaction is also applicable to 5- and 7-membered cyclic enol ethers.

Scheme 1.6: Synthesis of cyclic enol ether *via* a tandem ring-closing metathesis-alkene isomerization reaction



Later, Schmidt and co-workers reported a similar ring-closing metathesis-alkene isomerization approach to the synthesis of cyclic enol ethers from allyl homoallylic ethers (Scheme 1.7).[16, 17] For example, upon treatment with 5 mol% Grubbs 1st generation catalyst **4** followed by addition of sodium hydride at 110 ºC, cyclic enol ether **19** was generated in 87% yield from diene **14**. In this case, the ruthenium-based catalyst was activated in a separate step using a hydride donor, such as sodium hydride, to afford the isomerization product.

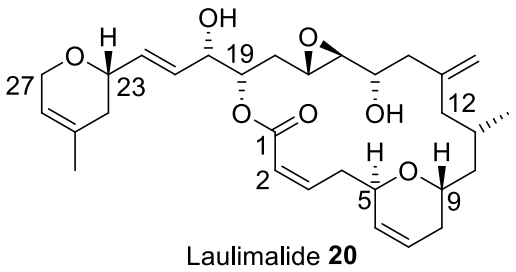
Scheme 1.7: Synthesis of cyclic enol ether *via* a tandem ring-closing metathesis-alkene isomerization reaction



Laulimalide **20**, which is a metabolite that has been isolated from various marine sponges, stabilises microtubules and has high activity against multidrug resistant cell lines (Figure 1.3).[18-21] Mulzer and co-workers completed the total synthesis

of Laulimalide **20**, where the synthesis of the C1-C12 dihydropyran segment of Laulimalide **20** was achieved *via* ring-closing metathesis (Scheme 1.8).[22, 23]

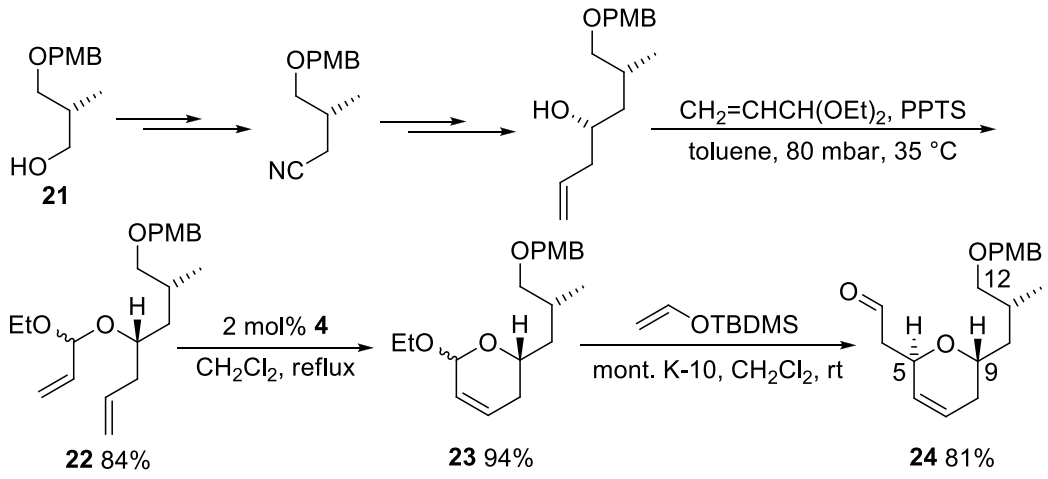
Figure 1.3: Structure of Laulimalide 20



Laulimalide **20**

Diene **22** was prepared from alcohol **21** in five steps. Upon treatment with Grubbs 1st generation catalyst **4**, diene **22** underwent smooth cyclisation to afford cyclic ether **23** in 94% yield. Subsequent displacement of the allylic ethoxy group with a silyl enol ether in the presence of montmorillonite K-10 as a Lewis acid furnished the desired tetrahydropyran **24**.

Scheme 1.8: Synthesis of tetrahydropyrans 24

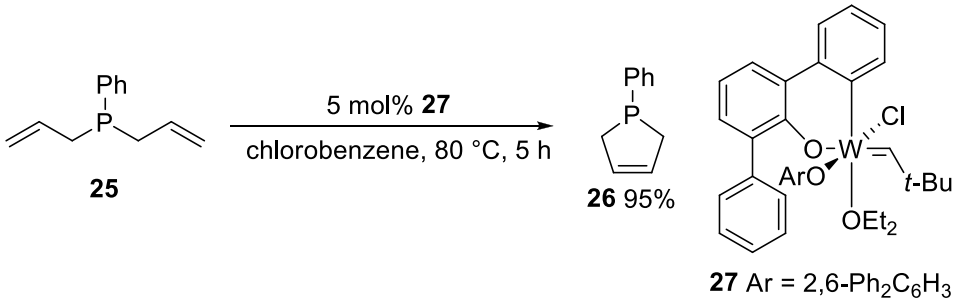


22 84% **23** 94% **24** 81%

1.2.4 Synthesis of Phosphine Heterocycles *via* Ring-Closing Metathesis

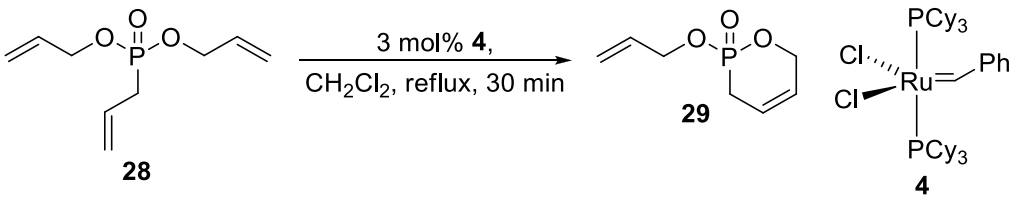
The second part of our project (Chapter 3) focuses on a ring-closing metathesis approach to novel phosphine heterocycles. Indeed, ring-closing metathesis has facilitated the construction of various phosphine heterocycles. In 1995, Basset and co-workers reported the first example of ring-closing metathesis to access a phosphine heterocycle.[24] They used a tungsten-based catalyst, previously developed in their group.[25] For example, diallyl phenylphosphine **25** was treated with 5 mol% of tungsten-based catalyst **27** to furnish the desired cyclic phosphine **26** in 95% yield (Scheme 1.9).

Scheme 1.9: Synthesis of a phosphine heterocycle *via* ring-closing metathesis



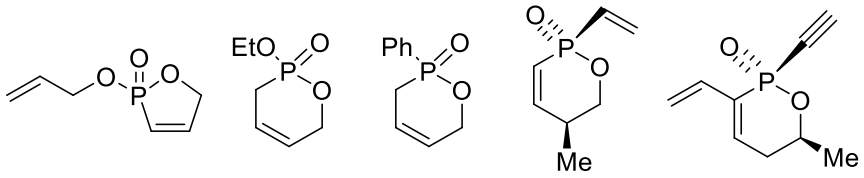
Subsequently, Hanson and co-workers developed the first synthesis of phosphine heterocycles utilising Grubbs ruthenium-based catalyst **4**.[26] Thus, cyclic phosphonate **29** was synthesised from diallyl allyl phosphonate **28** using 3 mol% of Grubbs catalyst **4** (Scheme 1.10). This approach allowed access to a range of 5-, 6- and 7-membered phosphonates and phosphinates, although the formation of trisubstituted alkenes was unsuccessful.

Scheme 1.10: Synthesis of a phosphonate heterocycle *via* ring-closing metathesis



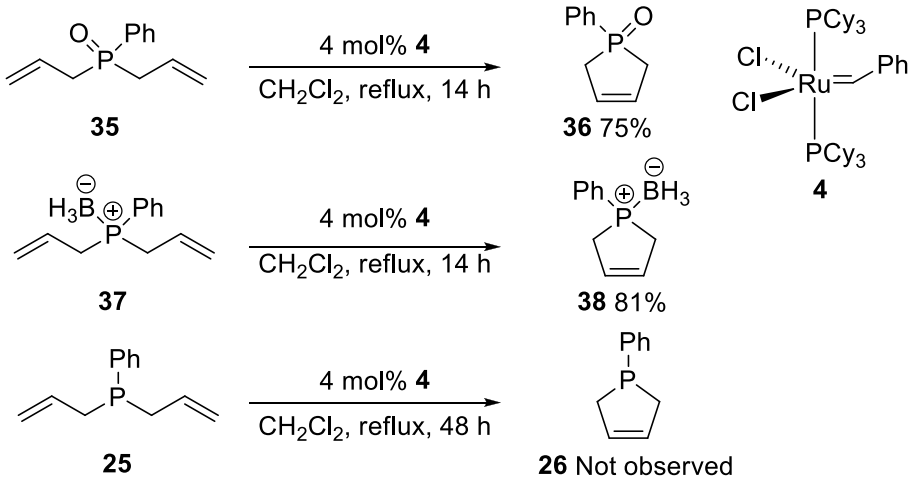
Several examples of ring-closing metathesis to access other phosphine heterocycles such as phosphonates and phosphinates are also known. A selection of examples is shown in Figure 1.4. These include racemic phosphonates **30**[27] and **31**,[28] racemic phosphinate **32**[29] and single diastereoisomers of phosphinates **33**[30] and **34**.[31] The remainder of this section will focus on the synthesis of carbocyclic phosphine heterocycles, which is of most relevance to the results presented in Chapter 3.

Figure 1.4: Examples of phosphine-containing heterocycles



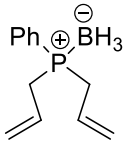
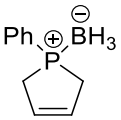
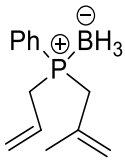
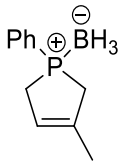
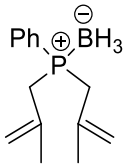
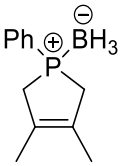
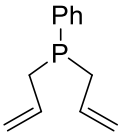
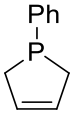
Gouverneur and co-workers studied the synthesis of cyclic phosphine oxides and phosphine boranes *via* ring-closing metathesis.[32, 33] Using Grubbs 1st generation catalyst **4**, ring-closing metathesis of bis(alkenyl)phosphine oxides and phosphine boranes afforded the corresponding cyclic products in good yield (Scheme 1.11). For example, phosphine oxide **35** was treated with 4 mol% of Grubbs catalyst **4** to give cyclic phosphine oxide **36** in 75% yield, whereas with 2 mol% of Grubbs catalyst **4**, phosphine borane **37** readily provided cyclic phosphine borane **38** in 81% yield. In contrast, diallyl phenyl phosphine **25** gave no conversion into the desired cyclic product **26** using Grubbs catalyst **4**.

Scheme 1.11: Ring-closing metathesis of phosphine dienes

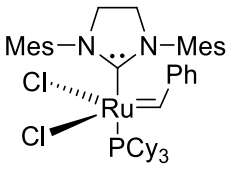


Later, the Gouverneur group expanded the scope of cyclic phosphine heterocycle synthesis by carrying out reactions on phosphine boranes, employing ruthenium-based catalyst **5** and molybdenum-based catalyst **3**.[34] Generally, the yield of the reactions improved dramatically compared with using Grubbs 1st generation catalyst **4** (Table 1.1). Using catalyst **5**, diene **37** was quantitatively transformed into the corresponding cyclic phosphine borane **38** (entry 1). With trisubstituted alkene **39**, cyclic phosphine borane **40** was formed in 90% yield using ruthenium catalyst **5** (entry 2). In contrast, with sterically hindered tetrasubstituted alkene **41**, either ruthenium- or molybdenum-based catalysts with extended reaction times of up to 192 h gave none of the desired product **42** (entry 3). This demonstrated the difficulty presented when synthesising sterically demanding cyclic phosphines. It is worth noting that in the presence of molybdenum-based catalyst **3**, transformation of unprotected phenylphosphine **25** into the desired product **26** was achieved in an excellent 95% yield (entry 4).

Table 1.1: Synthesis of phosphine heterocycles *via* ring-closing metathesis

Entry	Catalyst (mol%)	Substrate	Product	Time (h)	Yield (%)
1	**5** 4 mol%	 **37**	 **38**	18	100[a]
2	**5** 6 mol%	 **39**	 **40**	26	90[b]
3	**5** and **3** 4-14 mol%	 **41**	 **42**	Up to 192	0
4	**3** 12.5 mol%	 **25**	 **26**	84	95[b]

[a] Yield after purification by chromatography. [b] Conversion as determined by ^{1}H NMR spectrum of the crude mixture.



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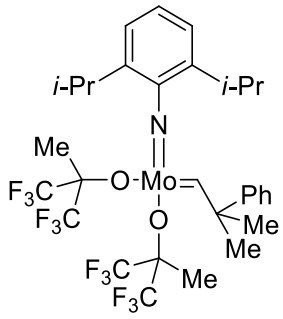
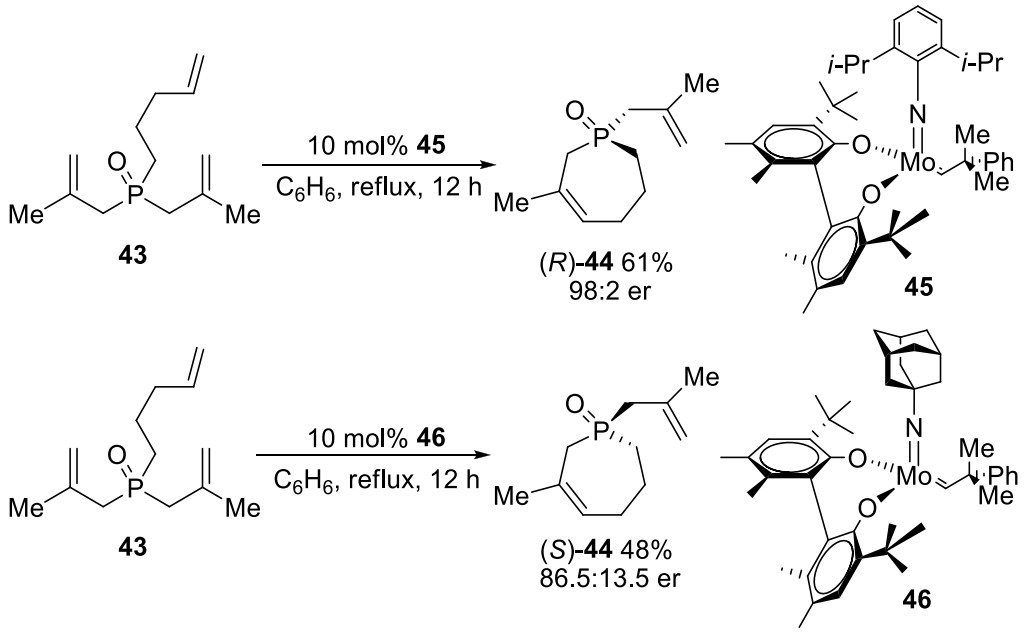


3

Recently, the asymmetric synthesis of *P*-stereogenic phosphinates and phosphine oxides was developed by Gouverneur and co-workers.[35] Trienes such as **43** were desymmetrised by asymmetric ring-closing metathesis using chiral molybdenum-based catalysts. For example, triene **43** was cyclised using 10 mol%

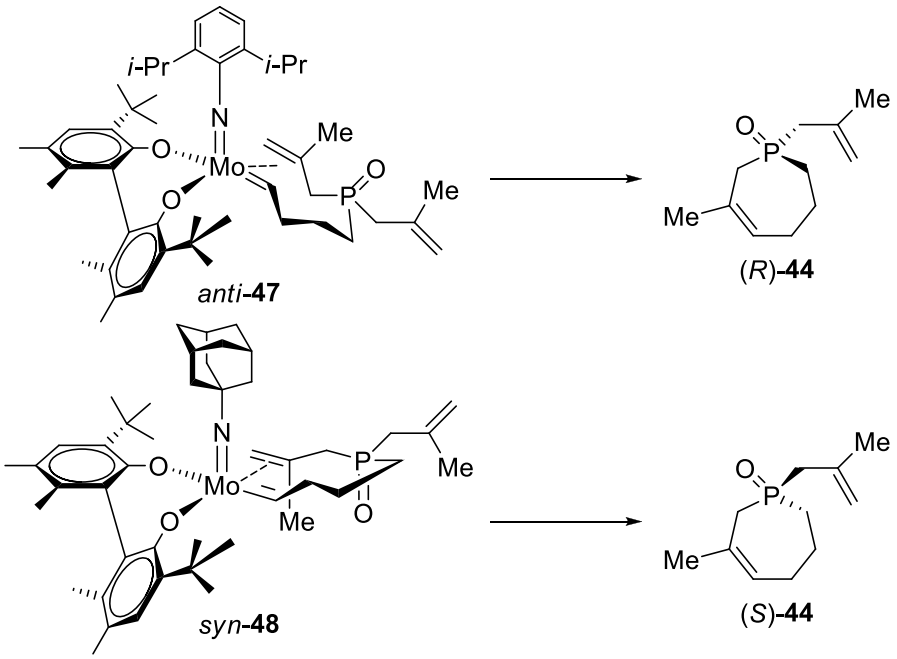
of molybdenum catalyst **45** to furnish cyclic phosphine oxide (*R*)-**44** in 61% yield and 98:2 er. Crucially, by modifying the structure of the achiral imido group in molybdenum complex **46**, the opposite enantiomer, (*S*)-**44**, could be synthesised in 48% yield and 86.5:13.5 er (Scheme 1.12).

Scheme 1.12: Asymmetric synthesis of *P*-stereogenic phosphinates



A model was proposed to explain the enantioselectivity of the reaction (Figure 1.5). Both molybdenum-based alkylidenes **45** and **46** have identical diolate ligands and are only distinguishable through their achiral imido ligand.

Figure 1.5: Proposed model for Mo-based ARCM reactions of phosphine-containing trienes, leading to the formation of (+) and (–) enantiomers



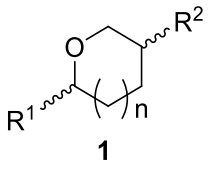
Intermediate *anti*-**47** reveals a significant steric repulsion between the group of the alkylidene and one of the *o*-*i*-Pr groups of the imido ligand. Therefore, *anti*-**47** was preferred to give cyclic phosphine oxide (*R*)-**44**. However, when the steric repulsion between the imido ligand and the alkylidene is small, *syn*-**48** was formed to give the opposite enantiomer. A range of chiral phosphine heterocycles were synthesised using this procedure but the seven-membered rings were produced with the highest enantioselectivity

In summary, ring-closing metathesis is a powerful reaction in organic synthesis and has become a routine transformation for the construction of cyclic systems, such as oxygen and phosphine heterocycles. Although sterically demanding oxygen heterocycles do not present a problem for ring-closing metathesis, the synthesis of tetrasubstituted phosphine heterocycles still remains a synthetic challenge.

Chapter 2. New Synthetic Routes to 2,5-Disubstituted Tetrahydropyrans

This part of the thesis contains the results of a project aimed at developing new synthetic routes for the synthesis of 2,5-disubstituted tetrahydropyrans (THPs) **1** (Figure 2.1). First, the origin of the project and its link to fragrance chemistry are presented in section 2.1. Then, a brief overview of the routes that have previously been developed for the synthesis of 2,5-disubstituted tetrahydropyran frameworks is provided (section 2.2). Section 2.3 states the overall aims of the project and provides an outline of the proposed research. Sections 2.4-2.6 are dedicated to the development of methodology for the synthesis of 2,5-disubstituted THPs in a racemic fashion, followed by the attempted synthesis of a specific target molecule. An asymmetric deprotonation and ring-closing metathesis route to cyclic ethers is then described (section 2.7). Finally, conclusions and future work for this part of the project are discussed in section 2.8.

Figure 2.1: Structure of 2,5-disubstituted tetrahydropyrans 1

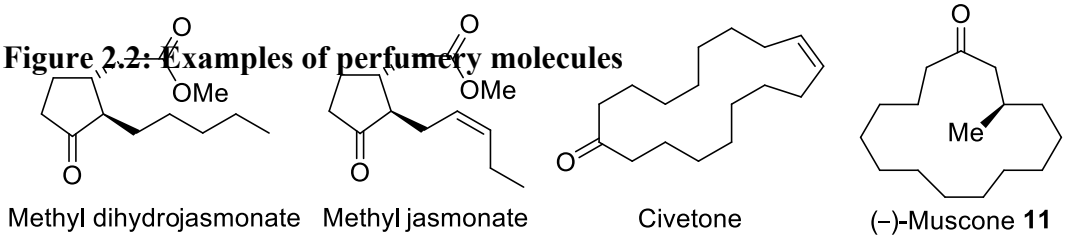


1

2.1 Introduction to Fragrance Chemistry

Fragrance is ubiquitous in the natural world, and its chemistry is a fascinating area of research. Generally, all compounds with a smell fall within the category of fragrance chemicals. Compounds with sufficiently high vapour pressure, i.e. typically those with molecular weight of less than 300, and containing a limited number of functional groups will have an odour. Some examples are shown in Figure 2.2. For example, methyl dihydrojasmonate, perhaps the most important fragrance ingredient, has a jasmine-like odour, which gradually becomes powerful when left to stand. This material differs from methyl jasmonate, the natural jasmine component, by the saturation in the side chain. Civetone and (−)-muscone **11** are responsible for the main musk odours among the animalic family. The presence of functional groups is not always essential to the odorous properties of a compound.[36] One example is 2,4,4-trimethylpentane, an alkane with a pronounced camphoraceous odour.

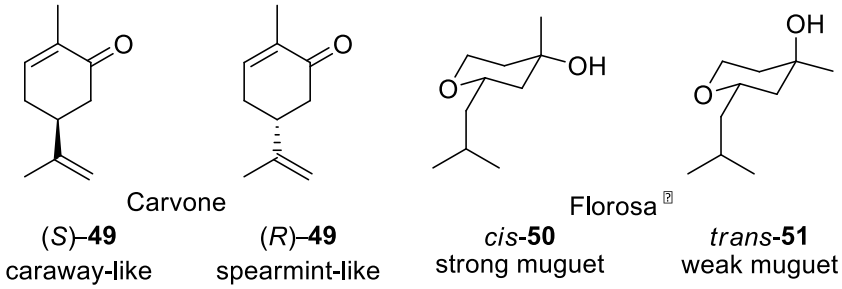
Figure 2.2: Examples of perfumery molecules



Stereoisomers also play important roles in determining the odorous properties of molecules. In most cases, the odour differences are very small and are often attributed to the presence of trace impurities. A very striking difference in odour properties is found for the two enantiomers of carvone **49** (Figure 2.3).[37] This has drawn attention to the fact that the absolute stereochemistry of a molecule can have a considerable influence on its odour properties. While (*R*)-**49** has typical spearmint character, (*S*)-**49** is described as caraway-like. Another example comes

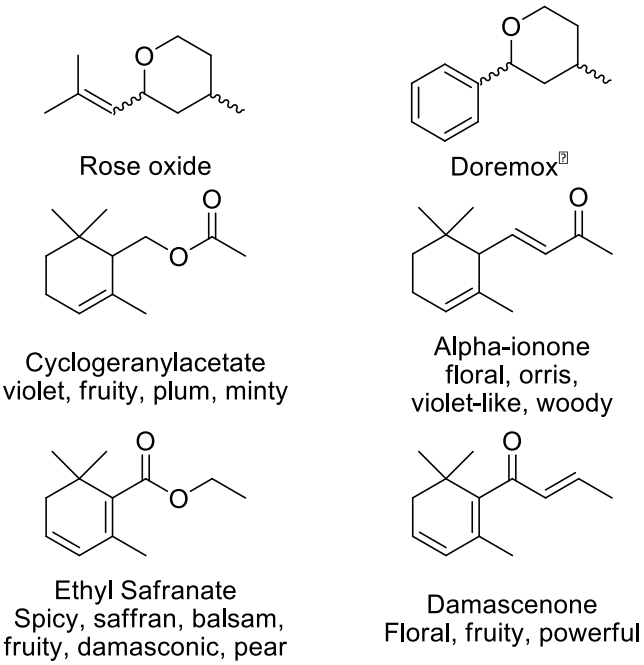
from the two diastereoisomers of Florosa® (Figure 2.3).[38] Both diastereoisomers have a muguet odour but *cis*-**50** is more potent than the *trans*-**51**. Therefore, for an accurate description of the odour profile, a purity of above 98% is normally required before a compound is submitted to be evaluated by the research perfumers.

Figure 2.3: Enantiomers of carvone and florosa®



Another interesting example of structure-odour relationship is illustrated by the design of a new class of compounds related to commercially available perfumery compounds. There is so-called 'character-impact structure' within a category of the fragrance compounds. By modifying the substituents on the character-impact structure, the resulting compounds can have similar odour profiles to the original compounds. For example, the *i*-butenyl group in rose oxide can be replaced by a phenyl group, and the resulting compound Doremox® still possesses a strong floral-green, rose odour reminiscent of rose oxide.[39, 40] Similarly, replacement of the electron dense oxygen atom in cyclogeranylacetate by an alkene gives alpha-ionone, which also possesses a violet note. Likewise, a fruity note is presented by both ethyl safranate and damascenone (Figure 2.4).[41]

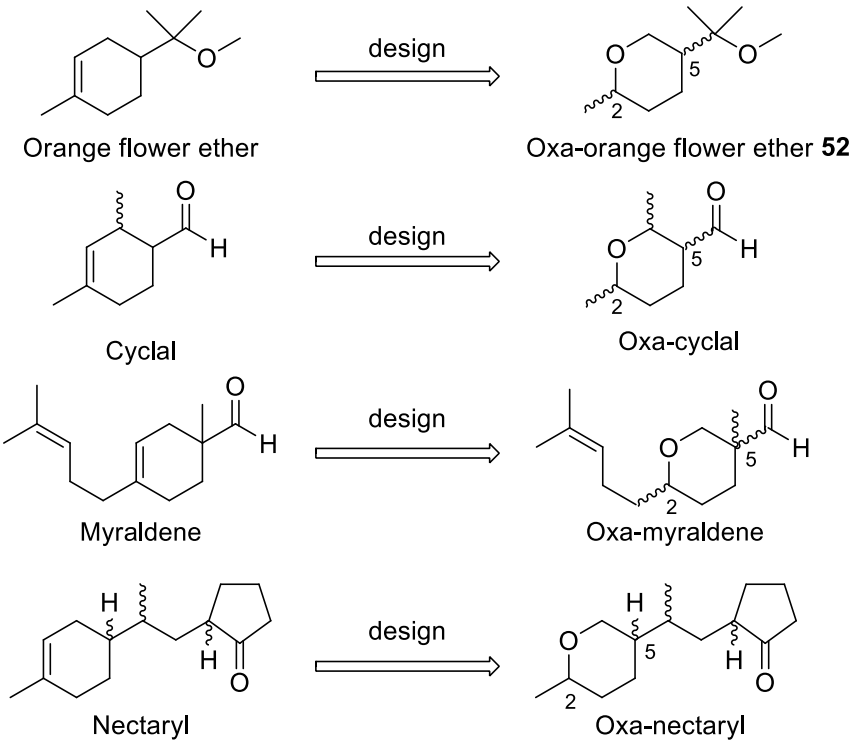
Figure 2.4: Examples of perfumery molecules that illustrate the structure-odour relationship



Conversely, the electron density of an alkene group could be replaced by an oxygen atom and the resulting compound may still possess a similar odour profile. Since there is a wide range of perfumery compounds that contains the cyclohexene motif, we considered replacing the cyclohexene with a cyclic ether (tetrahydropyran, THP). The design of four potential new perfumery compounds is shown in Figure 2.5. These are based on four known perfumery compounds: orange flower ether, cyclal, myraldene and nectaryl. By replacing the electron density on the oxygen atom with an alkene group, a range of cyclic ethers can be created. All of the "oxa" target molecules share a common feature: they have substituents at the 2- and 5-positions of the tetrahydropyran. The overall aim of this part of the project is to develop a general route to 2,5-disubsitituted THPs with a view to the synthesis of the oxa-analogues shown in Figure 2.5. The strategy should proceed *via* a short reaction sequence and allow the preparation of THPs with a wide variety of substituents. We also planned to explore racemic

and enantioselective syntheses of these compounds. Finally, it was hoped that the 2,5-disubstituted THPs would have attractive properties in the olfactory evaluation, which would be carried out by our industrial collaborator, Givaudan.

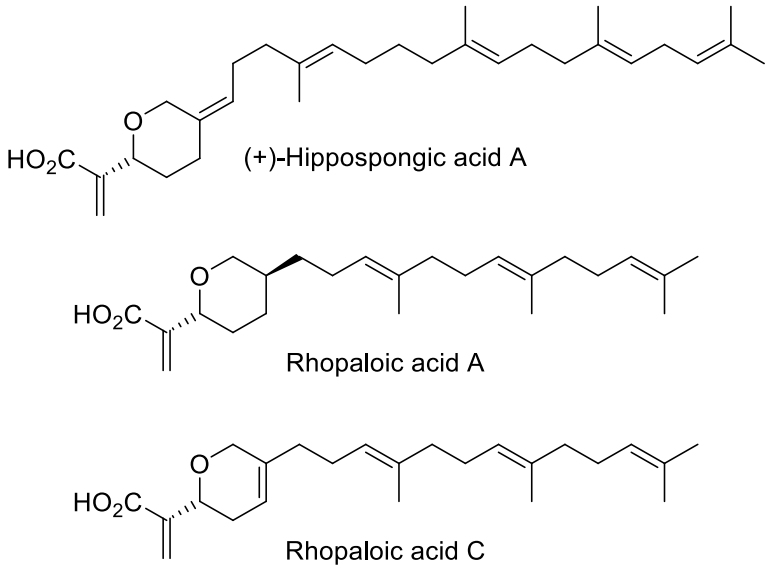
Figure 2.5: Design of potential perfumery compounds



2.2 Previous Strategies for the Synthesis of 2,5-Disubstituted Tetrahydropyrans (THPs)

Tetrahydropyran (THP) and its derivatives are present in many classes of natural products and are important intermediates in organic synthesis. There are, however, very few naturally occurring 2,5-disubstituted THPs. For example, both (+)-hippospongic acid A and the rhopaloic acids A and C contain 2,5-disubstituted THPs (Figure 2.6). The triterpenoic acid hippospongic acid A was isolated from the sponge *Hippospongia* sp.[42, 43] The rhopaloic acids are a class of norsesterpenes that were isolated from both the marine sponge *Rhopaloeides* sp.[42, 44] and from *Hippospongia* sp.[45] Hippospongic acid A and the rhopaloic acids A and C all exhibit considerable activity for inhibiting gastrulation in starfish embryos.

Figure 2.6: Examples of natural products that contain 2,5-disubstituted THP framework

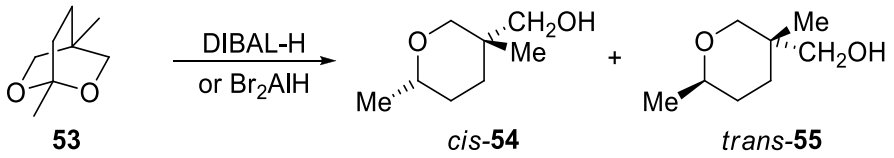


Interestingly, the synthesis of 2,5-disubstituted THP ring systems has not been intensively studied: only a few groups have developed methodologies for the

synthesis of 2,5-disubstituted THPs. In particular, there are no general approaches to those types of molecules.

In 1990, Yamamoto and co-workers studied the reduction of acetals and found that depending on the nature of the solvent, the symmetrical bicyclic acetal **53** could be reduced stereoselectively to give 2,5-disubstituted THPs *cis*-**54** and *trans*-**55** (Table 2.1). In a non-polar solvents such as toluene, the reaction gave predominately the 2,5-disubstituted THP *trans*-**55** (entry 1), while in polar solvents such as THF and Et_2O, the 2,5-disubsitituted THP *cis*-**54** was the major product (entries 2 and 3). The optimum reaction conditions used dibromoaluminium hydride in Et_2O and gave THP *cis*-**54** in 72% yield and 97:3 *cis*:*trans* selectivity (entry 3).

Table 2.1: Reductions of acetal 53



53 *cis*-**54** *trans*-**55**

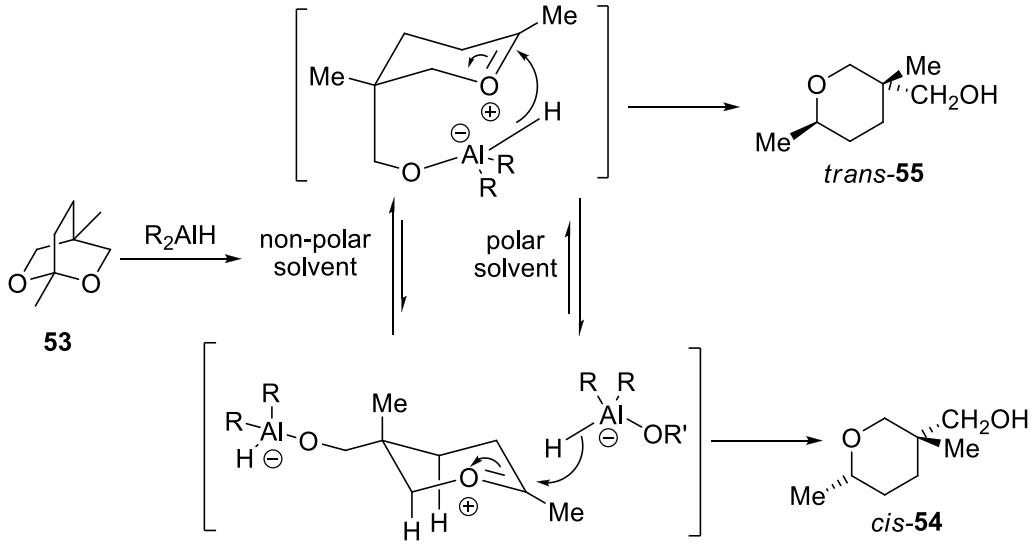
Entry	Reagent	Solvent	Temp.	Time (h)	Yield	*cis*-**54** : *trans*-**55**
1	DIBAL-H	toluene	rt	20	38	17:83
2	DIBAL-H	THF	rt	15	51	82:18
3	Br_2AlH	Et_2O	−20	0.25	72	97:3

[a] Yield of a mixture of *cis* and *trans* diastereoisomers after purification by chromatography.

Two different mechanisms were proposed in order to explain the stereoselectivity of the reaction (Scheme 2.1). In a non-polar solvent, the oxonium ion forms a tight ion pair and the hydride attacks the cationic centre on the *cis*-face in an intramolecular fashion to give *trans*-**55**. In contrast, in a polar solvent, the ion pair can exist in an open conformation, and the hydride attacks the less sterically hindered face of the cationic centre to give *cis*-**54**. This study revealed that the

mechanism of the reductive cleavage of acetals may proceed differently depending on the nature of the solvent. Thus, *cis*-**54** and *trans*-**55** could be obtained selectively. However, this methodology was not sufficiently versatile to be used as a general route to 2,5-disubstituted THPs.

Scheme 2.1: Proposed mechanism for the reduction of acetal 53

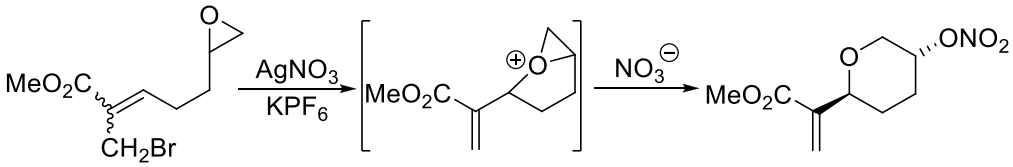


Ohkata and co-workers have reported the synthesis of 2,5-disubsitituted THPs by an epoxide ring expansion process (Table 2.2).[46] The epoxy bromide **56** was converted into tetrahydropyranylacrylate *trans*-**58** on treatment with silver nitrate. The silver salt, which has a high halide affinity, eliminates the bromide ion to afford a bridged oxonium ion intermediate **57** *via* intramolecular nucleophilic attack of the epoxy group. Then, the nitrate ion attacks the intermediate to produce 2,5-disubstituted THP *trans*-**58**.

The *cis*:*trans* diastereoselectivity was moderate and the use of CH_2Cl_2 as solvent resulted in an increase in yield (entry 2) compared with the Et_2O-H_2O solvent system (entry 1). Although this procedure allows access to the 2,5-disubstituted THP framework with a nitrate group on the 5-position of the THP, the formation

of key pyrans as a mixture of diastereoisomers is inefficient and gave a moderate *cis*:*trans* selectivity.

Table 2.2: Synthesis of 2,5-disubstituted THP *via* ring expansion

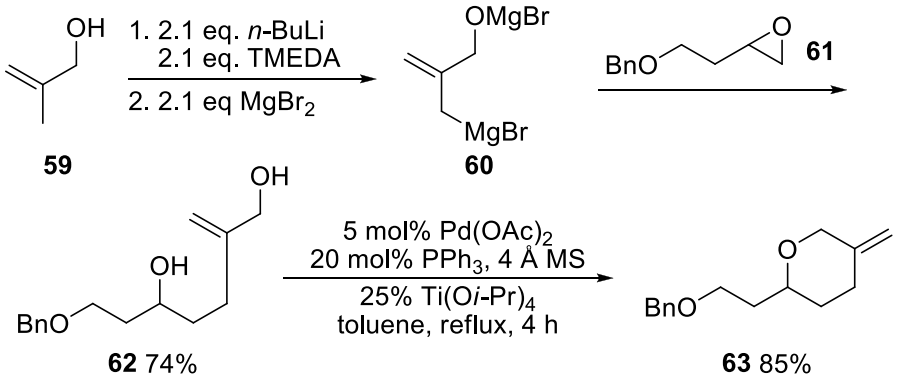


Entry	Solvent	Conditions	Yield (%)[a]	*cis*:*trans*[b]
1	Et_2O-H_2O (100:1)	25 ºC, 18 h	11	29:71
2	CH_2Cl_2	25 ºC, 6 h	56	33:67

[a] Yield of a mixture of *cis* and *trans* diastereoisomers after purification by chromatography. [b] Ratio of *cis*:*trans* determined from the ^{1}H NMR spectrum of the crude product.

More recently, Harrity's group reported the synthesis of 2,5-disubsitituted THPs using epoxides and an organomagnesium reagent (Scheme 2.2).[47] Furthermore, the methodology was then used to complete the total synthesis of rhopaloic acid A (Scheme 2.3).[48]

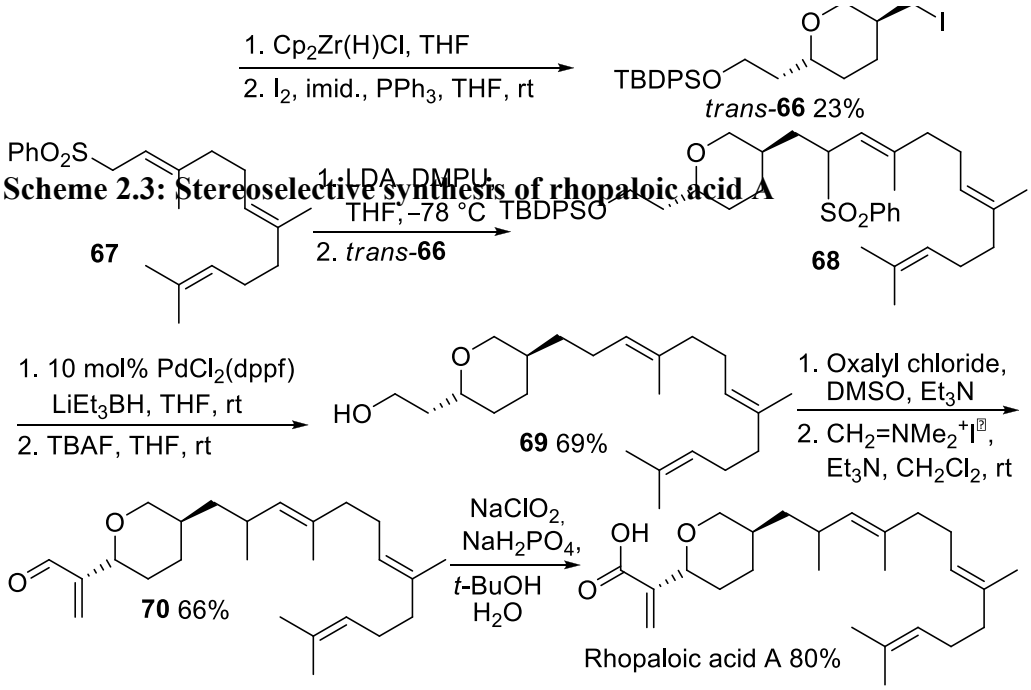
Scheme 2.2: Synthesis of a 2,5-disubstituted THP usingan epoxide



Methallyl alcohol **59** was first treated with an excess of *n*-BuLi in the presence of TMEDA followed by the addition of $MgBr_2$ to afford the key allyl Grignard

reagent **60**. Allyl Grignard reagent **60** was then reacted with epoxide **61** to provide the corresponding diol **62** in 74% yield. Treatment of diol **62** in a palladium-catalysed cyclisation gave THP **63** in high yield. A range of epoxides were employed in the reaction with allyl Grignard reagent **60**, but lower yields for the cyclisations were obtained when the diol has a tertiary centre at one of the alcohols.

To test the versatility of this methodology in stereoselective synthesis, the synthesis of rhopaloic acid A was explored (Scheme 2.3). The protected epoxy alcohol **64** was reacted with allyl Grignard reagent **60** and subsequent cyclisation gave the 2,5-disubstituted THP **65** in 54% yield.



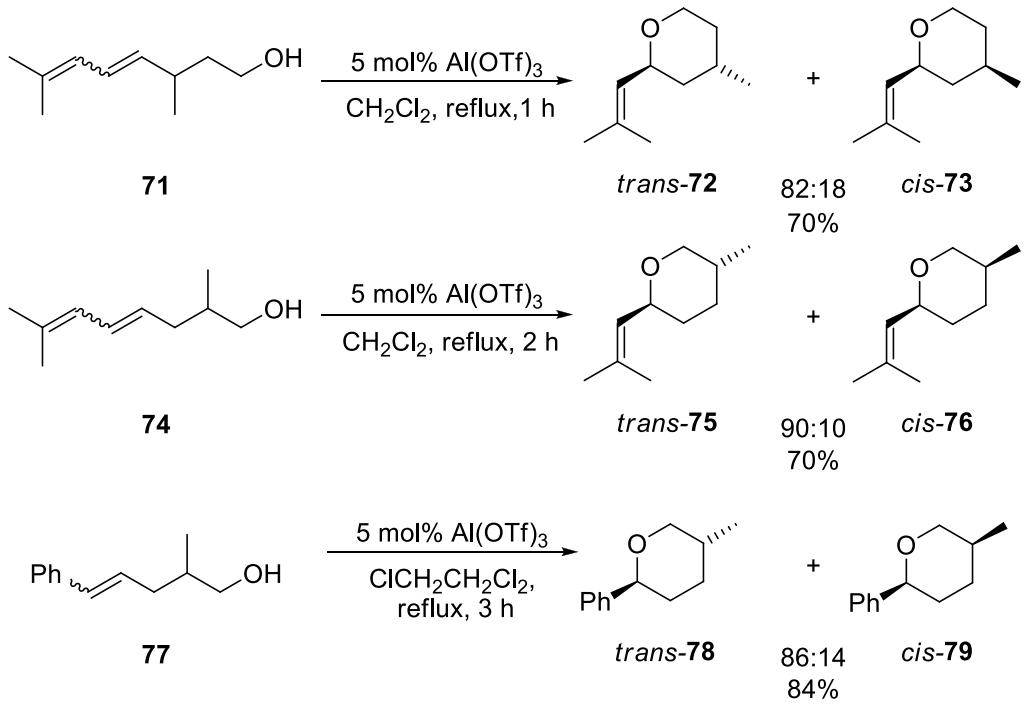
Scheme 2.3: Stereoselective synthesis of rhopaloic acid A

Treatment of **65** with $Cp_2Zr(H)Cl$ followed by iodine gave the desired iodide *trans*-**66** in 23% yield with the undesired *cis* diastereoisomer in 58% yield. Then, alkylation of sulfone **67** with iodide *trans*-**66** gave sulfone **68** with the farnesyl chain attached. Removal of the sulfone group followed by deprotection of the alcohol gave **69** in 69% yield. The primary alcohol **69** was then oxidised under Swern conditions to give the corresponding aldehyde, which was then reacted with dimethylmethylidene ammonium iodide under basic conditions to give unsaturated aldehyde **70** in 66% yield. Finally, oxidation of aldehyde **70** afforded rhopaloic acid A in 80% yield. Although a range of alcohols and pyrans could be synthesised utilising this procedure, it is hampered by the use of an excess

amount of Grignard reagent and the desired 2,5-disubstituted THP *trans*-**66** was produced in low yield.

The aluminium(III) triflate-catalysed cycloisomerisation of primary alcohols has been studied by Duñach and co-workers.[49, 50] Such methodology was used for the construction of rose oxide *trans*-**72** and *cis*-**73** and its analogues *trans*-**75**/*cis*-**76** and *trans*-**78**/*cis*-**79** (Scheme 2.4). The reaction involved the synthesis of primary alcohols **71**, **74** and **77**, followed by the aluminium(III) triflate-catalysed cycloisomerisation to afford disubstituted THPs both in high yield and high *trans*:*cis* diastereoselectivity.

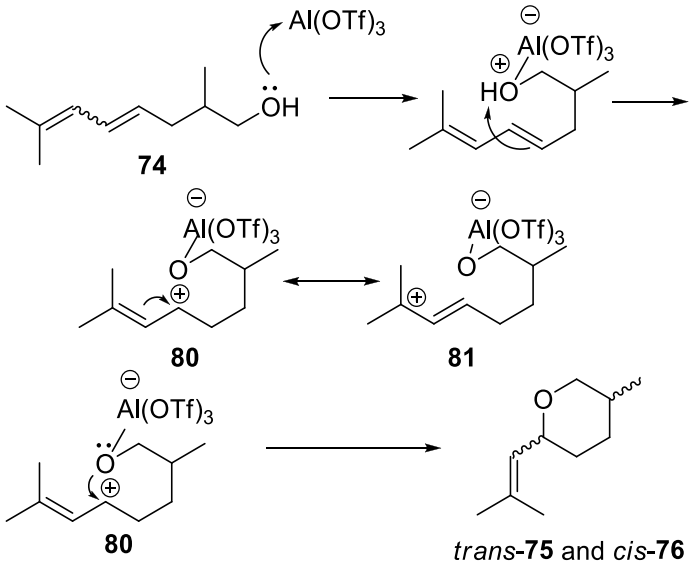
Scheme 2.4: Synthesis of 2,5-disubstituted THPs *via* cycloisomerisation



A mechanism was proposed by Duñach in order to explain the stereoselectivity and the regioselectivity of the formation of the 6-membered ether ring in the cycloisomerisation step (Scheme 2.5). First, the lone pair of electrons on the oxygen attacks the aluminium(III) centre in the Lewis acid to give an oxonium

ion. One of the alkenes is now protonated by abstracting the proton from the alcohol. This gives a positively charged carbocation **80**, which can be stabilised by resonance to give **81**. The lone pair of electrons on the oxygen can now attack the carbocation to give the 6-membered THP *trans*-**75** and *cis*-**76**.

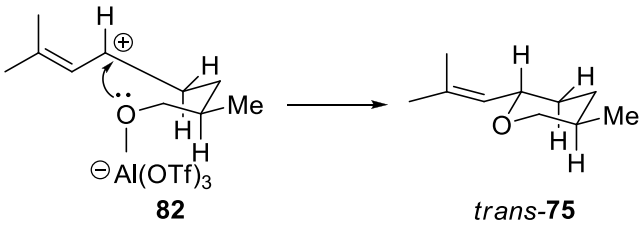
Scheme 2.5: Proposed mechanism for the cycloisomerisation



The high *trans*:*cis* diasteroeselectivity ratio could be explained by the conformation of the intermediate species **82** (Figure 2.7).[i] The alkene group is in an equatorial position as a result of the free rotation about the CH_2–CH bond and so as to avoid the sterically bulky aluminium triflate. Now, the lone pair of electrons from the oxygen can attack to form the THP. Therefore, the reaction gave a mixture of *trans*-**75** and *cis*-**76** from **74** in a *trans:cis* ratio of 90:10.

[i] The assignment of the *trans* and *cis* isomers were found to be erroneous in the original paper. After correspondence with the author, the stereoisomers were agreed as shown in Scheme 2.4.

Figure 2.7: Formation of *trans*-75

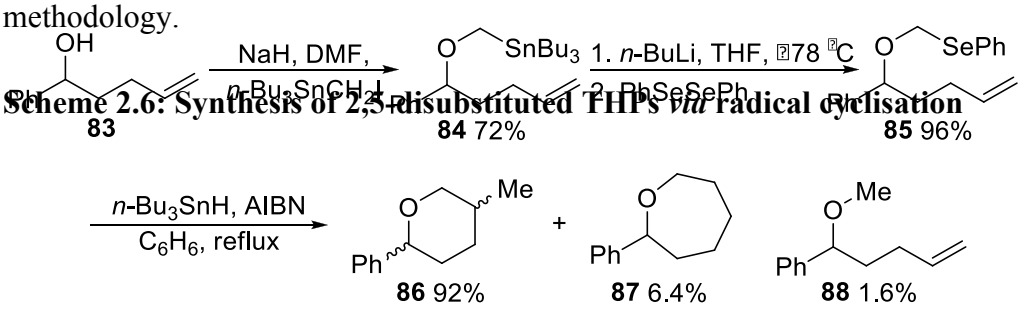


82 *trans*-**75**

The limitation of this regiospecific cycloisomerisation is that, in order to afford exclusively the corresponding THPs, it requires a benzylic- or allylic-type cation intermediate to stablise, by conjugation, the positive charge formed in the presence of the metal triflate. Rose oxide analogues *cis*-**75**/*trans*-**76** and *cis*-**78**/*trans*-**79** were submitted for olfactory evaluations, and it is interesting to note that they all carry some fruity notes.

A stereoselective alkoxymethyl radical cyclisation approach was developed by Rawal and co-workers to construct tetrahydrofurans and tetrahydropyrans (Scheme 2.6).[51] The required cyclisation precursor **85** was prepared in two steps from the corresponding alcohol **83**. Thus, alcohol **83** was treated with sodium hydride and (iodomethyl)tributylstannane in DMF to give the expected stannane **84** in moderate yield. Stannane **84** was then transformed into the desired selenoacetal **85** by tin-lithium exchange and quenching with $(PhSe)_2$. Under standard radical cyclisation conditions employing *n*-tributyltin hydride and AIBN, selenoacetal **85** gave an inseparable mixture of 6- and 7-membered cyclic ethers **86** and **87**. The yield of each compound was determined by GC. The major component in the 2,5-disubstituted THP **86** was the *trans* diastereoisomer. The 5:1 diastereomeric ratio was determined by NMR spectroscopy. The potential by-product **88** resulting from reduction was observed as a very minor component (<2%) by NMR spectroscopy. The cyclisation reaction has a high efficiency and can be used to access the 2,5-disubstituted THP framework. However, the use of

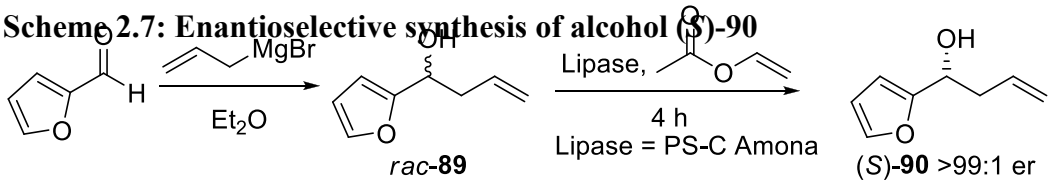
an organotin compound and AIBN may restrict the synthetic utility of this methodology.



Scheme 2.6: Synthesis of 2,5-disubstituted THFs *via* radical cyclisation

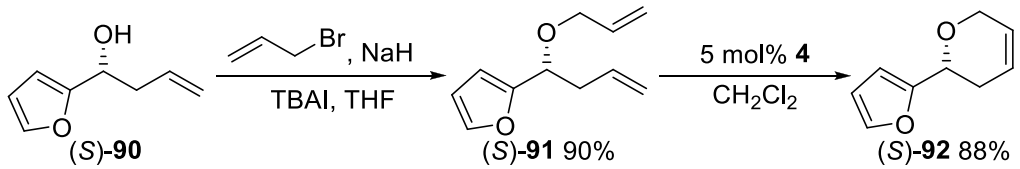
Finally, a stereoselective synthesis of optically pure dihydrofurans and dihydropyrans in >99:1 er was reported by Tanyeli and co-workers.[52] Their approach was first to construct racemic alcohols such as *rac*-**89**. Thus, nucleophilic addition of allyl magnesium bromide to furan-2-carbaldehyde resulted in alcohol *rac*-**89**. This was followed by enzyme-catalysed resolution to give enantiomerically enriched alcohol (*S*)-**90** in >99:1 er (Scheme 2.7).

Scheme 2.7: Enantioselective synthesis of alcohol (*S*)-90



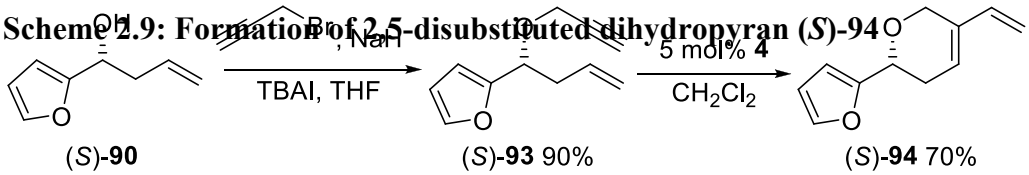
Diene (*S*)-**91** was then synthesised from the enantioenriched alcohol (*S*)-**90** by *O*-allylation. Use of sodium hydride and allyl bromide in the presence of TBAI in THF formed the diene (*S*)-**91**. Ring-closing metathesis using Grubbs' 1st generation catalyst **4** afforded dihydropyran (*S*)-**92** (Scheme 2.8).

Scheme 2.8: Formation of dihydropyran (*S*)-92



In order to prepare dihydropyrans with 2,5-substitution, propargyl bromide was employed in the *O*-allylation step. Alcohol (*S*)-**90** was reacted with sodium hydride together with propargyl bromide in the presence of TBAI in THF to afford enyne (*S*)-**93**. Under the same ring-closing metathesis conditions, 2,5-disubstituted dihydropyran (*S*)-**94** was synthesised in 70% yield.

Scheme 2.9: Formation of 2,5-disubstituted dihydropyran (*S*)-94



In summary, a number of strategies for the synthesis of the 2,5-disubstituted THPs have been developed. Harrity's methodology allows access to the 2,5-disubstituted THP framework in a few steps and the synthetic versatility was demonstrated by the synthesis of rhopaloic acid A. The aluminium triflate catalysed cycloisomerisation of primary alcohols afforded substituted THPs in good yield and high *trans*:*cis* diastereoselectivity. This procedure has been used in the synthesis of perfumery molecules such as rose oxide and its analogues. An enzyme-mediated stereoselective synthesis of dihydropyrans afforded unsaturated THPs in high ers.

2.3 Project Outline

2,5-Disubstituted THPs are a unique class of molecules that are interesting from both biological and structural standpoints. Although there has been synthetic work aimed at rhopaloic acid A, a general route to the 2,5-disubstituted THP framework is still required. Furthermore, establishing a synthetic route to these target compounds could be valuable in the search for new perfumery molecules.

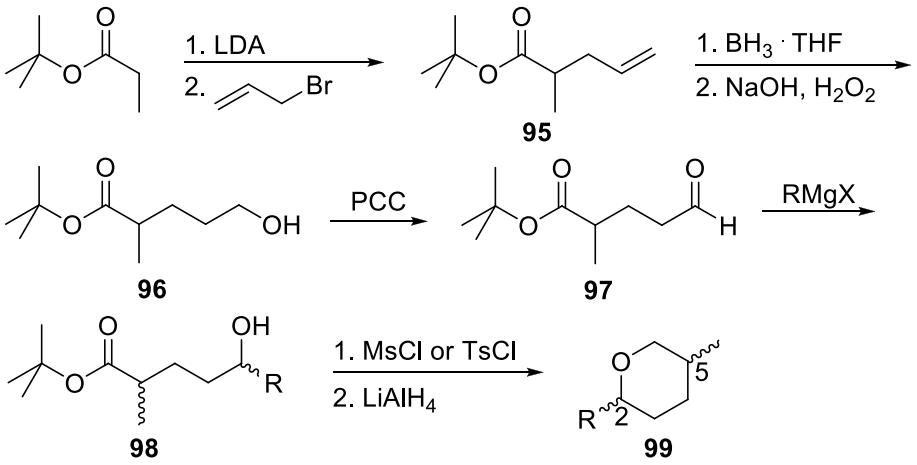
Tanyeli's methodology to the 2,5-disubstituted THPs is short and efficient, and one terminal alkene could serve as a synthetic handle for further manipulation. Therefore, we hoped that a similar procedure could be developed for the divergent synthesis of THPs. We would also like to apply the methodology developed to the synthesis of known perfumery compounds and some of the target molecules. Another aim of this part of the project is to develop the synthesis of enantioenriched homoallylic alcohols and 2,5-disubstituted THPs with high diastereoselectivity.

This part of the thesis is an account of our attempt to design and develop new strategies for the 2,5-disubstituted THP framework and the synthesis of the newly designed potential perfumery compounds.

2.4 Synthesis of 2,5-Disubstituted Tetrahydropyrans *via* an Alkylation, Reduction and Cyclisation Route

In this section, we focused our attention on developing two routes to 2,5-disubstituted THPs, both of which utilise commercially available *t*-butyl propionate as the key building block. The first route starts with alkylation of *t*-butyl propionate using allyl bromide to give unsaturated ester **95**. Hydroboration followed by oxidative work-up would then afford alcohol **96**. Oxidation of the primary alcohol would provide aldehyde **97**. Then, addition of Grignard reagents will provide the substituent at the 2-position in the final THP. Finally, mesylation or tosylation of the alcohol and reduction of the ester followed by cyclisation would afford the 2,5-disubstituted THPs **99** probably as a mixture of diastereoisomers (Scheme 2.10).

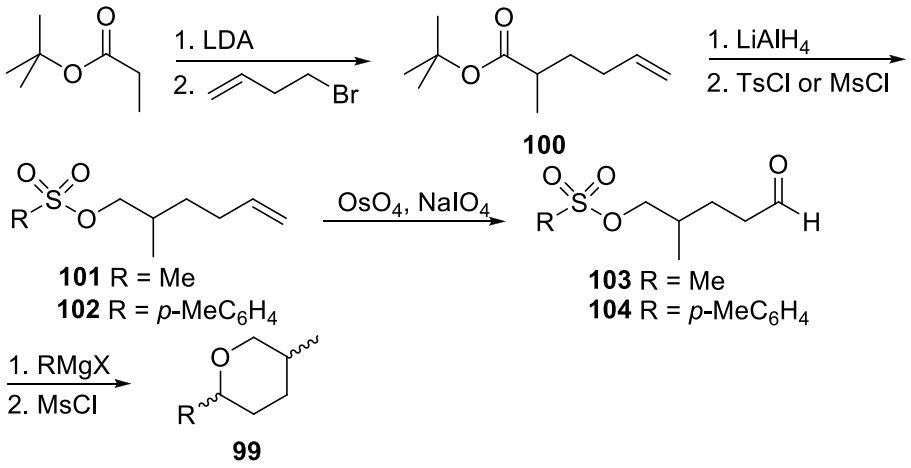
Scheme 2.10: Proposed route to 2,5-disubstituted THPs



The second proposed route starts with alkylation of *t*-butyl propionate with 4-bromobut-1-ene to give unsaturated ester **100**. Reduction of the ester followed by mesylation or tosylation would afford the activated alcohols **101** and **102**. Oxidation using osmium tetraoxide and sodium periodate-mediated cleavage of the diol would give aldehydes **103** and **104**. Finally, Grignard addition to the

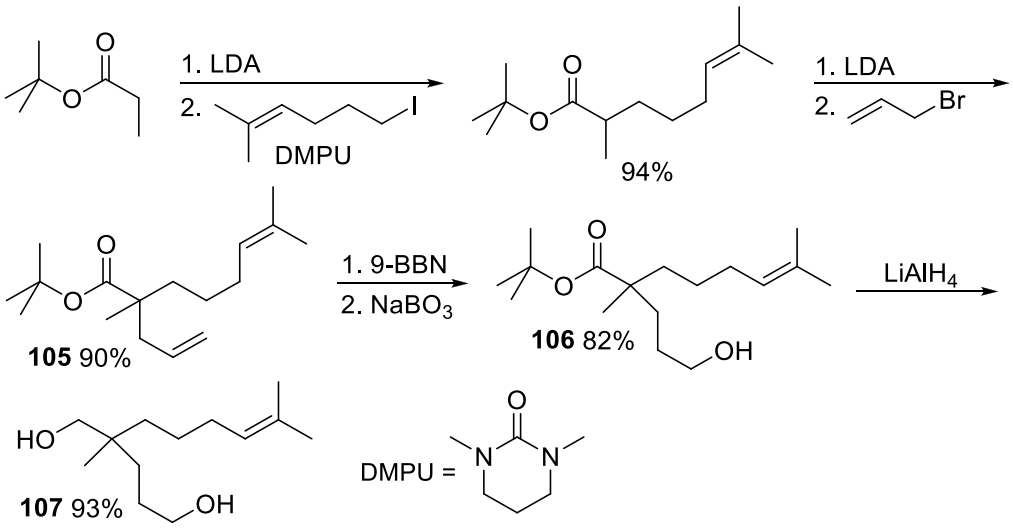
aldehyde should give an alkoxide which hopefully would be nucleophilic enough to cyclise to form a mixture of diastereomeric 2,5-disubstituted THPs **99** (Scheme 2.11).

Scheme 2.11: Proposed route to 2,5-disubstituted THPs



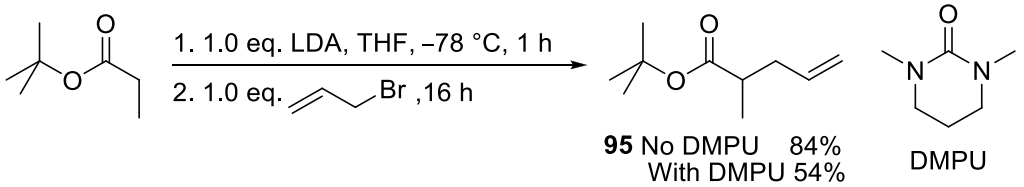
As outlined in Schemes 2.10 and 2.11, we envisaged that 2,5-disubstituted THPs **99** could be synthesised from *t*-butyl propionate. In 2001, Heathcock and co-workers reported the development of a new polycyclisation route for the synthesis of a range of natural products belonging to the family of *Daphniphyllum* alkaloids.[53] One of the reaction sequences described was found to be relevant to our project. Specifically, the synthesis of diol **107** began with sequential LDA-mediated alkylation of *t*-butyl propionate with an alkyl iodide and allyl bromide to provide ester **105** in excellent yield over two steps. Selective hydroboration of the less substituted alkene in ester **105** then afforded alcohol **106**. In the final step, reduction of the ester functionality in **106** efficiently provided the desired diol **107** in good yield (Scheme 2.12).

Scheme 2.12: Synthesis of alcohol 107 *via* sequential alkylation reactions



Notably, when a less reactive electrophile such as 6-iodo-2-methylhex-2-ene was employed in the enolate alkylation step, DMPU was required during the trapping step in order to obtain a high yield of product. In contrast, the use of DMPU was not necessary when allyl bromide, a more reactive electrophile, was employed in the alkylation step. Presumably, DMPU coordinates to the lithium cation in the enolate, making it more reactive. This observation is significant to our project since alkylation of *t*-butyl propionate was also investigated using electrophiles of different reactivities. Thus, deprotonation of *t*-butyl propionate with LDA as base and trapping with allyl bromide gave ester **95** in 84% yield on a 1.5 g scale (Scheme 2.13).

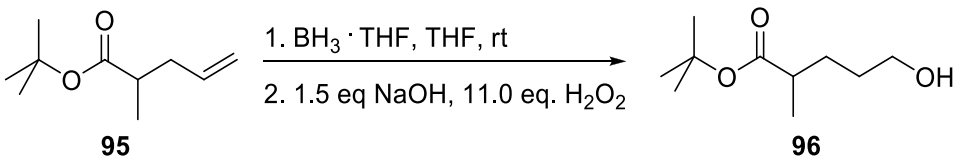
Scheme 2.13: Formation of ester 95 *via* alkylation



The use of DMPU was not necessary in this case, presumably due to the high reactivity of allyl bromide towards nucleophilic substitution. Curiously, the yield of product was in fact significantly lower with DMPU as additive. However, it should be noted that the reaction with DMPU was carried out on a small scale and ester **95** is volatile so that difficulties were experienced with handling the material. This could account for the lower yield from the reaction with DMPU.

With gram quantities of alkylated ester **95** in hand, hydroboration of the terminal alkene in **95** was next explored (Table 2.3). Use of 1.2 equivalents of $BH_3 \cdot THF$ and a reaction time of 4 hours gave alcohol **96** in modest (42%) yield (entry 1), which was not improved with an extended reaction time (entry 2). Disappointingly, the yield of product was even lower when the amount of borane was increased (entries 3 and 4). We first suspected that instability of alcohol **96** on silica gel could be the reason for the low isolated yields. Indeed, upon inspection of the ^1H NMR spectrum of the crude product, good conversion to alcohol **96** was consistently observed, and it was the chromatography purification step which appeared to account for the low isolated yields. Alcohol **96** also decomposed after storage at room temperature over a period of time. This was shown by TLC analysis and inspection of the ^1H NMR spectra.

Table 2.3: Hydroboration of ester 95



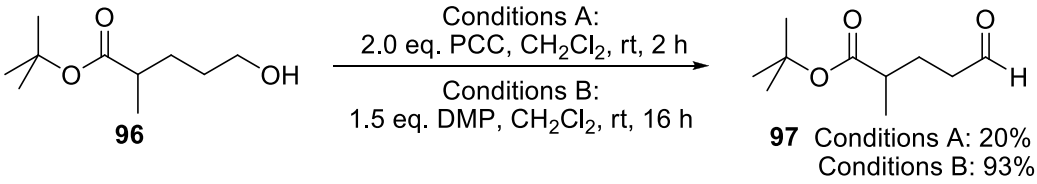
95 **96**

Entry	Eq. of borane	Time (h)	Yield (%)[a]
1	1.2	4	42
2	1.2	16	42
3	3	3	30
4	3	16	28

[a] Yield of **96** after purification by chromatography.

Despite the moderate isolated yield of alcohol **96**, the reaction was readily scaled up and sufficient quantities of material were obtained. Thus, two methods for oxidation of alcohol **96** to aldehyde **97** were explored. First, alcohol **96** was treated with pyridinium chlorochromate.[54] However, only a 20% yield of aldehyde **97** was obtained following a difficult purification by flash column chromatography (Scheme 2.14). Pleasingly, when Dess-Martin periodinane (DMP) was used as oxidant,[55] aldehyde **97** was obtained in 93% yield and no purification difficulties were encountered. Therefore, oxidation using Dess-Martin periodinane was the preferred method.

Scheme 2.14: Oxidation of alcohol 96

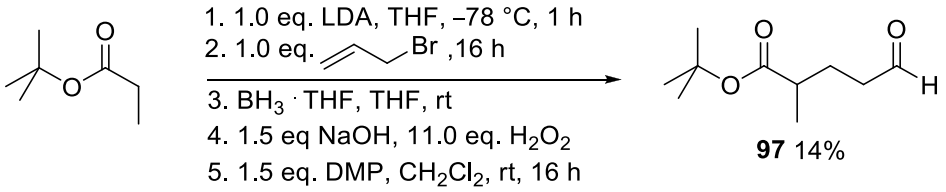


96 **97** Conditions A: 20%
Conditions B: 93%

Given the volatility issue with ester **95** and the purification difficulties we had encountered in the hydroboration step (despite apparent high conversion to

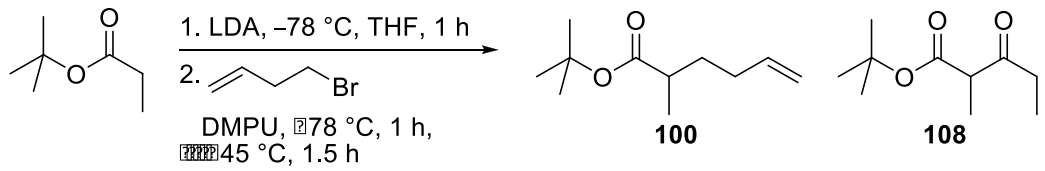
product), we attempted the alkylation, hydroboration and oxidation steps in a sequential reaction approach, where the crude product was used directly in the next steps. Unfortunately, the overall yield of aldehyde **97** over these three steps was only 14% after purification by flash column chromatography (Scheme 2.15). In contrast, a higher 33% overall yield was obtained where each of the individual intermediates had been isolated. Due to the low yield and difficulties experienced during the development of this approach, we decided to turn our attention to the alternative strategy.

Scheme 2.15: Three-step sequential approach to aldehyde 97



In our alternative strategy towards 2,5-disubstituted THPs, unsaturated ester **100** was synthesised by alkylating *t*-butyl propionate *via* deprotonation with LDA and trapping with 4-bromobutene as the electrophile under different conditions (Table 2.4). More specifically, treatment of *t*-butyl propionate with LDA and 4-bromobutene in the presence of DMPU furnished the desired product in 37% yield (entry 1). By increasing the amount of base and electrophile to 1.5 eq. and 1.0 eq., respectively, and with 1.5 eq. of *t*-butyl propionate in the presence of DMPU, the yield of the reaction was improved to 62% based on 4-bromobutene as the limiting reagent (entry 2). From this reaction, β-keto ester **108** (14% yield) was also formed *via* a Claisen self-condensation reaction. This indicates the bulky *t*-butyl group has a small contribution, in this case, in preventing the self-condensation reaction. Since 4-bromobutene is not a very reactive electrophile in S_N2 reactions, an identical reaction but in the absence of DMPU led, as expected, to a lower yield of product (entry 3).

Table 2.4: Alkylation of *t*-butyl propionate

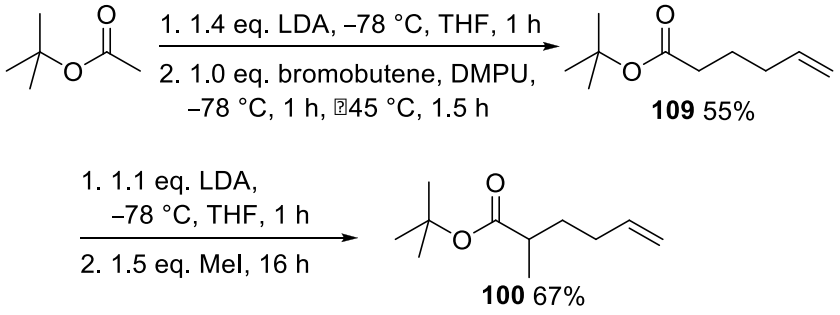


Entry	Eq. of ester	Eq. of LDA	Eq. of electrophile	Eq. of DMPU	Yield (%)[a]
1	1.0	0.95	0.7	2.0	37
2	1.5	1.4	1.0	2.0	62[b]
3	1.5	1.4	1.0	0	22

[a] Yield of **100** after purification by chromatography. [b] β-keto ester **108** was also isolated in 14% yield.

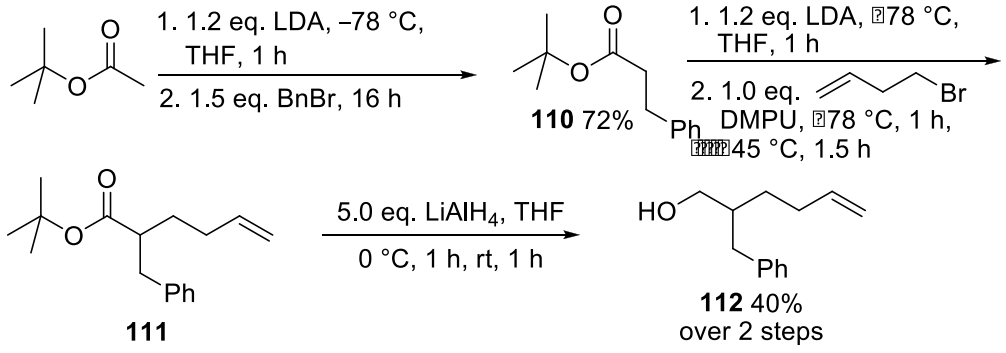
In order to broaden the substrate scope in our THP synthesis, we also studied the alkylation of *t*-butyl acetate (Scheme 2.16), as this would provide the opportunity to introduce a range of substituents in the 5-position of the THP. Thus, treatment of *t*-butyl acetate with LDA and trapping of the resulting enolate with 4-bromobutene in the presence of DMPU afforded ester **109** in a respectable 55% yield. Alkylation of **109** with LDA and trapping with methyl iodide gave ester **100** in 67% yield. Crucially, subsequent methylation of ester **109** not only provided an alternative means of obtaining ester **100**, but it also suggested that through the use of alternative alkylation agents, access to differentially 5-substituted THPs would be possible.

Scheme 2.16: Synthesis of ester 100



A benzyl group was also introduced by deprotonation of *t*-butyl acetate using LDA followed by trapping with benzyl bromide (Scheme 2.17). This gave ester **110** in 72% yield. Subsequent deprotonation and electrophilic trapping with 4-bromobutene in the presence of DMPU afforded unsaturated ester **111** in only 5% yield. The low yield was mainly due to the difficulties in purification by column chromatography. It was shown that ester **111** can be used as a crude product in later steps. For example, alkylation of ester **110** with 4-bromobutene gave crude ester **111** and subsequent reduction produced alcohol **112** in 40% yield over the two steps.

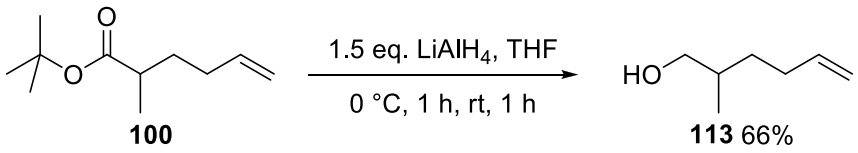
Scheme 2.17: Synthesis of alcohol 112



Reduction of ester **100** with $LiAlH_4$ in THF furnished alcohol **113** in 66% yield (Scheme 2.18). Full conversion was established by analysis of the ^1H NMR

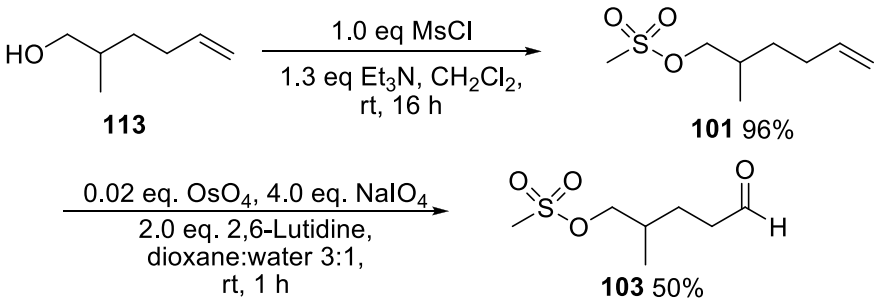
spectrum of the crude product and we attributed the moderate yield of alcohol **113** to its volatility.

Scheme 2.18: Reduction of ester 100



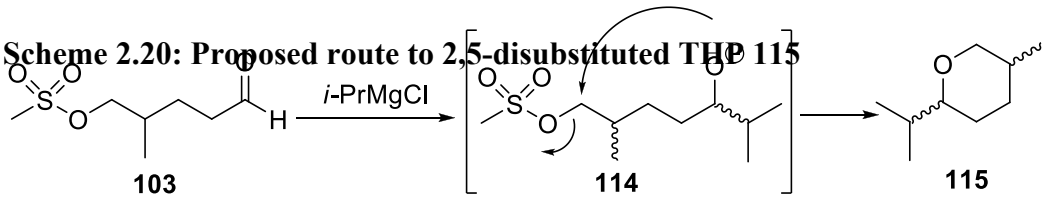
It was pleasing to find that mesylation of primary alcohol **113** afforded mesylate **101** in excellent (96%) yield (Scheme 2.19). Oxidative cleavage of the terminal alkene in **101** with osmium tetraoxide and sodium periodate, using a procedure developed by Jin and co-workers,[56] provided aldehyde **103** in 50% crude yield (Scheme 2.19). As aldehyde **103** proved to be unstable on silica, it was used in the next step without further purification.

Scheme 2.19: Synthesis of aldehyde 103



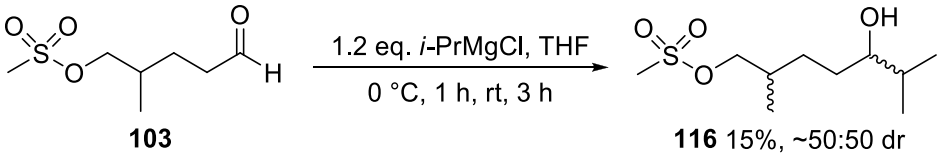
It was anticipated that, if aldehyde **103** was treated with *i*-propyl magnesium chloride, then upon chemoselective nucleophilic attack of the *i*-propyl group onto the aldehyde, the alkoxide anion thus formed in intermediate **114** would readily undergo an intramolecular cyclisation to provide the 2,5-disubstituted THPs **115** in a single operation (Scheme 2.20).

Scheme 2.20: Proposed route to 2,5-disubstituted THP 115



Based on the small quantity of the mesylate **103** obtained, we were only able to carry out the reaction once. Disappointingly, only a small amount of secondary alcohol **116** (15%) as a 50:50 mixture of diastereomers was obtained (Scheme 2.21). The ratio was determined by integration of the signals due to the CH*Me* group: δ_H 1.01 (d, J = 7.0 Hz, 3H) and δ_H 1.00 (d, J = 7.0 Hz, 3H). The desired cyclised ether **115** was not observed in the ^{1}H NMR spectrum of the crude product.

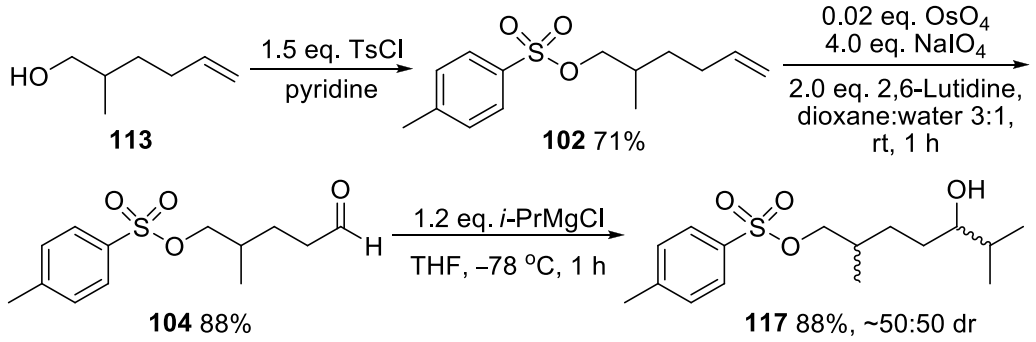
Scheme 2.21: Formation of alcohol 116 *via* Grignard addition



We encountered volatility issues during the isolation process of mesylate **101**. Therefore, we decided to introduce a tosyl group as the activating group. By doing so, it increases the molecular weight of the molecule and could potentially overcome the volatility issue. The tosylate would also serve a second purpose: it is a better leaving group than a mesylate and this could facilitate the final cyclisation step of the alkoxide into the desired THP **115**. Thus, alcohol **113** was treated with tosyl chloride in pyridine to give tosylate **102** in 71% yield. Under osmium tetraoxide and sodium periodate conditions, we were pleased to find that aldehyde **104** was isolated in an excellent 88% yield after purification. Finally, nucleophilic addition of *i*-propyl magnesium chloride gave secondary alcohol **117** (as a ~50:50 mixture of diastereoisomers as revealed by ^{13}C NMR

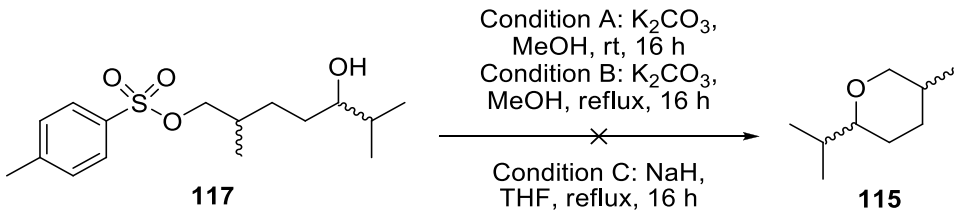
spectroscopy) in 88% yield (Scheme 2.22). This was a significant improvement compared to the addition to mesylate **103**, but cyclisation to the diastereomeric THPs **115** was still not observed.

Scheme 2.22: Synthesis of alcohol 117



With alcohol **117** in hand, cyclisation of the secondary alcohol to the final THP **115** in a separate step was next explored. Three sets of reaction conditions were investigated (Scheme 2.23). Following a literature procedure,[57] alcohol **117** was first treated with potassium carbonate in methanol at rt and stirred for 16 h. However, only starting material was observed in the ^{1}H NMR spectrum of the crude product. We then decided to increase the reaction temperature. Thus, alcohol **117** was refluxed with potassium carbonate in methanol for 16 h. However, no desired product was observed and only starting material was recovered. Next, a stronger base, sodium hydride, was used and the reaction mixture was refluxed for 16 h. Disappointingly, the resulting ^{1}H NMR spectrum of the crude product showed a complex mixture with no sign of either product or starting material. We presume that competing β-elimination process may be responsible for the unsuccessful outcome of this reaction. Unfortunately, at this stage, our initial attempts to carry out the cyclisation reaction were unsuccessful and we were unable to continue due to lack of material.

Scheme 2.23: Attempted synthesis of 2,5-disubstituted THP 115

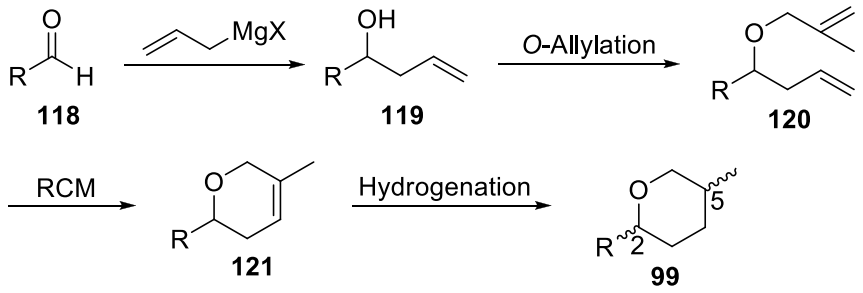


Thus far, our efforts on the alkylation, reduction and cyclisation route were not successful, and the route was rather long. A short strategy to directly access the 2,5-disubstituted THP framework would be more attractive. Hence, we focused our attention on an entirely different approach.

2.5 Synthesis of 2,5-Disubstituted Tetrahydropyrans *via* Grignard Addition, *O*-Alkylation, Ring-Closing Metathesis and Hydrogenation

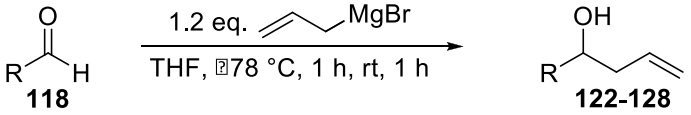
In this section, an alternative synthesis of 2,5-disubstituted THPs will be discussed. In this context, ready access to THPs of type **99** could be available in just four well-established steps from aldehydes **118** (Scheme 2.24). Specifically, allyl Grignard addition to aldehydes **118** would afford alcohols **119** which upon deprotonation and reaction with an allylic halide would generate dienes **120**. The strategically placed alkenes in **120** would then be ready for a ring-closing metathesis reaction to furnish the cyclic dihydropyrans **121**. In the final step, 2,5-disubstituted THPs **99** would be obtained by hydrogenation of the alkene in **121**, conceivably with induction of 2,5-diastereocontrol.

Scheme 2.24: Proposed route to 2,5-disubstituted THPs



Seven aldehydes were chosen for this study and the reaction sequence towards THPs **99** outlined above proved to be efficient in all cases. Grignard addition using 1.2 eq. of allyl magnesium bromide to all seven aldehydes in THF at –78 ºC produced homoallylic alcohols **122-128** in 51-98% yield and in multi-gram quantities (Scheme 2.25).

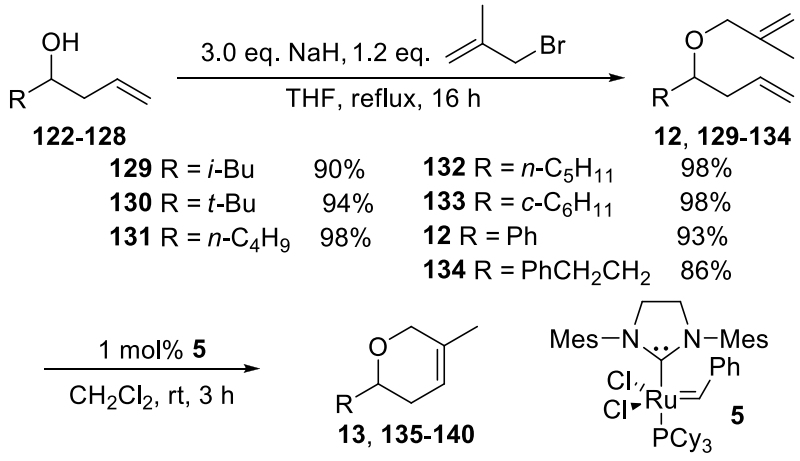
Scheme 2.25: Synthesis of alcohols *via* Grignard addition



122 R = *i*-Bu	90%	**125** R = *n*-C_5H_{11}	98%
123 R = *t*-Bu	56%	**126** R = *c*-C_6H_{11}	82%
124 R = *n*-C_4H_9	94%	**127** R = Ph	90%
		128 R = $PhCH_2CH_2$	51%

O-Alkylation with sodium hydride as a base and 3-bromo-2-methylpropene as an electrophile afforded the terminal dienes **12** and **129-134** in excellent yields throughout (84-98%). At this stage, ring-closing metathesis using Grubbs 2nd generation catalyst **5** constructed the cyclic ether framework in dihydropyrans **13** and **135-140** in excellent yield. This represents a very efficient route to dihydropyrans. The ring-closing metathesis route to such compounds has also been carried out previously by Grubbs[12] and Schmidt.[16, 17]

Scheme 2.26: Synthesis of 2,5-disubstituted dihydropyrans *via O*-alkylation and ring-closing metathesis

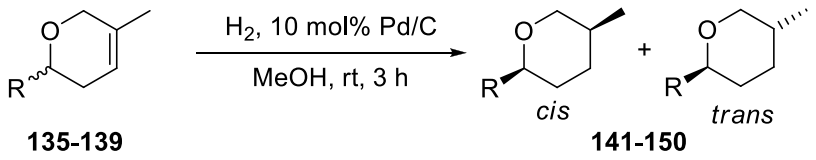


129 R = *i*-Bu	90%	**132** R = *n*-C_5H_{11}	98%
130 R = *t*-Bu	94%	**133** R = *c*-C_6H_{11}	98%
131 R = *n*-C_4H_9	98%	**12** R = Ph	93%
		134 R = $PhCH_2CH_2$	86%

135 R = *i*-Bu	82%	**138** R = *n*-C_5H_{11}	96%
136 R = *t*-Bu	80%	**139** R = *c*-C_6H_{11}	89%
137 R = *n*-C_4H_9	97%	**13** R = Ph	98%
		140 R = $PhCH_2CH_2$	89%

Finally, hydrogenation using 10 mol% palladium on carbon in methanol at rt for 3 h efficiently provided the desired 2,5-disubstituted THPs **78**, **79** and **141**-**152**. These reactions were carried out several times in order to isolate the products with reasonable yields. This is due to the volatility issues of such low molecular weight molecules. The highest yielding results are presented in Tables 2.5 and 2.6. The yield was generally moderate for all seven examples (57-80%). We were pleased to discover that a good level of *cis*-diastereoselectivity was induced in the hydrogenation process for the non-aromatic substituents (Table 2.5). The *cis*:*trans* diastereomeric ratio was determined from the ^{1}H NMR spectrum of the products (both crude and isolated). The assignment of the relative stereochemistry is discussed in detail later. In general, an 83:17-89:11 ratio of *cis* and *trans* diastereomers was obtained for the alkyl substituted THPs (**141**-**150**). The slight decrease in the *cis*:*trans* diastereoisomeric ratio for cyclic ethers **147** and **148** from the crude product to the isolated product (entry 4) is probably due to some loss of the major diastereoisomer, *cis*-**147**, during the purification by chromatography.

Table 2.5: Hydrogenation of 2,5-disubstituted dihydropyrans 135-139



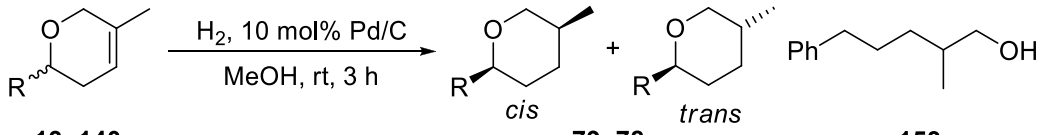
135-139 **141-150**

Entry	Compound	R	Product	*cis*:*trans* (crude)[a]	Yield (%)[b]	*cis*:*trans* (isolated)[c]
1	**135**	*i*-Bu	**141 142**	83:17	23	83:17
2	**136**	*t*-Bu	**143 144**	89:11	77	89:11
3	**137**	*n*-C_4H_9	**145 146**	88:12	23	88:12
4	**138**	*n*-C_5H_{11}	**147 148**	88:12	86	83:17
5	**139**	*c*-C_6H_{11}	**149 150**	87:13	57	87:13

[a] Diastereomeric ratio determined from the ^{1}H NMR spectrum of the crude product. [b] Yield of *cis*/*trans*-mixture after purification by chromatography. [c] Diastereomeric ratio determined from the ^{1}H NMR spectrum of the purified product.

In the case of tetrahydropyrans **13** and **140**, a lower level of *cis*-diastereoselectivity was observed. A *cis*:*trans* ratio of 55:45 was obtained for cyclic ethers **79** and **78** (Table 2.6, entry 1), and a slightly higher *cis*:*trans* ratio of 65:35 for cyclic ethers **151** and **152** was found (entry 2). When the phenyl group is directly attached to the carbon bearing the oxygen as in **13**, palladium on carbon reaction conditions not only resulted in hydrogenation to afford 2,5-disubstituted THPs *trans*-**78** and *cis*-**79**, but a small amount (13%) of alcohol **153** was also isolated (entry 1). This observation is due to the benzylic C–O bond being cleaved under these conditions.

Table 2.6: Hydrogenation of dihydropyrans 13 and 140



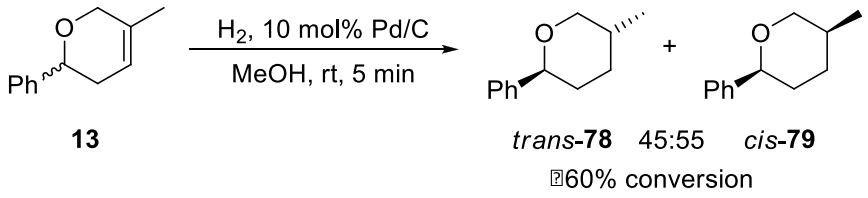
13, **140** **79**, **78** **151**, **152** **153**

Entry	Compound	R	Product	*cis*:*trans* (crude)[a]	Yield (%)[b]	*cis*:*trans* (isolated)
1	**13**	Ph	**79 78**	55:45	57[d]	52:48
2	**140**	$PhCH_2CH$	**151 152**	65:35	80	65:35

[a] Diastereomeric ratio determined from the ^{1}H NMR spectrum of the crude product. [b] Yield of *cis*/*trans*-mixture after purification by chromatography. [c] Diastereomeric ratio determined from the ^{1}H NMR spectrum of the purified product. [d] 13% of 2-methyl-5-phenylpentan-1-ol **153** was also isolated.

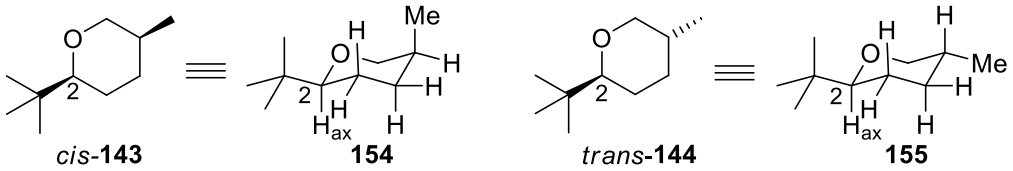
We then decided to investigate the competitive reactions between hydrogenation of dihydropyran **13** and the breaking of the benzylic C-O bond in the molecule. By submitting the compound to identical hydrogenation conditions with a shorter reaction time, the ratio of the two products would then give information on the rate of the two reactions. Thus, dihydropyran **13** was hydrogenated with palladium on carbon in methanol for 5 min to give the crude mixture (Scheme 2.27). A 60% conversion from dihydropyran **13** to tetrahydropyrans *cis*-**79** and *trans*-**78** was determined from the ^{1}H NMR spectrum of the crude mixture, and a *cis*:*trans* ratio of 55:45 was calculated. Interestingly, none of alcohol **153** was observed. This demonstrated that the rate of hydrogenation of dihydropyran **13** was much faster than the breaking of the benzylic C–O bond. Despite this competing process, the *cis*:*trans* diastereoselectivity in the hydrogenation of phenyl-substituted dihydropyran **13** is clearly lower than the alkyl-substituted dihydropyrans **135**-**139**.

Scheme 2.27: Hydrogenation of 2,5-disubstituted dihydropyrans 13



The relative stereochemistry in THPs **78**, **79** and **143**-**152** was assigned in the following way. In THP **143** and **144**, since the interaction between an axial *t*-butyl group and the 1,3-diaxial hydrogen atom is so severe, the *t*-butyl group is locked in the equatorial position. Therefore, cyclic ether *cis*-**143** would exist in conformer **154**, and cyclic ether *trans*-**144** would be preferred in conformer **155** (Figure 2.8).

Figure 2.8: Conformational analyses of *cis*-143 and *trans*-144



The equatorial position of the *t*-butyl group was confirmed by analysis of the protons in the axial position on C_2 in each diastereoisomer and is summarised in Figure 2.9. The protons in the axial position have a large ^3J coupling (11.0 Hz) in both **154** (*cis*-**143**) and **155** (*trans*-**144**). This corresponds to the *trans*-diaxial interaction with the axial protons. The other coupling constants for the signal at δ_H 2.85 (2.0 Hz) in **154** and δ_H 2.80 (2.0 Hz) in **155** are due to axial-equatorial ^3J coupling. Analysis of the ^{1}H NMR spectrum for the diastereotopic protons on C_6 revealed that **154** was the major diastereoisomer from the hydrogenation. In **154**, the axial proton at C_6 is assigned at δ_H 3.71 ppm (dd, J = 11.0, 2.0 Hz). This is recognised due to a large ^2J coupling constant (11.0 Hz) with the other diastereotopic proton and a small ^3J axial-equatorial coupling constant (2.0 Hz)

with the proton in the equatorial position on C_5. In the alternative configuration, the proton in the axial position on C_6 should have a large ^2J coupling constant as well as a large ^3J *trans*-diaxial coupling constant with the proton in the axial position on C_5. This could potentially give a triplet splitting pattern. The signal at δ_H 2.96 with a triplet splitting pattern and J values of 12.0 Hz was thus assigned to the proton in the axial position on C_6 for **155**.

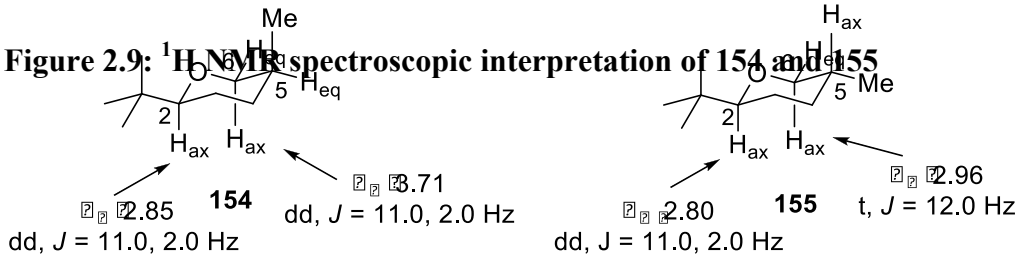
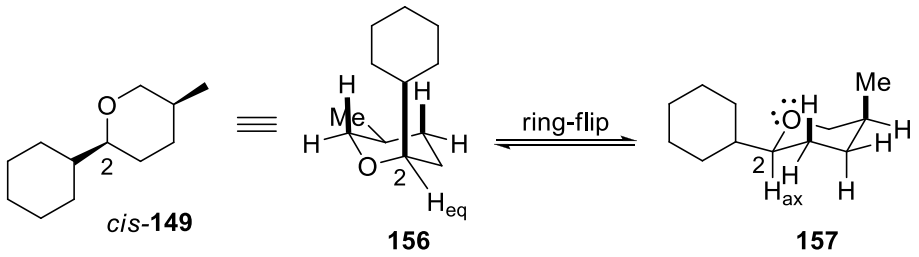


Figure 2.9: ^{1}H NMR spectroscopic interpretation of 154 and 155

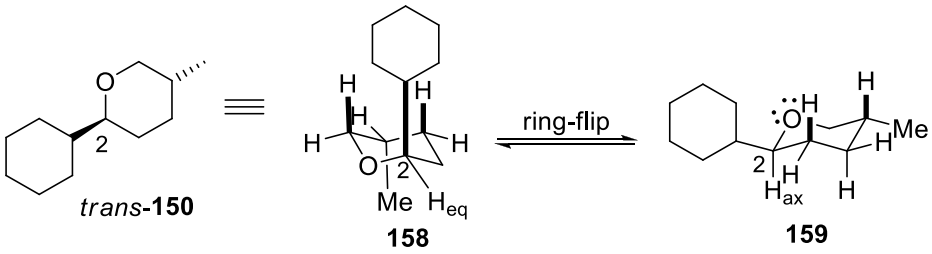
The relative stereochemistry in cyclic ethers **141**, **142** and **145-150**, which do not possess a fully conformational locking group, was assigned in the following way. First, the conformations of cyclic ethers **141**, **142** and **145-150** were predicted. Using *cis*-**149** with a cyclohexyl group as an example, the two possible conformations are shown in Figure 2.10. In conformer **156**, we placed the sterically bulky cyclohexyl group in the axial position. Hence, there is a 1,3-diaxial clash between the cyclohexyl group and the two hydrogens as indicated by the bold bonds. In contrast, when the cyclohexyl group is in the equatorial position (conformer **157**), there is only the steric hindrance between the methyl group and the hydrogen and the much smaller lone pair on the oxygen atom. Therefore, our analysis predicted that conformer **157** should have a lower energy than conformer **156**.

Figure 2.10: Conformational analysis of *cis*-149



In the case of *trans*-**150** (Figure 2.11), with the cyclohexyl group in the axial position, as shown in conformer **158**, there is not only a 1,3-diaxial clash between the cyclohexyl group and the hydrogens as indicated by the bold bonds, but as the methyl group is also in an axial position, there is a further 1,3-diaxial clash. In the ring-flipped conformer **159**, both cyclohexyl and methyl groups are in equatorial positions, and the steric hindrance is reduced. Hence, conformer **159** should be lower in energy than conformer **158**.

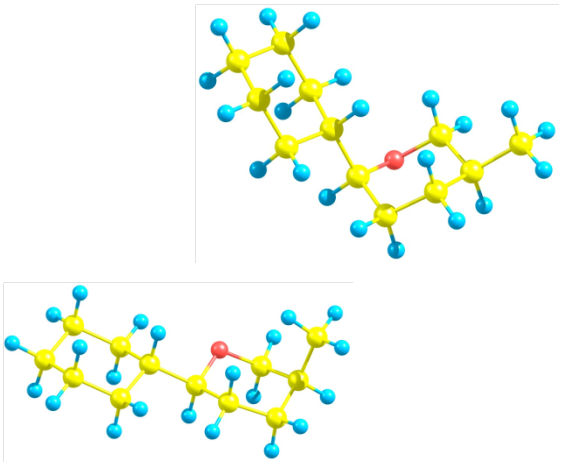
Figure 2.11: Conformational analysis of *trans*-150



The relative stability of the conformations of diastereomeric THPs *cis*-**149** and *trans*-**150** was also studied using DFT calculations.[58] All structures were optimised at the B3LYP/6-31G** and MP2/6-31G** levels of theory, under the Gaussin 'VeryTight' convergence criteria. The B3LYP calculations utilised the Gaussin 'UltraFine' denser integration grid. It was found that for *cis*-**149**, conformer **156** is 8 kJ mol^{-1} higher in energy than that of conformer **157** at both B3LYP/6-31G** and MP2/6-31G** level (Figure 2.12). In the case of *trans*-**150**, conformer **158** is 22 kJ mol^{-1} higher in energy than that of conformer **159** at

B3LYP/6-31G** level, and 16 kJ mol^{-1} higher at MP2/6-31G** level (Figure 2.12). Therefore, the DFT calculations supported our prediction of the conformational analysis: cyclic ether *cis*-**149** would exist in conformer **157** and *trans*-**150** would exist in conformer **159**.

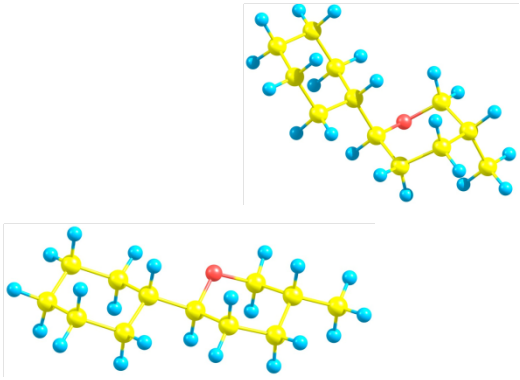
Figure 2.12: Energy minimized structures for *cis*-149 and *trans*-150



156 **157**

B3LYP/6-31G** level: 8 kJ mol^{-1} 0 kJ mol^{-1}

MP2/6-31G** level: 8 kJ mol^{-1} 0 kJ mol^{-1}



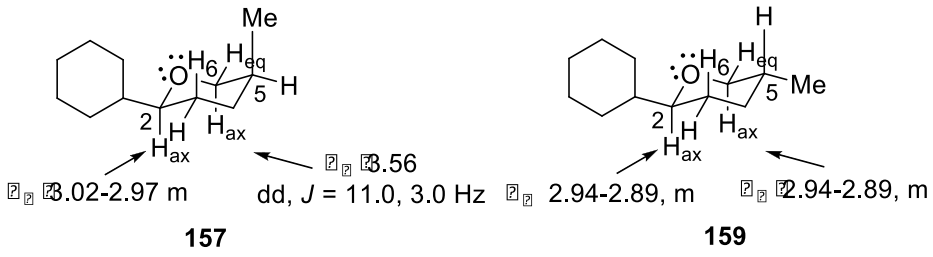
158 **159**

B3LYP/6-31G** level: 22 kJ mol^{-1} 0 kJ mol^{-1}

MP2/6-31G** level: 16 kJ mol^{-1} 0 kJ mol^{-1}

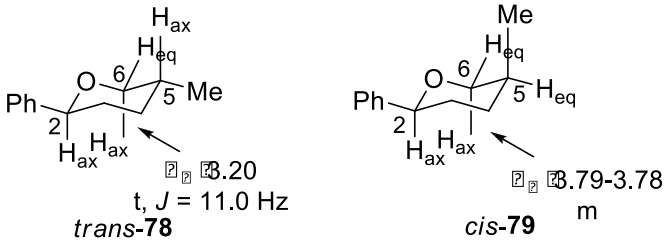
The conformation of cyclic ethers was ultimately established by ^{1}H NMR spectroscopic analysis of the protons in the axial position on C_2 in each diastereoisomer, as was carried out for THPs **149** and **150**. Both protons in the axial position should have a large ^{3}J coupling in both *cis*-**149** and *trans*-**150** to correspond to the *trans*-diaxial interaction with the axial positions (Figure 2.13). Although these protons in **157** (*cis*-**149**) and **159** (*trans*-**150**) all have a multiplet splitting pattern, the large ^{3}J coupling values resulting from the *trans*-diaxial interactions were featured in the majority of cyclic ethers. Some of the key ^{1}H NMR spectroscopic data are similar to that of cyclic ether *cis*-**143** and *trans*-**144**, and the relative stereochemistry was assigned using the same analytical approach. For example, in **157**, the axial proton at C_6 is assigned at δ_H 3.56 ppm (J = 11.0, 2.0 Hz). The double doublet splitting pattern is due to a large ^{2}J coupling constant (11.0 Hz) with the diastereotopic proton and a small ^{3}J axial-equatorial coupling constant (2.0 Hz) with the proton in the equatorial position on C_5. In **159**, a double doublet splitting with large J values could not be observed. The signal at δ_H 2.94-2.89 ppm (m) which integrates for two protons is assigned to the protons on C_6 for **159**. The splitting pattern for the proton in the axial position should be a doublet of doublet, or a triplet with large J values. However, this splitting pattern was not observed clearly due to overlapping with other signals.

Figure 2.13: ^{1}H NMR spectroscopic interpretation of 157 and 158



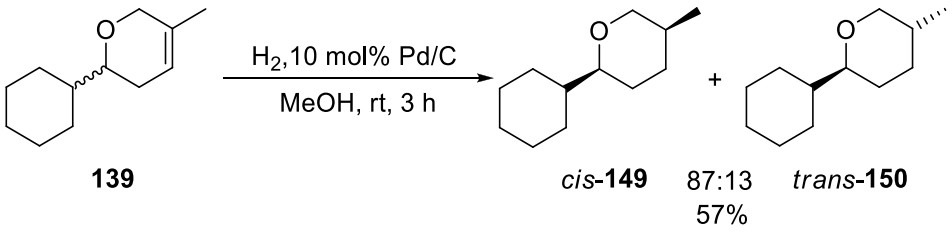
It should also be noted that 2,5-tetrahydropyrans *trans*-**78** and *cis*-**79** are known compounds previously synthesised by Duñach and co-workers in their work on the synthesis of rose oxide and its analogues.[49] Their aluminium triflate-catalysed cycloisomerisation approach afforded an 86:14 mixture of *trans*-**78** and *cis*-**79** in 84% yield. Both the diastereoselectivity and the yield are higher than our result (55:45 dr, 66% yield). However, we believe that the ^{1}H NMR spectroscopic assignment for *trans*-**78** and *cis*-**79** reported in their paper is erroneous.[49] Our approach to the stereochemical assignment allowed us to identify the proton at 3.20 ppm with a triplet splitting pattern to be the axial proton on C_6 in *trans*-**78**. The triplet splitting was due to the ^{3}J *trans*-diaxial interaction between the protons on C_6 and C_5 and the large ^{2}J coupling with the diastereotopic proton on C_6.

Figure 2.14: ^{1}H NMR spectroscopic interpretation of *trans*-78 and *cis*-79



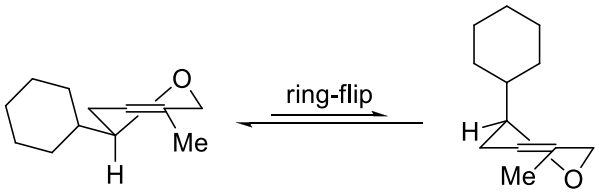
Cyclic ethers **135**-**139** which all have alkyl substituents at the 2-position gave good *cis* diastereoselectivity ranging from 75:25-98:11. Using dihydropyran **139** as an example, hydrogenation employing palladium on carbon furnished *cis*-**149** and *trans*-**150** with 87:13 dr (Scheme 2.28).

Scheme 2.28: Hydrogenation of 2,5-disubstituted dihydropyran 139



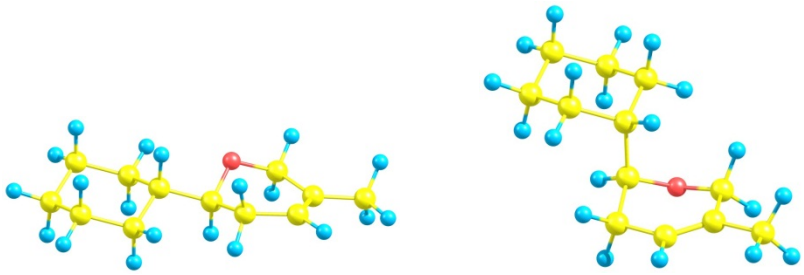
The following is our attempt to rationalise the diastereoselectivity observed in the hydrogenation of cyclic ethers **135-139** with an alkyl substituent. First, the conformation of the dihydropyran needs to be considered. The two possible half-chair conformations for dihydropyran **135** are shown in Figure 2.15. On inspection, conformer **160** would be predicted to be the more stable conformation; conformer **161** is higher in energy due to the 1,3-diaxial interaction between the cyclohexyl group and the pseudo-axial hydrogen atom.

Figure 2.15: Conformation of 2,5-disubstituted dihydropyran 160



DFT calculations using both B3LYP/6-31G** and MP2/6-31G** levels of theory were carried out on the two conformations of dihydropyran **139** (Figure 2.16). It was found that conformer **161** is 23 kJ mol^{-1} higher in energy than that of conformer **160** at the B3LYP/6-31G** level, and 17 kJ mol^{-1} higher in energy at the MP2/6-31G** level. DFT calculations for dihydropyran **139** in the half-boat conformations for either a pseudo-equatorial or pseudo-axial substituent were also attempted. However, those conformers were too high in energy and relaxed to the half-chair conformations.

Figure 2.16: Energy minimized structures for dihydropyran 139



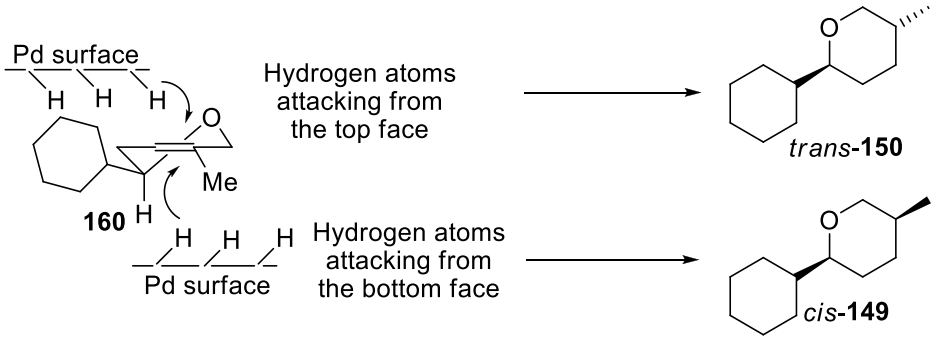
160 **161**

B3LYP/6-31G**: 0 kJ mol^{-1} 23 kJ mol^{-1}

MP2/6-31G**: 0 kJ mol^{-1} 17 kJ mol^{-1}

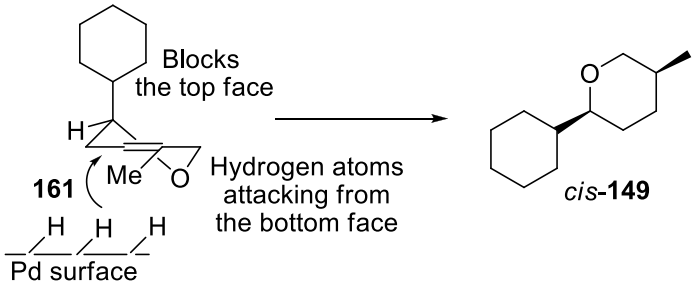
In the hydrogenation process, provided both hydrogen atoms are added to the alkene in a *syn* fashion, the face of the attack on the alkene would determine the configuration of the product, i.e. when the hydrogen atoms are added opposite to the R group, it would result in *cis*-**149**, and when the hydrogen atoms are added from the same face as the R group, *trans*-**150** is formed (Figure 2.17). This suggests that in the energetically more stable conformer **160**, both *cis* and *trans* diastereoisomers are likely to be formed in approximately equal amounts. This is due to both the top and bottom face being equally accessible, since there is no distinguishable steric hindrance. This can also be seen in the calculated DFT conformer **160**. Hence the hydrogen atoms on the catalyst surface could attack the double bond from either face. However, this is at odds with the results we observed (e.g. 87:13 mixture of *cis*-**149** and *trans*-**150**).

Figure 2.17: Rationale for the stereoselective hydrogenation of 160



In order to explain the observed *cis* selectivity, we suggest that the reaction could proceed *via* the less favorable conformation **161**. In conformer **161**, the pseudo-axial cyclohexyl group would block the top face, so the hydrogen atoms could only attack the alkene from the more accessible bottom face, which is opposite to the cyclohexyl group, to furnish *cis*-**149** (Figure 2.18). Although conformer **161** is higher in energy, it could be more reactive in the hydrogenation process under the palladium on carbon conditions and the equilibrium of the dihydropyran conformers **160** and **161** will shift to facilitate the progression of the reaction.

Figure 2.18: Rationale for the stereoselective hydrogenation of 161

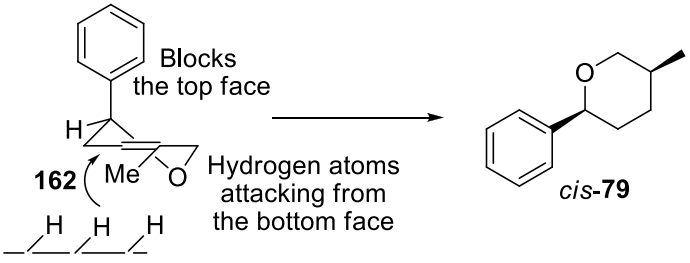


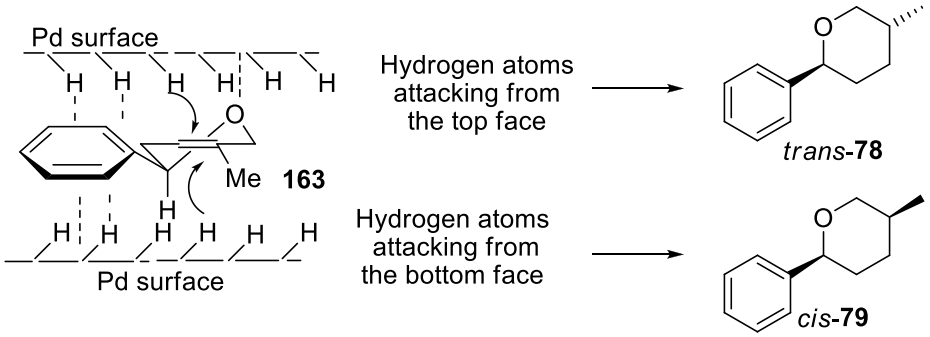
This could explain the *cis* diastereoselectivity observed from the hydrogenation reaction when the R groups are alkyl substituents. However, with a *t*-butyl substituent, this theory does not apply due to the locking effect of the bulky

group. At this time, we do not have a suitable explanation for the high *cis* diastereoselectivity observed in the formation of *cis*-**143** and *trans*-**144**.

In the hydrogenation of phenyl-substituted dihydropyran **13**, a 55:45 diastereomeric ratio of *cis*-**79** and *trans*-**78** was obtained. This could be explained by considering the potential coordination of the dihydropyran **13** to the catalyst surface. The two possible conformations for dihydropyran **13** are shown in Figure 2.19. The steric argument discussed earlier is also appropriate for conformer **162** which would provide the *cis* diastereoisomer (*cis*-**79**). In conformer **163**, when the phenyl group is in the pseudo-equatorial position, the π system from the phenyl group could coordinate with the catalyst surface from either the bottom or the top face. However, when the molecule approaches the catalyst surface from the top, there is another potential favorable coordination arising from the axial oxygen lone pair. Therefore, we suggest that the hydrogen atoms are more likely to attack the alkene from the top face to give *trans*-**78**. As a result, approximately equal reactivity from conformers **162** and **163** could occur to give the 55:45 dr observed.

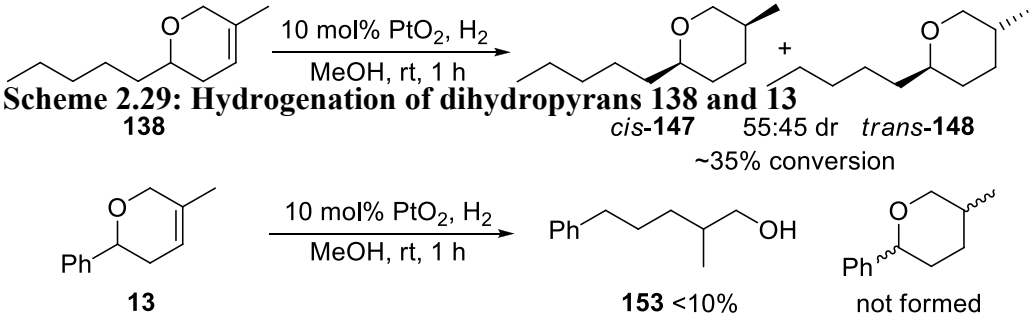
Figure 2.19: Rationale for the stereoselective hydrogenation of 162 and 163





In dihydropyran **140**, the phenyl group is further away from the oxygen atom, and there is flexibility in the alkyl chain. Therefore, the interaction of the π system from the phenyl group with the catalyst is less significant, the steric factors dominate and most of the reaction proceeds *via* the axial conformer. Therefore, the *cis*/*trans* diastereoselectivity for cyclic ether **140** (65:35 dr) is higher than for cyclic ether **13** (55:45 dr), but is lower than when the substituents are alkyl groups.

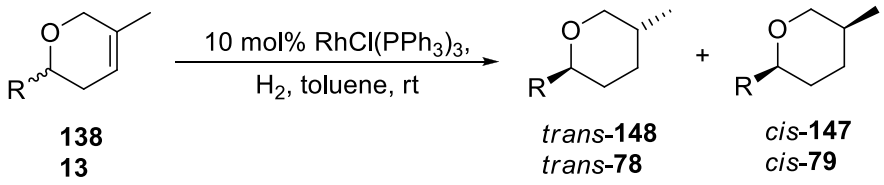
Next, we decided to carry out hydrogenation using other catalysts to study their effect on the diastereoselectivity. To start with, hydrogenation of cyclic ether **138** was performed using heterogeneous Adam's catalyst (platinum(II) oxide) in methanol at rt for 1 h. A low conversion (35%) to a 55:45 mixture of *cis*-**147** and *trans*-**148** was calculated from the ^{1}H NMR spectrum of the crude mixture. Thus, much lower diastereoselectivity with Adam's catalyst was observed. When the same reaction conditions were used with phenyl-substituted ether **13**, only a small amount (<10%) of the alcohol **153** resulting from benzylic ether cleavage was seen: no evidence for the formation of cyclic ether *trans*-**78** or *cis*-**79** was observed in the ^{1}H NMR spectrum of the crude product.



Scheme 2.29: Hydrogenation of dihydropyrans 138 and 13

In contrast, more interesting results were obtained using homogenous hydrogenation with Wilkinson's catalyst [$(PPh_3)_2RhCl$]. The results are presented in Table 2.7. For example, with dihydropyran **138**, a 70:30 mixture of cyclic ether *trans*-**147** and *cis*-**148** was generated (entry 2). A similar result was also obtained for cyclic ether **13** (entry 4).

Table 2.7: Hydrogenation of dihydropyrans 138 and 13



Entry	Compound	R	Time (h)	Conversion (%)[a]	Product	*trans*:*cis* (crude)[b]
1	**138**	*n*-C_5H_{11}	1	10	**148 147**	n.d[c]
2	**138**	*n*-C_5H_{11}	16	60	**148 147**	70:30
3	**13**	Ph	1	10	**78 79**	n.d
4	**13**	Ph	16	20	**78 79**	75:25

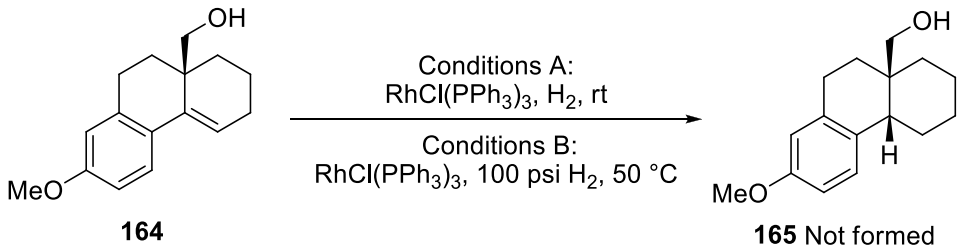
[a] Conversion determined from the ^{1}H NMR spectrum of the crude product. [b] Diastereomeric ratio determined from the ^{1}H NMR spectrum of the crude product. [c] n.d. = Not determined.

Although we have now identified reaction conditions for a complementary route to *trans*-**148** and *cis*-**147** and *trans*-**78** and *cis*-**79**, the rate of hydrogenation using Wilkinson's catalyst was considerably slower than with the two heterogeneous

catalysts (palladium on carbon and platinum oxide). For example, when the reaction mixture was stirred at rt for 1 h, only 10% conversion to cyclic ethers *trans*-**148** and *cis*-**147** and *trans*-**78** and *cis*-**79** was observed (entries 1 and 3). With a prolonged reaction time of 16 h, 60% conversion was calculated from the ^{1}H NMR spectrum of the crude product for cyclic ether *trans*-**148** and *cis*-**147** (entry 2), but formation of cyclic ether *trans*-**78** and *cis*-**79** had only proceed to 20% conversion (entry 4).

There are precedents for the slow conversion of the trisubstituted alkene of dihydropyrans such as **138** and **13** towards hydrogenation with Wilkinson's catalyst.[59, 60] For example, when hydrogenation was carried out with Wilkinson's catalyst, the trisubstituted alkene in **164** was unreactive at atmospheric pressure and rt, and even at 100 psi and 50 ºC (Scheme 2.30). The slow reaction was attributed to the steric hindrance of the trisubstituted double bond, which renders it less able to coordinate to the rhodium.

Scheme 2.30: Hydrogenation of alcohol 164

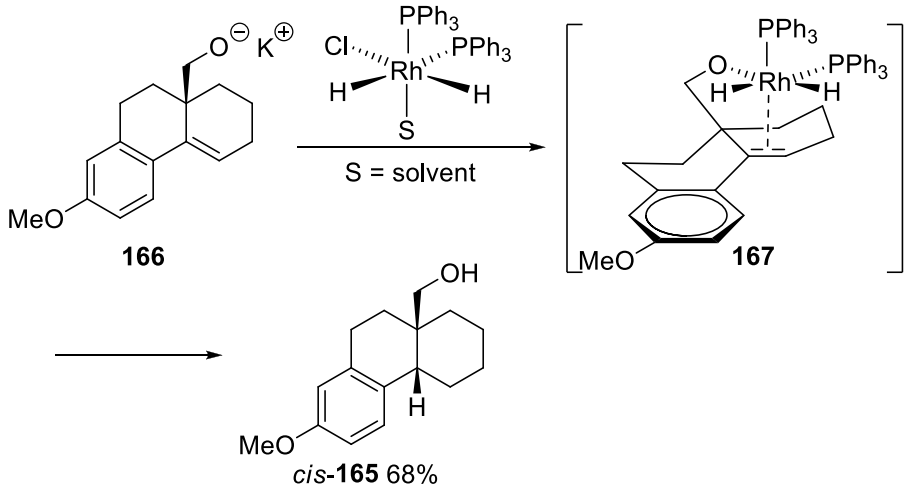


164 **165** Not formed

The same study also showed that when a metal alkoxide was employed together with 3.6 mol% of the rhodium catalyst, the reaction proceeded with 7-68% yield depending on the metal used (potassium > sodium > lithium) and afforded *cis*-**165** exclusively. The proposed mechanism is shown in Scheme 2.31. The protonated alcohol in tricyclic compound **164** is not nucleophilic enough to displace the chloride ligand. However, formation of the potassium alkoxide

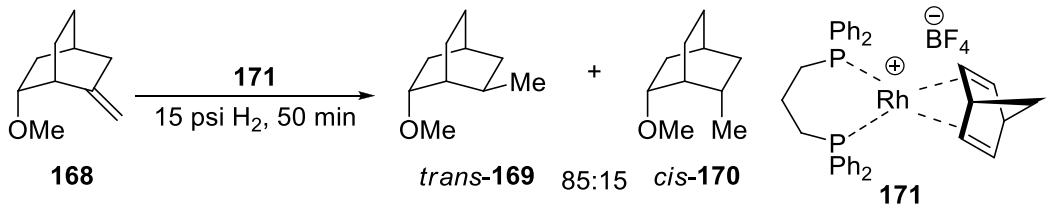
resulted in effective displacement of the chloride ligand. Therefore, the hydrogen atoms, alkene and the directing group are all associated to the rhodium, and hydrogen atoms were delivered from the same face to afford *cis*-**165**.

Scheme 2.31: Hydrogenation of 166



Methyl ethers have also been shown to effectively bind to cationic rhodium to give good levels of diastereoselectivity *via* metal-directed hydrogenation.[61] For example, bicyclic methyl ether **168** was hydrogenated with a rhodium-based catalyst **171** to afford an 85:15 mixture of saturated ethers *trans*-**169** and *cis*-**170**.

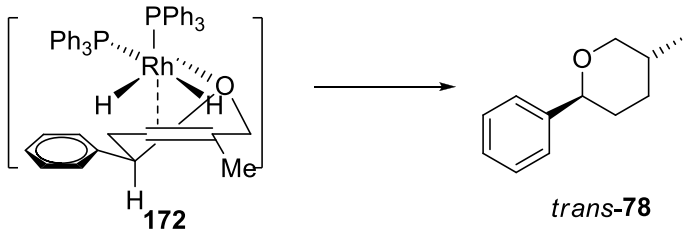
Scheme 2.32: Stereoselective hydrogenation of ether 168



Although no precedent was found for cyclic ethers as directing groups in hydrogenation reactions, we believe such an effect can explain the observed *trans* diastereoselectivity for formation of cyclic ethers *trans*-**148** and *cis*-**147**

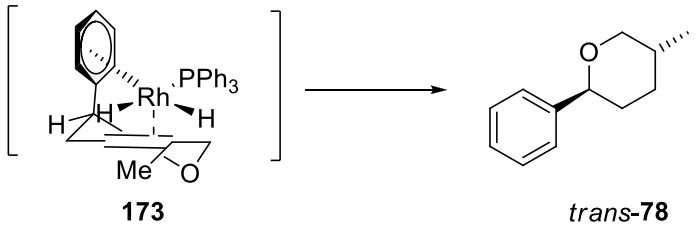
and *trans*-**78** and *cis*-**79**. Treatment of dihydropyran **138** and **13** with Wilkinson's catalyst under hydrogen at rt for 16 h furnished cyclic ethers *trans*-**148** and *cis*-**147** and *trans*-**78** and *cis*-**79** with 70:30 and 75:25 dr respectively, predominately as the *trans* product. The reaction intermediate for dihydropyran **13** is proposed as shown in Figure 2.20. In conformer **172**, the rhodium metal could coordinate with the oxygen atom as well as the alkene from the top face. Hence, hydrogen would be delivered from the top face which led the formation of *trans*-**78**.

Figure 2.20: Rationale for the stereoselective hydrogenation of 172



In conformer **173**, there is also the potential of a favorable association between the π-system in the phenyl group and rhodium, which would also lead to the diastereoisomer *trans*-**78**. These are shown in Figure 2.21.

Figure 2.21: Rationale for the stereoselective hydrogenation of 173



Even though both conformations for dihydropyran **13** could coordinate to the rhodium, the hydrogen would be delivered from the top face in both cases to give *trans*-**78**. Hence, the stereochemistry for formation of cyclic ethers *trans*-**78** and

cis-**79** showed predominately *trans* diastereoselectivity using Wilkinson's catalyst.

Finally, since the overall aim of preparing 2,5-disubstituted THPs was to investigate their odour properties, cyclic ethers **78**, **79** and **141**-**152** were submitted for olfactory evaluation at Givaudan. The odour profiles are presented in Table 2.8. It was interesting to see that some ethers possess a floral note, while the majority has citrus odour. Unfortunately, none of the compounds synthesised had sufficiently interesting odours for further exploration by Givaudan.

Table 2.8: Olfactory evaluation of THPs

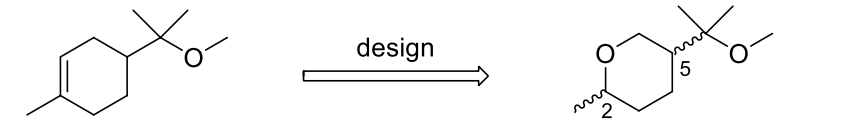
Entry	Cyclic ether	Odour Profile
1	*cis*-**141** and	floral, indolic
2	*cis*-**143** and	chemical, woody, dusty
3	*cis*-**145** and	citrus, zesty
4	*cis*-**147** and	peachy, lactonic
5	*cis*-**149** and	overwhelmingly citrus, zesty
6	*cis*-**79** and *trans*-**78**	citrus, zesty, slightly minty
7	*cis*-**151** and	citrus, chemical

To summarise, we have developed a route for the synthesis of 2,5-disubstituted tetrahydropyrans in a racemic fashion *via* Grignard addition to aldehydes, *O*-alkylation, ring-closing metathesis and hydrogenation. This procedure generates products in good yield and generally gives good *cis*-diastereoselectivity from the hydrogenation reaction. A lower yielding route to *trans*-**148** and *trans*-**78** was also developed.

2.6 Attempted Synthesis of Oxa-Orange Flower Ether

Having investigated the Grignard addition, *O*-alkylation and ring-closing metathesis route for the synthesis of 2,5-disubstituted THPs **78**, **79** and **141**-**152**, we then decided to apply the methodology to one of the target molecules, namely oxa-orange flower ether **52**, which is closely related to the perfumery ingredient orange-flower ether (Figure 2.22).

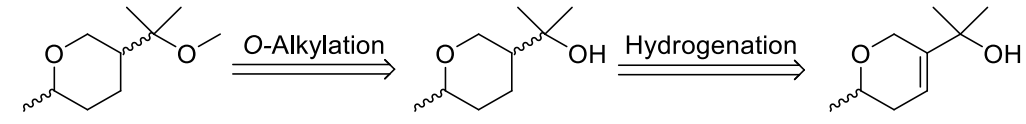
Figure 2.22: Design of oxa-orange flower ether 52



Orange flower ether Oxa-orange flower ether **52**

The first part of the retrosynthetic analysis of oxa-orange flower ether **52** is shown in Scheme 2.33. Thus, it was envisaged that the methyl ether in **52** will be constructed by *O*-methylation of the tertiary alcohol **174**, which would be obtained by hydrogenation of alkene **175**.

Scheme 2.33: Retrosynthetic analysis of oxa-orange flower ether 52

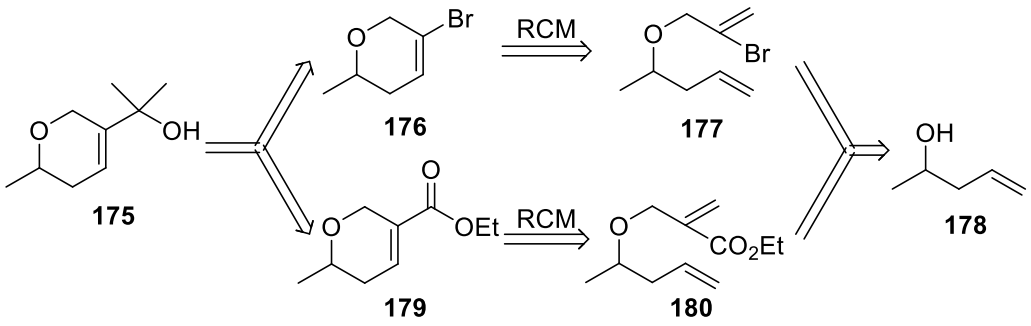


Oxa-orange flower ether **52** **174** **175**

The remainder of the retrosynthetic analysis is shown in Scheme 2.34. It was anticipated that treatment of vinyl bromide **176** with magesium would result in the formation of a Grignard reagent *in situ*, which could then be reacted with acetone to afford tertiary alcohol **175**. The cyclic vinyl bromide **176** could be constructed by ring-closing metathesis from the terminal diene **177**, which in turn would be obtained by *O*-alkylation of commercial pent-4-en-2-ol **178**.

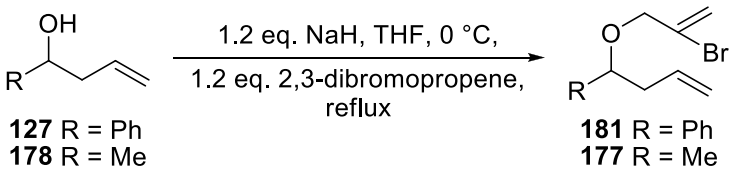
Importantly, vinyl bromide **176** is also a strategic point for the divergent synthesis of a variety of analogues of **175** using, for example, Pd-catalysed coupling processes. Alternatively, a different synthetic strategy for the preparation of oxa-orange flower ether **52** is also presented (Scheme 2.34). In this approach, the bromide in **177** is replaced with an ester functionality (**180**). Thus, tertiary alcohol **175** would be prepared by means of a double addition of methyl magnesium halide to ester **179**. The diene-ester **180** itself would be synthesised from pent-4-en-2-ol **178**. It was hoped that the electron-withdrawing nature of the ester moiety might aid the desired *O*-alkylation.

Scheme 2.34: Retrosynthetic analysis of ether 175



The attempted synthesis of oxa-orange flower ether **52** began with the *O*-alkylation of pent-4-en-2-ol **178** with 2,3-dibromopropene. Given the volatility of the product derived from addition to pent-4-en-2-ol **178**, and the potential difficulties associated with its isolation, the less volatile 1-phenylbut-3-en-1-ol **127** was also used as a starting material. Thus, secondary alcohols **127** and **178** were each treated with sodium hydride and 2,3-dibromopropene and the mixtures refluxed for 16 h. On inspection of the ^{1}H NMR spectrum of the crude products, no reaction had taken place (Table 2.9, entries 1 and 2). With an extended reaction time of 72 h, we were pleased to discover that the desired bromodiene **181** was isolated in 33% yield (entry 3). However, in the case of alcohol **178**, the reaction resulted in a complex mixture (entry 4).

Table 2.9: *O*-Alkylation of alcohols 127 and 178



127 R = Ph
178 R = Me

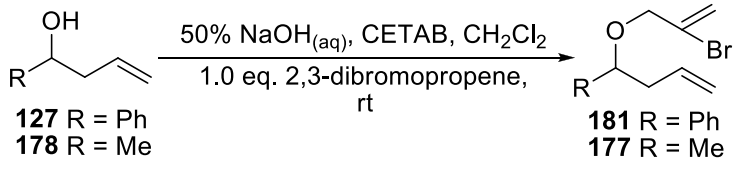
181 R = Ph
177 R = Me

Entry	Compound	R	Time (h)	Product	Yield (%)[a]
1	**127**	Ph	16	**181**	0
2	**178**	Me	16	**177**	0
3	**127**	Ph	72	**181**	33
4	**178**	Me	72	**177**	0

[a] Yield after purification by chromatography.

As the yield of **181** was only moderate and the *O*-alkylation of pent-4-en-2-ol **178** was not successful, phase transfer catalysis conditions (based on literature precedent[62]) were investigated. Thus, homoallylic alcohols **127** and **178** were treated with 2,3-dibromopropene, in the presence of cetyltrimethylammonium bromide in a biphasic mixture of aqueous sodium hydroxide and dichloromethane (Table 2.10).

Table 2.10: *O*-Alkylation of alcohols 127 and 178



127 R = Ph
178 R = Me

181 R = Ph
177 R = Me

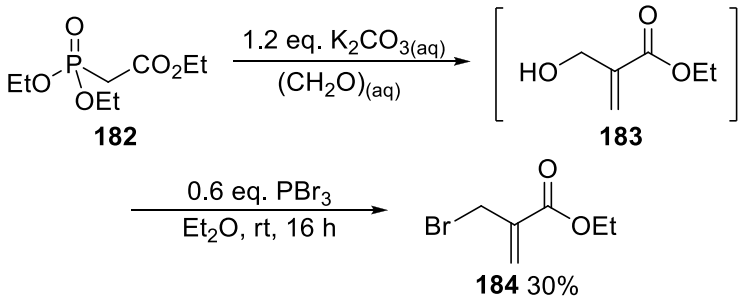
Entry	Compound	R	Time (h)	Product	Yield (%)[a]
1	**127**	Ph	1	**181**	19
2	**178**	Me	1	**177**	0
3	**127**	Ph	16	**181**	11
4	**178**	Me	16	**177**	7

[a] Yield after purification by chromatography.

In the case of alcohol **127**, the desired bromodiene **181** was isolated in 19% yield from a 1 h reaction (entry 1), whereas under the same conditions, *O*-alkylation of alcohol **178** was unsuccessful (entry 2). With a prolonged reaction time of 16 h, the yield of bromodiene **181** was still low (11%, entry 3). However, we were pleased to find that bromodiene **177** could finally be isolated, albeit in a low (7%) yield (entry 4). As these results were not satisfactory, we turned our attention to the alternative route.

Using a literature procedure,[63] bromoester **184** was prepared from treatment of formaldehyde with triethylphosphonoacetate **182** to form the crude alcohol **183**. Phosphorus tribromide was then added to give the crude product. Purification by Kügelrohr distillation afforded bromoacrylate **184** in 30% yield.

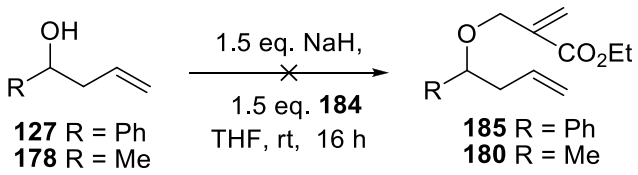
Scheme 2.35: Synthesis of bromoacrylate 184



We then carried out the *O*-alkylation of phenyl homoallylic alcohol **127** with sodium hydride and bromoacrylate **184** in THF at rt for 24 h.[64] However, no conversion to product **185** could be detected. The *O*-alkylation with pent-4-en-2-ol **178** under the same reaction conditions was then performed, and the result was also disappointing: no desired product could be observed in the ^{1}H NMR spectrum of the crude product. It was anticipated that a higher reaction temperature could in principle facilitate product formation. Thus, alcohol **127** was treated with sodium hydride and bromide **184** in THF at reflux for 16 h. This

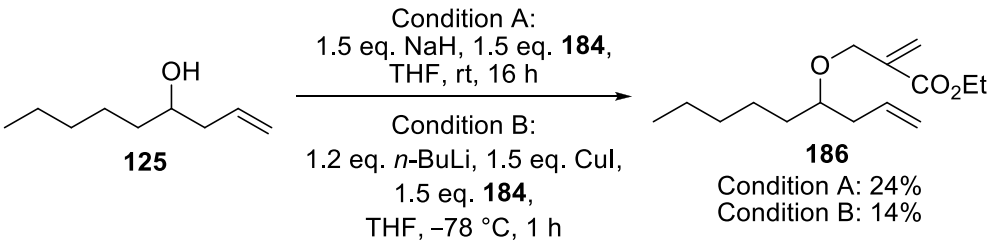
resulted in a mixture of unidentified compounds. The desired product **185** was also not detected using mass spectrometry on the crude product.

Scheme 2.36: Attempted *O*-alkylations of alcohols 127 and 178



When the same *O*-alkylation conditions using sodium hydride was performed on alcohol **125**, a 24% yield of diene-ester **186** was obtained (Scheme 2.37). Following a literature procedure,[65] we then carried out *O*-alkylation of alcohol **125** using *n*-BuLi followed by trapping with bromide **184**. Thus, alcohol **125** was deprotonated using *n*-BuLi in the presence of CuI in THF at ‒78 ºC, and the intermediate formed was then trapped with bromide **184**. Diene **186** was isolated in 14% yield together with 58% recovered starting material **125**. On comparison with the 24% yield obtained using sodium hydride and alcohol **125**, neither the conversion or the isolated yield of the desired product was improved using this procedure. These results suggest the bromoacrylate **184** traps slowly under these reaction conditions so that the starting material was recovered.

Scheme 2.37: Synthesis of diene 186

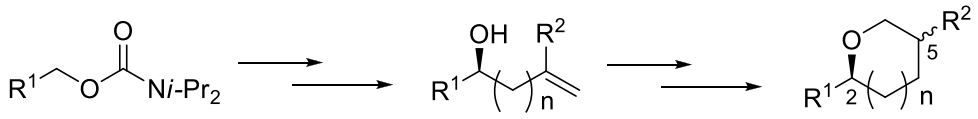


Although we were able to obtain diene-ester **186**, the reaction was not robust enough to produce a large amount of material. Therefore, the synthesis of oxa-orange flower ether **52** was not pursued further.

2.7 Asymmetric Deprotonation and Ring Closing Metathesis Route to Enantioenriched Oxygen Heterocycles

In this section, an investigation of a route for the synthesis of 2,5-disubstituted THPs *via* asymmetric deprotonation and ring closing metathesis is described (Scheme 2.38). Thus, the enantioenriched alcohols **188** would be synthesised from *O*-alkyl carbamates **187** *via* asymmetric deprotonation using *s*-BuLi and the chiral diamine (−)-sparteine. *O*-Alkylation using allyl bromides, ring closing metathesis and hydrogenation (as described in Section 2.5) would ultimately afford the enantioenriched 2,5-disubstituted THPs **189**.

Scheme 2.38: Proposed synthesis of THP 189

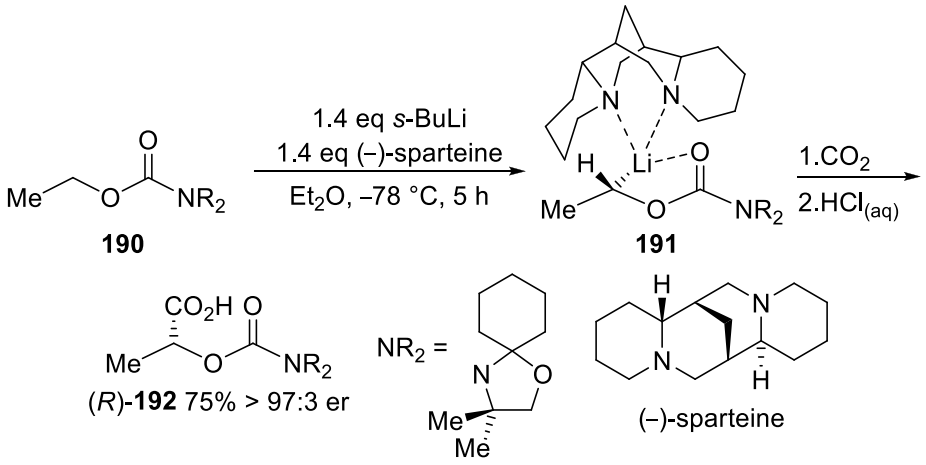


187 **188** n = 0, 1 **189**

2.7.1 Background Literature on Asymmetric Deprotonation of *O*-Alkyl Carbamates

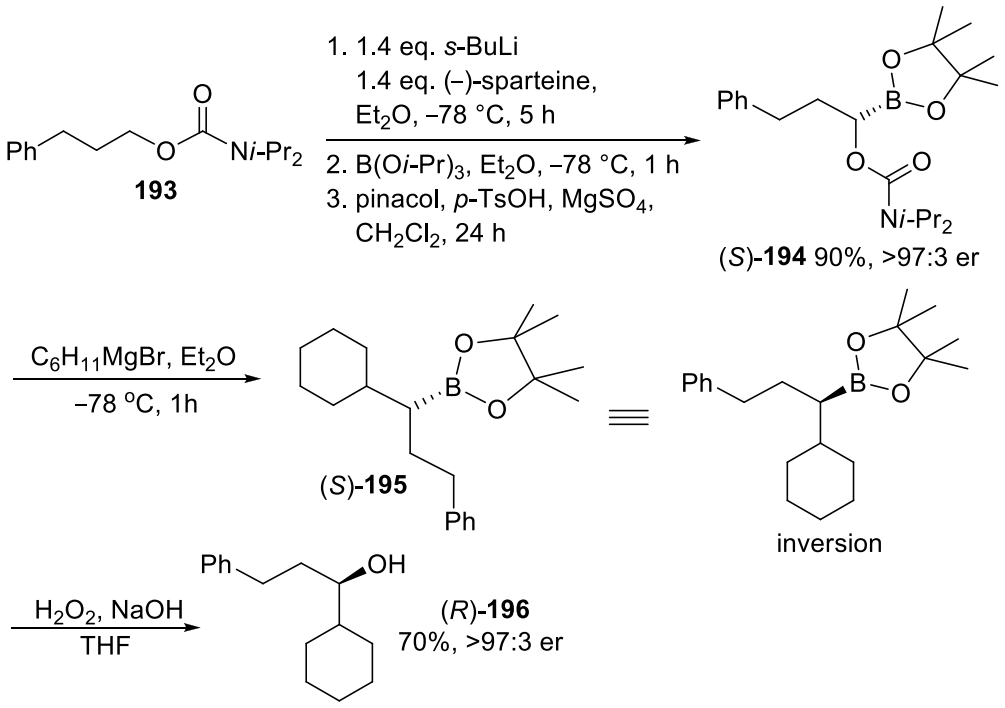
The asymmetric deprotonation of *O*-alkyl carbamates was first reported by Hoppe and co-workers in 1990.[66] An example is shown in Scheme 2.39. In this reaction, a complex of *s*-BuLi and the chiral diamine (−)-sparteine is used to affect the lithiation of an *O*-alkyl carbamate such as **190**. The reaction proceeds *via* preliminary complexation of the *s*-BuLi/(−)-sparteine complex to the carbamate oxygen. This brings the reactive complex into the correct arrangement to abstract an α proton to form the lithiated species **191**. The lithiated species **191** can then be trapped with CO_2 to give carboxylic acid (*R*)-**192** in 75% yield and >97:3 er (Scheme 2.39).

Scheme 2.39: Asymmetric lithiation/trapping of carbamate 190



Hoppe has extensively studied this type of *O*-alkyl carbamate methodology.[67] In 2004, Hoppe and co-workers reported the application of the asymmetric lithiation of *O*-alkyl carbamates to the synthesis of enantioenriched alcohols (Scheme 2.40).[68] For example, treatment of carbamate **193** with *s*-BuLi/(–)-sparteine in Et_2O at –78 ºC for 5 h was followed by trapping with tri-*i*-propylborate.

Scheme 2.40: Asymmetric synthesis of alcohol (*R*)-196

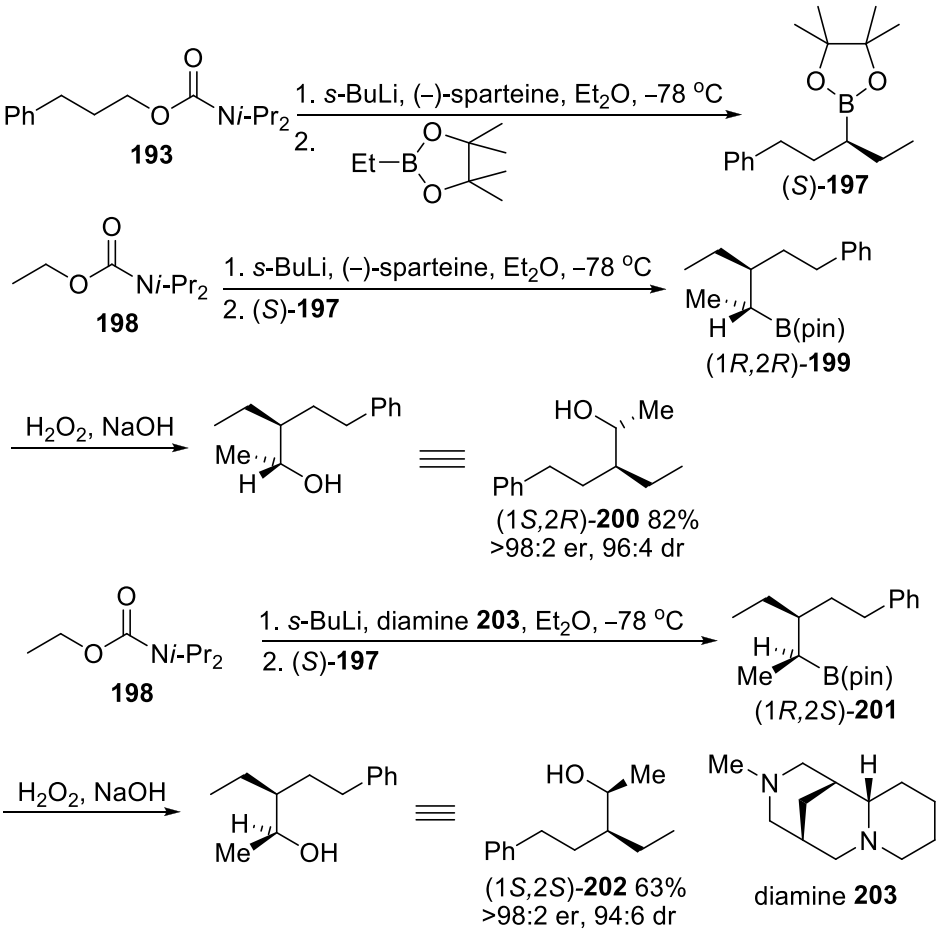


Then, transesterification took place by treating the crude organoboron compound with pinacol in the presence of *p*-toluenesulfonic acid and $MgSO_4$. The boron ester (*S*)-**194** was isolated in 90% yield with >97:3 er. Addition of a Grignard reagent followed by alkyl migration in an intermediate 'ate' complex furnished boronate (*S*)-**195**. Finally, oxidative work-up afforded alcohol (*R*)-**196** in high yield (70%) and enantioselectivity (>97:3 er).

Building on this work, Aggarwal and co-workers developed an iterative homologation of boronic esters using lithiated *O*-alkyl carbamates to build up a molecule bearing two adjacent stereocentres with high diastereo- and enantioselectivities (Scheme 2.41).[69] First, *O*-alkyl carbamate **193** was deprotonated using *s*-BuLi/(−)-sparteine and then trapped with tri-*i*-propylborate. Transesterification gave boronate ester (*S*)-**197**. Then, asymmetric deprotonation of *O*-alkyl carbamate **198** was carried out with *s*-BuLi/(−)-sparteine to give the lithiated species, which was reacted with boronate ester (*S*)-**197** as an

electrophile to form the 'ate' complex. This was then rearranged by migration of a ligand group from boron to an electron deficient carbon. The leaving group here is the carbamate group, which was replaced by the ligand group with inversion of configuration to give boronate (1*R*,2*R*)-**199**. After oxidative work-up, alcohol (1*S*,2*R*)-**200** was obtained in 82% yield, >98:2 er and 96:4 dr. By using *s*-BuLi/(+)-sparteine surrogate **203** complex, diastereoisomeric alcohol (1*S*,2*S*)-**202** was formed in 63% yield, >98:2 er and 96:4 dr.

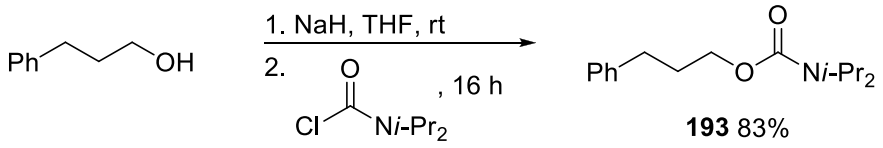
Scheme 2.41: Diastereoselective synthesis of alcohols (1*S*,2*R*)-200 and (1*S*,2*S*)-202



2.7.2 Synthesis of Cyclic Ethers *via* Asymmetric Deprotonation

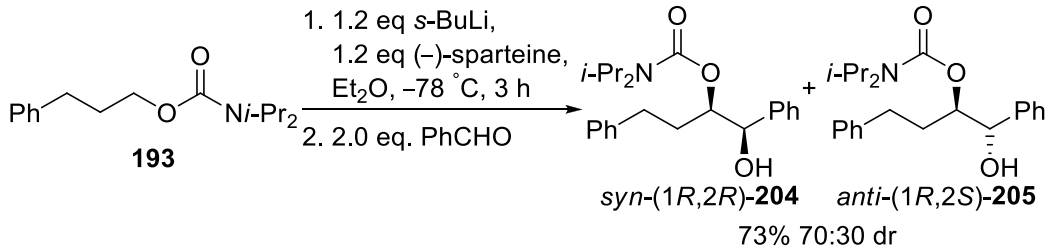
Our plan was to use the Hoppe-Aggarwal methodology to synthesise some enantioenriched alcohols for conversion into THPs. To start with, *O*-alkyl carbamate **193** was prepared using a procedure developed by Hoppe *et al*.[70] Deprotonation of 3-phenylpropanol with sodium hydride followed by nucleophilic attack of the deprotonated alcohol on di-*i*-propylcarbamoyl chloride gave *O*-alkyl carbamate **193** in 83% yield after purification by flash column chromatography (Scheme 2.42).

Scheme 2.42: Synthesis of carbamate 193



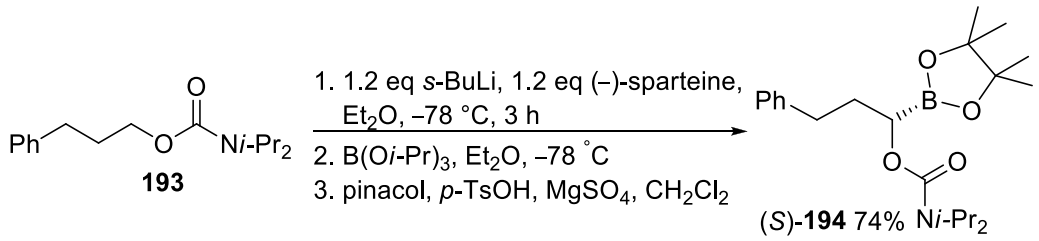
As a test reaction, asymmetric lithiation was first carried out on carbamate **193** using *s*-BuLi/(−)-sparteine. Trapping with benzaldehyde gave diastereomeric alcohols *syn*-(1*R*,2*R*)-**204** and *anti*-(1*R*,2*S*)-**205** in 73% yield as an inseparable mixture. A 70:30 mixture of alcohols *syn*-(1*R*,2*R*)-**204** and *anti*-(1*R*,2*S*)-**205** was observed (by ^{1}H NMR spectroscopy). The ratio was determined by integration of the signals due to OC*H*Ph: δ_H 5.12-5.08 (m) for *anti*-(1*R*,2*S*)-**205** and δ_H 5.06-5.01 (m) for *syn*-(1*R*,2*R*)-**204**. The relative stereochemistry was assigned based on other work carried out in the group.[71]

Scheme 2.43: Lithiation/trapping of carbamate 193



Then, the asymmetric deprotonation/trapping with tri-*i*-propyl borate was investigated. Thus, carbamate **193** was lithiated using *s*-BuLi/(−)-sparteine and trapped with tri-*i*-propyl borate. Transesterification was achieved by treating the crude organoboron compound with pinacol in the presence of *p*-toluenesulfonic acid based on Hoppe's procedure.[68] Boron ester (*S*)-**194** was isolated in 74% yield over these three steps after purification by column chromatography (Scheme 2.44).

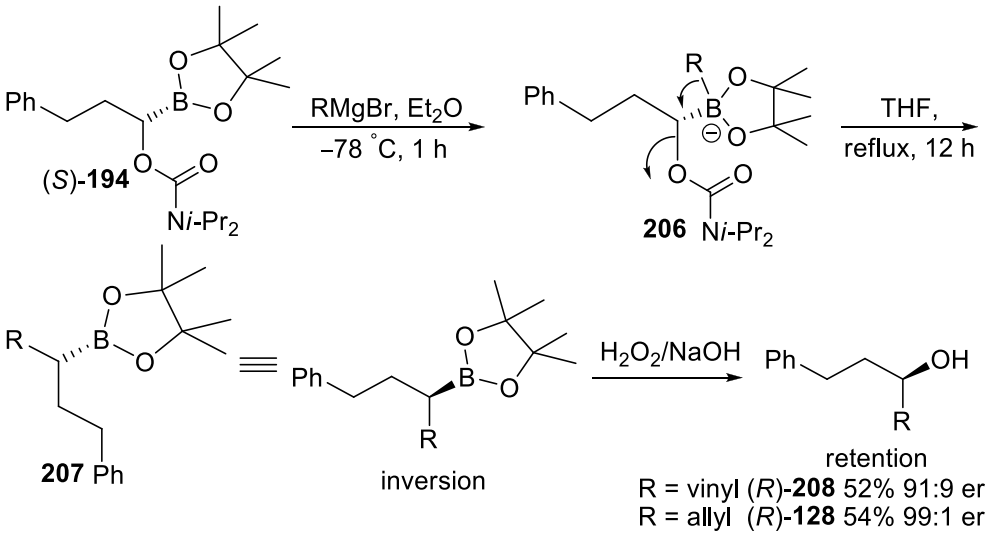
Scheme 2.44: Lithiation/trapping of carbamate 193



With the enantioenriched boronate ester (*S*)-**194** in hand, we were able to access the corresponding vinyl alcohol (*R*)-**208** and allyl alcohol (*R*)-**128** in 52% and 54% yield respectively, by treating boronate ester (*S*)-**194** with vinyl and allyl Grignard reagents respectively, followed by oxidative work-up (Scheme 2.45). Using CSP-HPLC, alcohol (*R*)-**128** was shown to be formed in 99:1 er, whereas alcohol (*R*)-**208** had 91:9 er. The er of the alcohols should be the same as the er of the starting boronate ester (*S*)-**194**. It is therefore surprising that alcohols

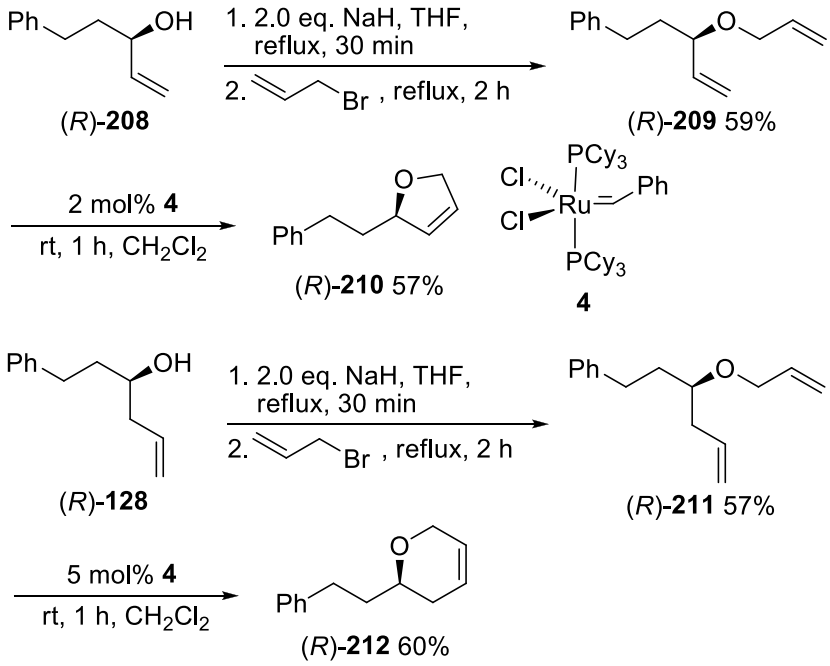
(*R*)-**208** and (*R*)-**128** do not have the same er. It appears that addition-rearrangement of the vinyl Grignard reagent to the boronate ester (*S*)-**194** proceeds with some loss of er. A slight erosion of enantioselectivity has also been reported for other carbamates and boronates, and is likely to be due to a lack of stereospecifity in the boronate rearrangement. [71-73]

Scheme 2.45: asymmetric synthesis of alcohols (*R*)-208 and (*R*)-128



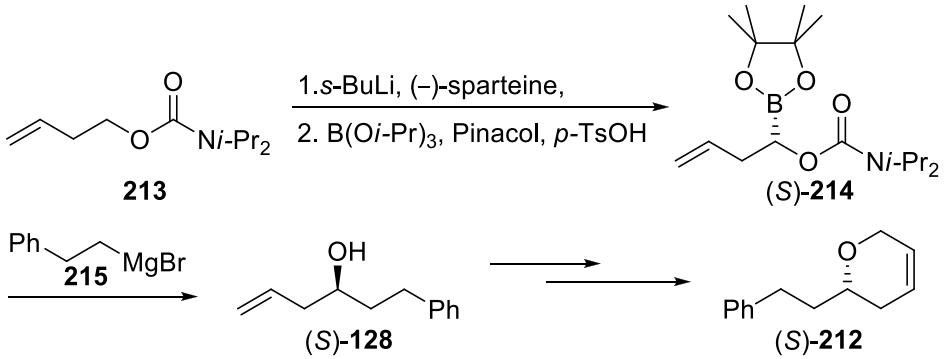
The enantioenriched alcohols (*R*)-**208** and (*R*)-**128** were then reacted with sodium hydride and allyl bromide to give (*R*)-**209** and (*R*)-**211** in 59% and 57% yield respectively.[22] Ring-closing metathesis was carried out using Grubbs' 1st generation catalyst **4** to give (*R*)-**210** and (*R*)-**212** in 59% and 60% yield.[23] The er of (*R*)-**210** and (*R*)-**212** are assumed to be the same as in (*R*)-**208** and (*R*)-**128** (Scheme 2.46).

Scheme 2.46: Synthesis of dihydropyrans (*R*)-210 and (*R*)-212



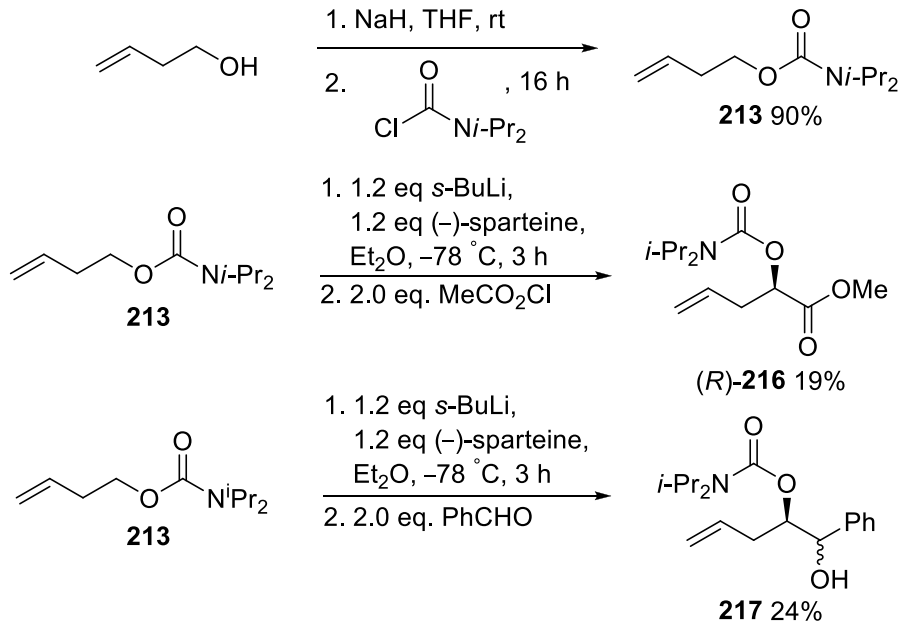
We then decided to synthesise cyclic ether (*S*)-**212**, the enantiomer of the previously synthesised (*R*)-**212**. The (+)-sparteine surrogate **203** has shown particularly high enantioselectivity as a ligand for organolithium reagents and generates the opposite enantiomer to (−)-sparteine in a range of reactions.[74-76] Hence, the stereochemistry in (*S*)-**212** could be introduced in the asymmetric lithiation step using diamine **203** in place of (−)-sparteine. However, the stereochemistry at the stereogenic centre could also be inverted using (−)-sparteine as the diamine ligand but reversing the addition order with carbamate **213** and Grignard reagent **215**. Our plan is shown in Scheme 2.47. Thus, deprotonation of *O*-alkyl carbamate **213** using *s*-BuLi/(−)-sparteine and trapping with tri-*i*-propylborate followed by transesterification would give boronate ester (*S*)-**214**. Addition of Grignard reagent **215** and boronate rearrangement would then furnish alcohol (*S*)-**128**. Finally, alkylation with allyl bromide and subsequent ring closing metathesis would afford cyclic ether (*S*)-**212**.

Scheme 2.47: Proposed synthesis of dihydropyran (*S*)-212



O-Alkyl carbamate **213** was synthesised in 90% yield from 3-butene-1-ol. Next, we studied the deprotonation of carbamate **213** using methyl chloroformate and benzaldehyde as electrophiles (Scheme 2.48).

Scheme 2.48: Synthesis and lithiation/trapping of carbamate 213

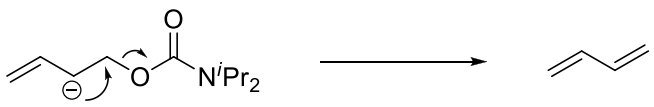


Unfortunately, neither reaction gave satisfactory results (Scheme 2.48). Ester (*R*)-**216** was isolated in only 19% yield. With benzaldehyde, alcohol **217** was isolated in only 24% yield and starting carbamate **213** was recovered in 65%

yield. Due to the low yield, the er of each product (*R*)-**216** and **217** was not determined.

We believe that the problem with the lithiation-trapping of *O*-alkyl carbamate **213** can be explained as follows. Treatment of carbamate **213** with *s*-BuLi could result in competitive allylic deprotonation to give **218** and subsequent β-elimination of the carbamate would then furnish butadiene (Scheme 2.49). Such a process has been suggested previously by Aggarwal *et al*.[77] Since the deprotonation of carbamate **213** gave disappointing yields, trapping with tri-*i*-propyl borate and the synthesis of cyclic ether (*S*)-**212** were not pursued further.

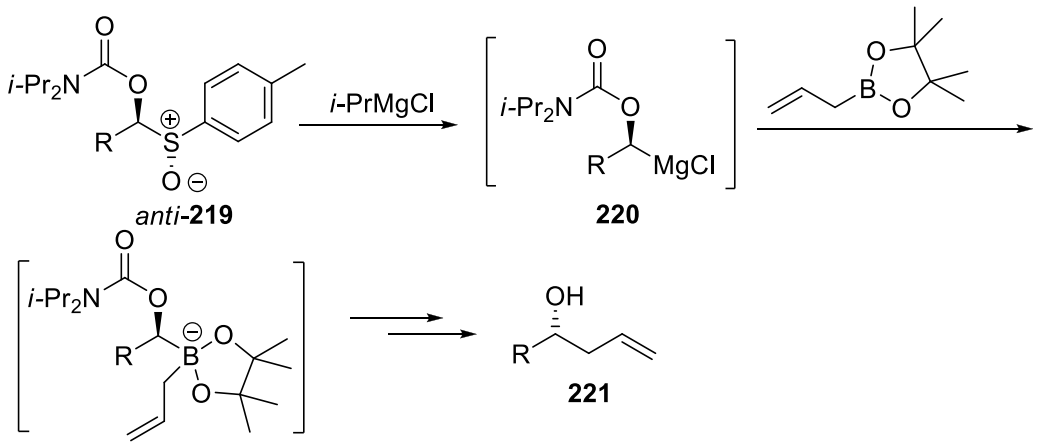
Scheme 2.49: Proposed mechanism for the formation of butadiene



218

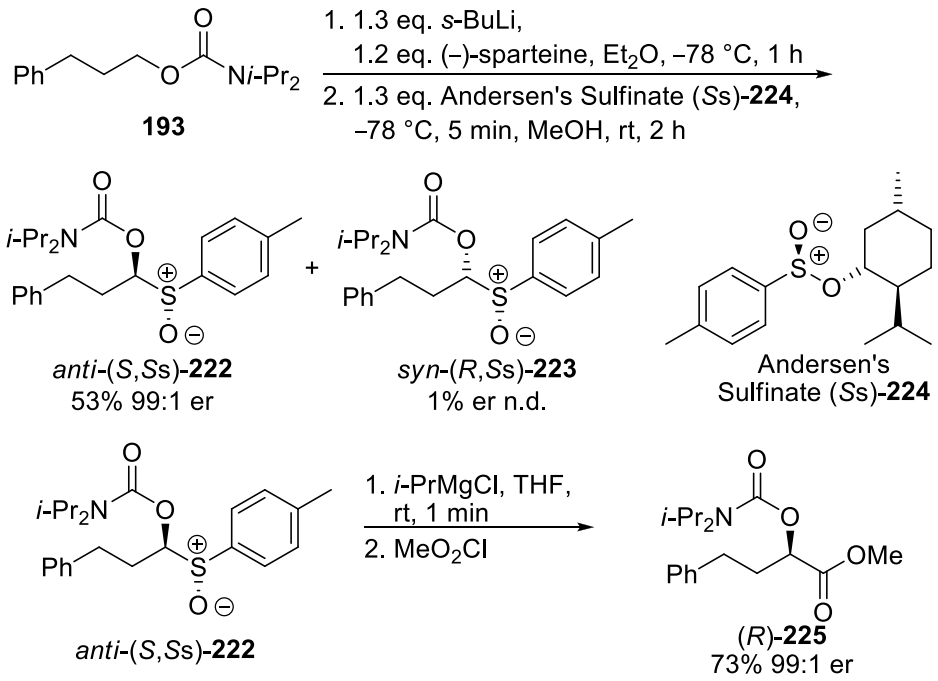
An alternative strategy towards the synthesis of alcohol (*S*)-**128** was also proposed. This involves sulfoxide → magnesium exchange on an α-alkoxy sulfoxide such as *anti*-**219** to generate the chiral α-functionalised Grignard reagents **220** in ≥99:1 er. Subsequent trapping with allyl boronate and oxidative work-up of the boron intermediate would then furnish enantioenriched alcohol **221** (Scheme 2.50).

Scheme 2.50: Proposed synthesis of alcohol 221



The synthesis of enantioenriched sulfoxides such as *anti*-**219** and the sulfoxide → magnesium exchange procedure have been recently developed in our group[71] as a route to enantiomerically pure products derived from *O*-alkyl carbamates. For example, lithiation of carbamate **193** using *s*-BuLi/(−)-sparteine and trapping with Andersen's sulfinate (*S*s)-**224** furnished sulfoxide *anti*-(*S*,*S*s)-**222** in 53% yield and 99:1 er, together with *syn*-(*R*,*S*s)-**223** (Scheme 2.51). This enhancement of enantiomeric ratio is due to the combination of two chiral species combining in the same reaction.[69] Then, sulfoxide → magnesium exchange on sulfoxide *anti*-**222** using *i*-propyl magnesium chloride followed by trapping with methyl chloroformate afforded ester (*R*)-**225** in 73% yield and 99:1 er.

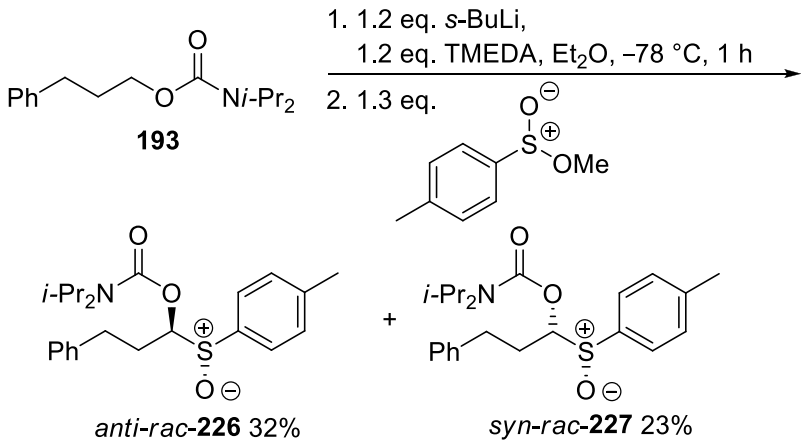
Scheme 2.51: Synthesis of ester (*R*)-225 *via* sulfoxide → magnesium exchange



Although there has been much work on the use of α-alkoxy sulfoxides in our group, catalytic asymmetric deprotonation and trapping with Andersen's sulfinate (*S*s)-**224** has not previously been carried out. In addition, we also planned to determine if the enantioselectivity could be maintained using a Grignard reagent with allylboronic pinacol ester as an electrophile, since there was some loss of er observed in the formation of (*R*)-**128** from (*S*)-**194**.

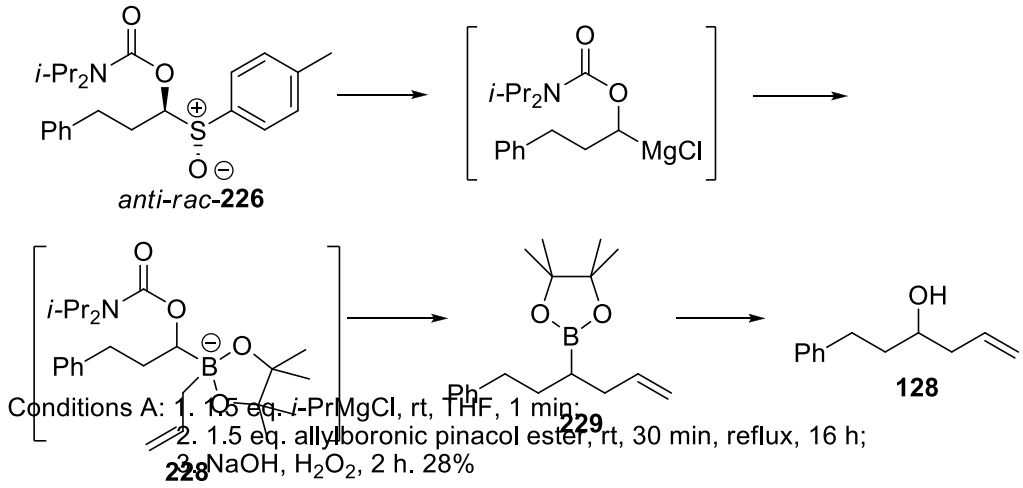
To evaluate the α-alkoxy sulfoxide approach, initial efforts were focussed on racemic reactions. Thus, carbamate **193** was treated with *s*-BuLi in the presence of TMEDA in Et_2O at ⁻78 ºC for 1 h. Addition of the reaction mixture to a solution of methyl *p*-toluenesulfinate in Et_2O gave a 60:40 mixture of diastereomeric sulfoxides *anti-rac*-**226** and *syn-rac*-**227** (based on the ^1H NMR spectrum of the crude product). After purification by column chromatography, sulfoxides *anti-rac*-**226** and *syn-rac*-**227** were isolated in 32% and 23% yield respectively (Scheme 2.52).

Scheme 2.52: Synthesis of sulfoxides *anti-rac*-226 and *syn-rac*-227



Next, we attempted sulfoxide → magnesium exchange, boronate trapping and oxidation to give allylic alcohol **128**. There is precedent in the group for the use of *i*-propyl magnesium chloride to facilitate the exchange reaction. Thus, treatment of *anti-rac*-**226** with *i*-propyl magnesium chloride in THF at rt for 1 min, followed by trapping with allylboronic pinacol ester afforded boronate **229** *via* a 1,2-metalate rearrangement of the ate-complex **228**. It was then further oxidised to the alcohol **128** using $NaOH/H_2O_2$. Initially, after sulfoxide → magnesium exchange, intermediate **228** was stirred at rt for 30 min before refluxing, and the subsequent oxidation of the boronate **229** was carried out over 2 h. This gave alcohol **128** in a low 28% yield (Conditions A, Scheme 2.53). The reaction time was then prolonged from 2 h to 4 h after the addition of allylboronic pinacol ester, as well as a longer reaction time for the conversion to the alcohol. This led to an improved result and gave alcohol **128** in a respectable 56% yield (Conditions C).

Scheme 2.53: Investigation of different rearrangement conditions



Conditions A: 1. 1.5 eq. *i*-PrMgCl, rt, THF, 1 min;
2. 1.5 eq. allylboronic pinacol ester, rt, 30 min, reflux, 16 h;
3. NaOH, H_2O_2, 2 h. 28%

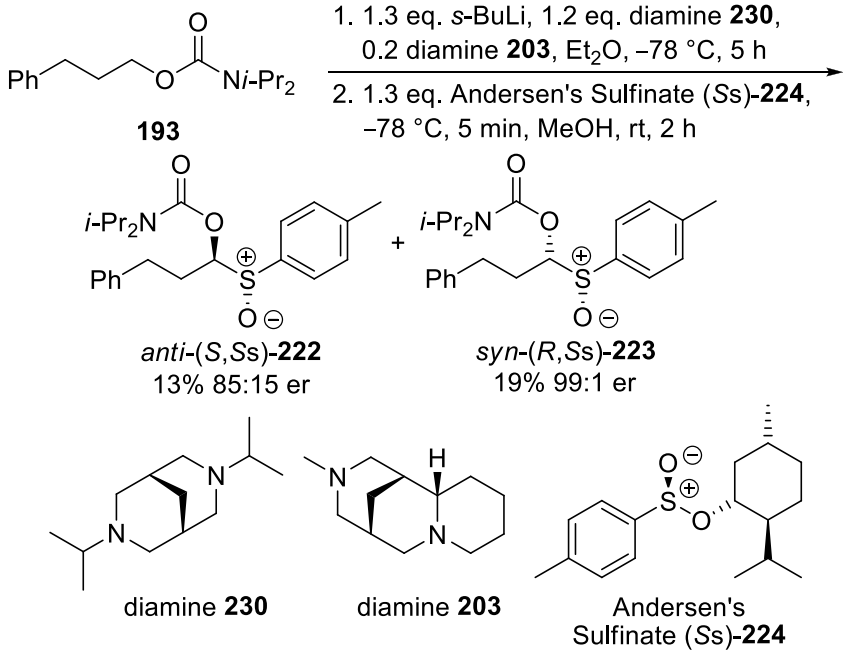
Conditions B: 1. 1.5 eq. *i*-PrMgCl, rt, THF, 1 min;
2. 1.5 eq. allylboronic pinacol ester, rt, 2 h, reflux, 16 h;
3. NaOH, H_2O_2, 2 h. 39%

Conditions C: 1. 1.5 eq. *i*-PrMgCl, rt, THF, 1 min;
2. 1.5 eq.allylboronic pinacol ester, rt, 4 h, reflux, 16 h;
3. NaOH, H_2O_2, 4 h. 56%

Having established a suitable procedure for the racemic lithiation/trapping of *O*-alkyl carbamate **193** followed by sulfoxide → magnesium exchange, we then moved on to development of the asymmetric lithiation/trapping using catalytic asymmetric deprotonation. Our group has previously developed a two-ligand catalytic system, and this methodology has been applied to the asymmetric lithiation of *N*-Boc pyrrolidine and an *O*-alkyl carbamate.[78] In both cases, the best enantioselectivity at a specific loading of the chiral diamine was obtained with diamine **203**. Therefore, the use of (+)-sparteine surrogate **203** in sub-stoichiometric amounts was explored. Thus, carbamate **193** was lithiated with *s*-BuLi/achiral diamine **230** in the presence of just 0.2 eq. of diamine **203** followed by trapping with Andersen's sulfinate (*S*s)-**224**. Encouragingly, sulfoxide *anti*-(*S*,*S*s)-**222** was obtained in 13% yield and 85:15 er, together with

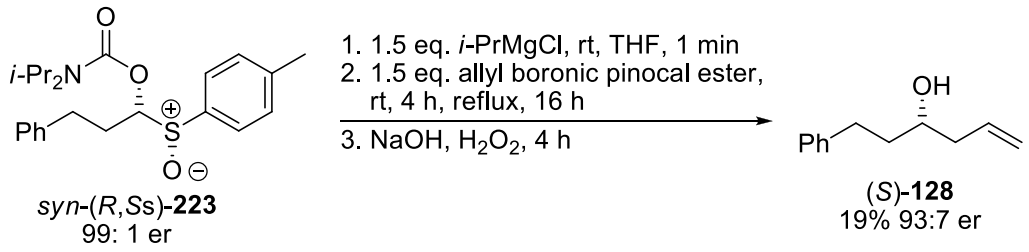
syn-(*R*,*S*s)-**223** in 19% yield and 99:1 er (Scheme 2.54). The stereochemistry was assigned by comparison with other work in the group.[71]

Scheme 2.54: Catalytic asymmetric lithiation/trapping of carbamate 193



Before optimizing the lithiation-trapping further, the sulfoxide → magnesium exchange with *syn*-(*R*,*S*s)-**223** was investigated. Using the optimised condition previously developed, sulfoxide *syn*-(*R*,*S*s)-**223** was transformed into alcohol (*S*)-**128** in 19% yield and 93:7 er (Scheme 2.55). Comparison with the product formed *via* the asymmetric lithiation approach (see Scheme 2.54) proved that the reaction proceeded with retention of configuration at carbon. There was a slight decrease in enantioselectivity for the 1,2-metelate rearrangement. Blakemore had shown that a higher enantioselectivity could be retained using Li-carbenoid instead of Mg-carbenoid, although the use of an allyl substituent as a migrating group was not studied.[79, 80] However, there was insufficient time to optimise this reaction further.

Scheme 2.55: Synthesis of alcohol (*S*)-128 *via* sulfoxide → magnesium exchange

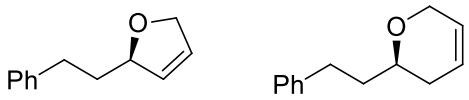


syn-(*R*,*S*s)-**223**
99: 1 er

(*S*)-**128**
19% 93:7 er

To summarise, we have demonstrated that cyclic ethers (*R*)-**210** and (*R*)-**212** could be synthesised in high yield and er *via* an asymmetric deprotonation, *O*-alkylation and ring-closing metathesis approach (Figure 2.22). The catalytic asymmetric lithiation of carbamate **193** and trapping with Andersen's sulfinate (*S*s)-**224** was less successful. An approximately 50:50 mixture of sulfoxides *anti*-(*S*,*S*s)-**222** and *syn*-(*R*,*S*s)-**223** were furnished in low yield. Although the sulfoxide → magnesium exchange protocol to (*S*)-**128** was developed, there was a loss of er in the rearrangement step.

Figure 2.22



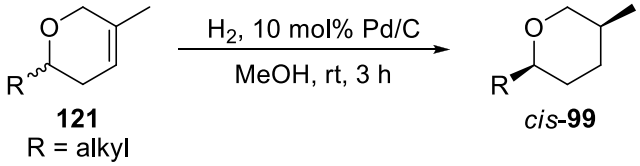
(*R*)-**210** (*R*)-**212**

2.8 Conclusions and Future Work

In conclusion, the synthesis of 2,5-disubstituted THPs *via* alkylation, reduction and cyclisation was investigated. Alcohols **116** and **117** were obtained using this route and we were able to broaden the reaction scope by introducing a benzyl group as one of the substituents *via* alkylation. However, cyclisation of these compounds was not successful. Therefore, we were unable to access the 2.5-disubstituted THPs utilising this approach.

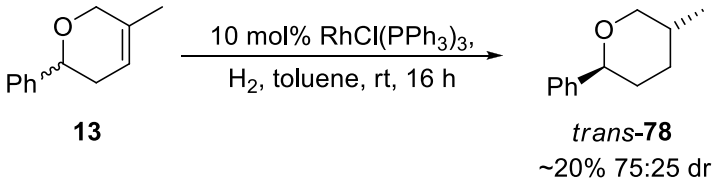
In contrast, the Grignard addition, ring-closing metathesis and hydrogenation approach was identified as a route to 2,5-disubstituted tetrahydropyrans in a racemic fashion. Using this route, seven potential perfumery compounds were produced. Moreover, when the R group is an alkyl substituent, high *cis* selectivity in the range of 83:17 to 89:11 dr was observed from the hydrogenation reaction (Scheme 2.56).

Scheme 2.56: Hydrogenation of THP 121



Two other hydrogenation catalysts (Wilkinson's catalyst and Adam's catalyst) were tested and we were pleased to find a complementary diastereoselectivity in the hydrogenation step, i.e. the *trans*-diastereomer was the major product. In a key example, using Wilkinson's catalyst [$(PPh_3)_3RhCl$], cyclic ethers *trans*-**78** and *cis*-**79** were generated in 75:25 dr (Scheme 2.57). However, the rate of conversion to the cyclic ether was much slower.

Scheme 2.57: Hydrogenation of dihydropyran 13



13 *trans*-**78**
~20% 75:25 dr

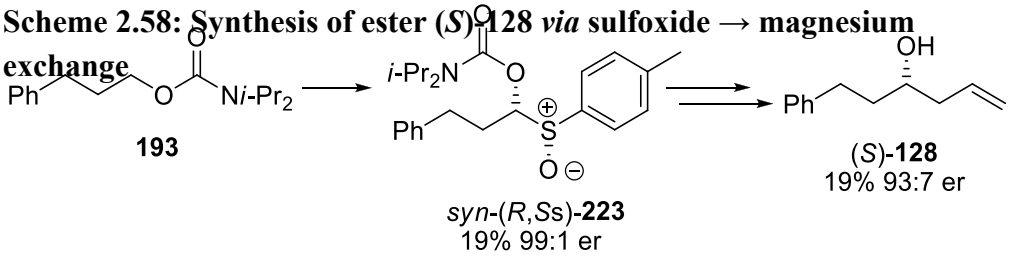
The synthesis of cyclic ethers (*R*)-**210** and (*R*)-**212** (Figure 2.23) *via* asymmetric deprotonation followed by ring-closing metathesis has also been developed. Chiral alcohols (*R*)-**208** and (*R*)-**128** were synthesised *via* asymmetric deprotonation in 52% and 54% yield respectively. Then, ring closing metathesis was used to form the 5- and 6-membered oxygen heterocycles (*R*)-**219** and (*R*)-**212** in 57% and 60% yield.

Figure 2.23: Structures of dihydropyrans (*R*)-210 and (*R*)-212

(*R*)-**210** (*R*)-**212**

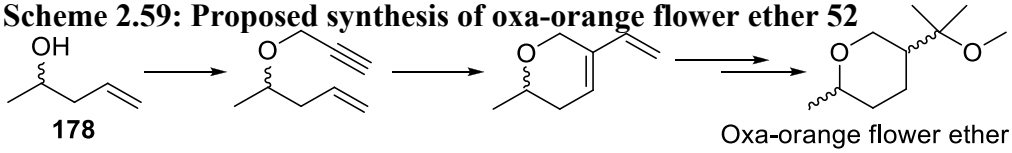
Enantioenriched sulfoxide *syn*-(*R*,*S*s)-**223** was synthesised in 19% yield and 99:1 er by catalytic asymmetric deprotonation and trapping with Andersen's sulfinate (*S*s)-**224**. We have shown that treatment of sulfoxide *syn*-(*R*,*S*s)-**223** with *i*-propyl magnesium chloride at rt for 1 min, and trapping with allyl boronic pinacol ester followed by oxidative work-up proceeds mostly with retention of stereochemistry. Thus, alcohol (*R*)-**128** was synthesised using this protocol in 19% yield and 93:7 er (Scheme 2.58).

Scheme 2.58: Synthesis of ester (*S*)-128 *via* sulfoxide → magnesium exchange



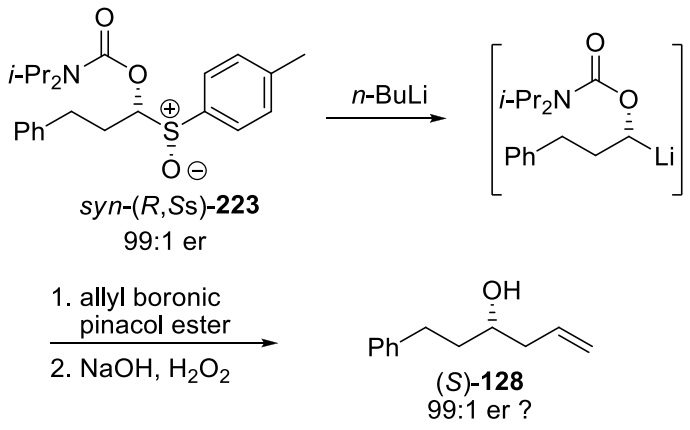
Although *O*-alkylation with hetero-homoallyl substituents as electrophiles has proved difficult, future work on the synthesis of oxa-orange flower ether **52** could involve a detailed study of the *O*-alkylation of alcohol **178**. This should involve the use of using other electrophiles, *e.g.* 3-bromoprop-1-yne, to provide a synthetic handle (Scheme 2.59).

Scheme 2.59: Proposed synthesis of oxa-orange flower ether 52



Future work on the investigation of the loss of er from sulfoxide → magnesium exchange might involve the employment of an organolithium reagent to furnish a lithiated carbamate. In 2006, Blakemore and co-workers reported the use of enantioenriched α-chloroalkyllithium regents and trapping with boronic esters in good yields.[80] Higher enantioselectivity was observed when lithium was compared to magnesium. We could also investigate whether use of a lithium carbamate could improve the enantioselectivity (Scheme 2.60). Furthermore, if the sulfoxide → lithium exchange and trapping with allyl boronic ester still proceeds with loss of er, this would indicate that the lack of stereospecifity is due to the use of an allyl migrating group.

Scheme 2.60: Proposed route to alcohol (*S*)-128



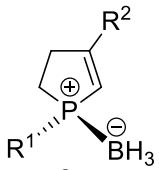
syn-(*R*,*S*s)-**223**
99:1 er

(*S*)-**128**
99:1 er ?

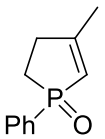
Chapter 3. Asymmetric Synthesis of Phosphine Heterocycles

This part of the thesis contains the results of a project aimed at developing new methodology for the asymmetric synthesis of *P*-stereogenic phospholene boranes **2** (Figure 3.1) *via* lithiation/trapping of phosphine boranes and ring-closing metathesis. Section 3.1 describes a brief overview of the utility of a commercially available racemic phosphine oxide *rac*-**231** (Figure 3.1) in catalytic reactions. Then, the aims of this project are discussed. Section 3.2 starts with a literature summary of the asymmetric lithiation/trapping of phosphine boranes. Then, the synthesis of several diamine ligands is described, followed by the results of their use in the lithiation/trapping of phosphine borane **285**. Two strategies to access *P*-stereogenic phospholene boranes are provided in Section 3.3. Then, the synthesis of a cyclic phosphine borane in a racemic fashion is discussed. Finally, we focus on the asymmetric synthesis of *P*-stereogenic phospholene boranes *via* asymmetric lithiation/trapping and subsequent ring-closing metathesis.

Figure 3.1: Structures of *P*-stereogenic phospholene boranes and *rac*-231



2



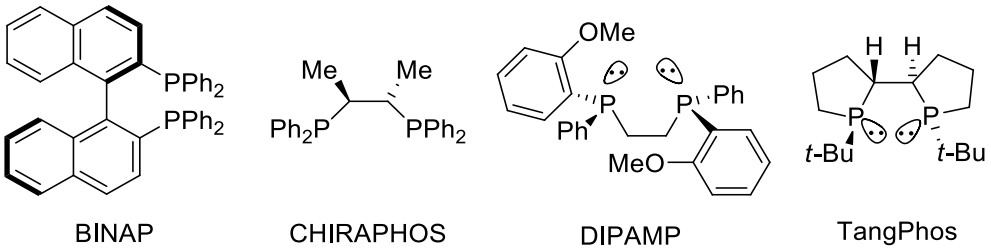
rac-**231**

3.1 Introduction

3.1.1 Literature Background

Chiral phosphine compounds form one of the most important class of ligands for the development of efficient transition metal-catalysed reactions.[81-83] A selection of chiral phosphine compounds is shown in Figure 3.2. For ligands such as BINAP[84] and CHIRAPHOS,[85] the chirality is in the carbon backbone connecting the two phosphine fragments. In contrast, DIPAMP[86] and TangPhos[87] are *P*-stereogenic compounds, with four different substituents attached to each phosphorus atom.

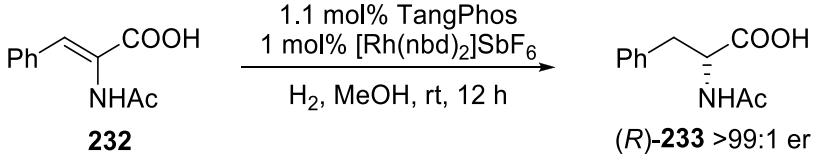
Figure 3.2: Phosphine-containing ligands



BINAP CHIRAPHOS DIPAMP TangPhos

One of the most studied metal-catalysed reactions using chiral phosphines is asymmetric hydrogenation. Zhang and co-workers found that TangPhos gave high enantioselectivity in the rhodium-catalysed asymmetric hydrogenation of α-(acylamino)acrylic acid and its derivatives.[87] For example, rhodium-catalysed hydrogenation of unsaturated acid **232** using TangPhos as a catalyst afforded amino acid (*R*)-**233** in >99:1 er.

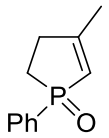
Scheme 3.1: Asymmtric hydrogenation of unsaturated acid 232



232 (*R*)-**233** >99:1 er

Although there are numerous examples of *P*-stereogenic chiral phosphines in transition metal-catalysed reactions, there are fewer examples of organocatalytic reactions.[83] Recently, phosphine heterocycles such as phosphine oxide *rac*-**231** has been used in two catalytic processes: (i) catalytic aza-Wittig reactions and (ii) catalytic Wittig reactions.

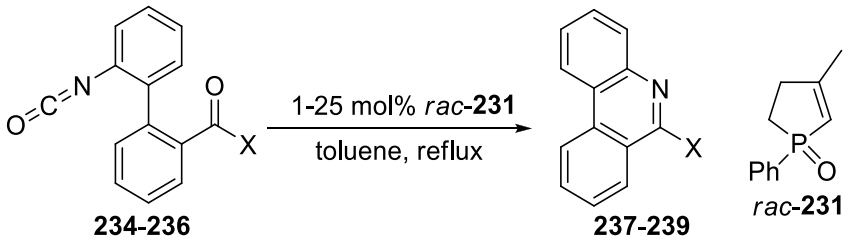
Figure 3.3: Phosphine oxide *rac*-231



rac-**231**

In 2008, Marsden and co-workers reported an aza-Wittig cyclisation in the synthesis of heteroaromatics using phosphine oxide *rac*-**231** as a catalyst.[88] The synthesis of the phenanthridine system from a range of isocyanates was explored. For example, isocyanates **234**-**236** were treated with catalytic phosphine oxide *rac*-**231** (1-25 mol%) in refluxing toluene to give phenanthridines **237**-**239** in good yield (Table 3.1). With a 1 mol% loading of the catalyst and an extended reaction time (88 h), phenanthridine **238** was formed in 80% yield (entry 2). In comparison, with amide **236**, which has a less electrophilic carbonyl group, the formation of phenanthridine **239** required a high loading of phosphine oxide *rac*-**231** (25 mol%) and the yield of **239** was significantly lower (entry 3).

Table 3.1: Catalytic aza-Wittig cyclisations: phenanthridine synthesis.



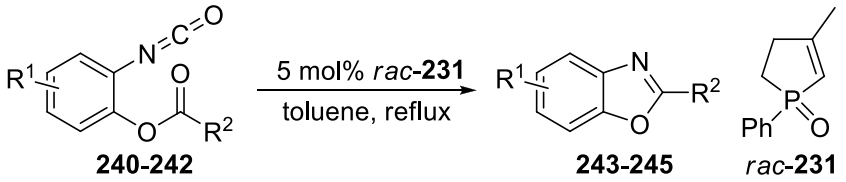
234-236 237-239

Entry	Compound	Product	X	**231**	conc (M)	Time (h)	Yield (%)[a]
1	**234**	**237**	OMe	25	0.03	21	87
2	**235**	**238**	OMe	1	0.1	88	59
3	**236**	**239**	NEt_2	25	0.03	23	48

[a] Yield after purification by chromatography.

As an extension of this methodology, the synthesis of azoles was also studied using phosphine oxide *rac*-**231**. It was found that a broad range of alkyl substituents and carboxyl substituents could be employed regardless of the nature of those groups. For example, reaction of isocyanate ester **240** with 5 mol% of phosphine oxide *rac*-**231** in refluxing toluene gave benzoxazole **243** in 87% yield (Table 3.2, entry 1). With electron-donating groups attached to the aromatic ring and to the ester, isocyanate ester **241** provided benzoxazole **244** in 59% yield (entry 2), whereas with two electron-withdrawing groups as substituents, benzoxazole **245** was formed in 48% yield (entry 3).

Table 3.2: Catalytic aza-Wittig cyclisations: benzoxazole synthesis



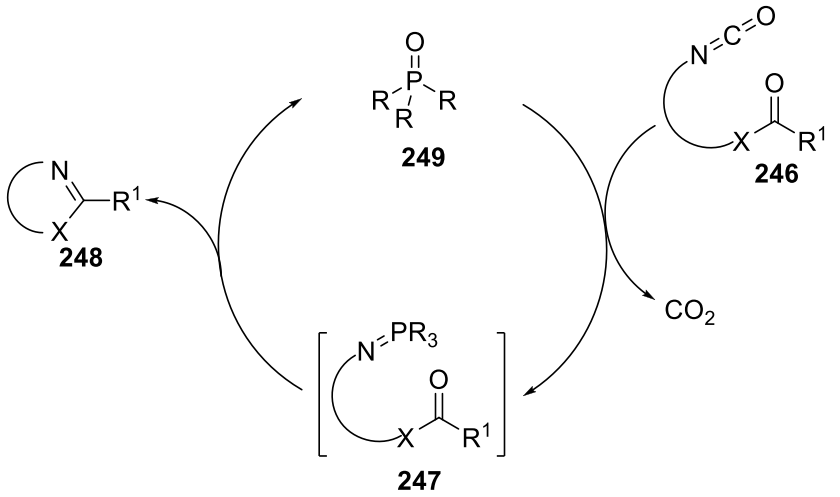
240-242 **243-245** ***rac*-231**

Entry	Compound	Product	R^1	R^2	Yield (%)[a]
1	**240**	**243**	H	Ph	87
2	**241**	**244**	7-MeO	4-$MeOC_6H_4$	59
3	**242**	**245**	5-F	4-FC_6H_4	48

[a] Yield after purification by chromatography.

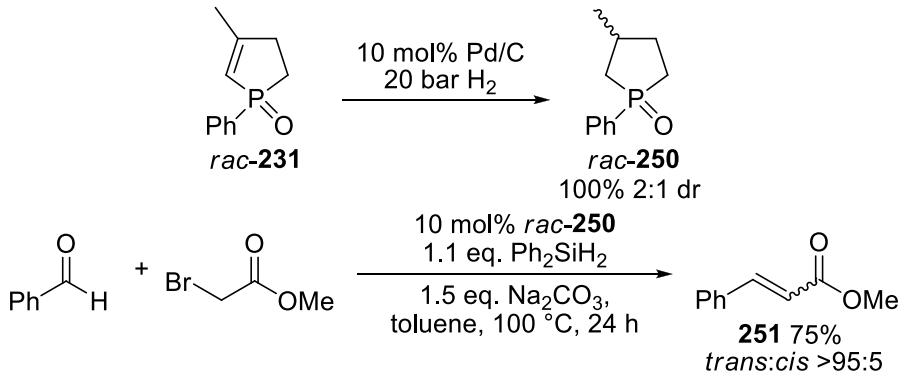
The self-condensation of isocyanates to give carbodiimides under phosphine oxide catalysis has been known since the 1960s.[89, 90] A proposed catalytic cycle for the formation of phenanthridines and benzoxazoles *via* Marsden's methodology is shown in Scheme 3.2. Campbell and co-workers suggested that nucleophilic attack of the oxygen in the polarised phosphorus-oxygen bond on the isocyanate in compound **246** would give an intermediate iminophosphorane **247** together with carbon dioxide. The iminophosphorane **247** would then undergo intramolecular aza-Wittig reaction with the carbonyl group to furnish the desired carbodiimide **248**, as well as regenerating the phosphine oxide *rac*-**249** for the next reaction cycle.

Scheme 3.2: Proposed catalytic aza-Wittig cyclisation



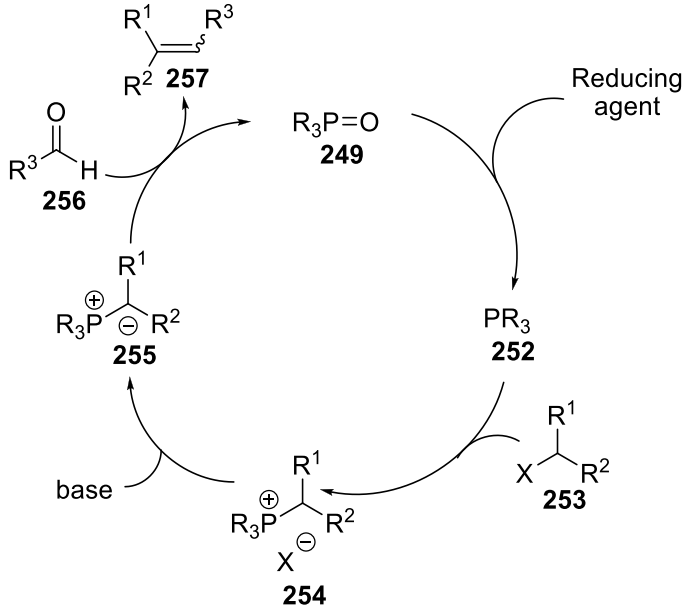
In seemingly unrelated work, O'Brien and co-workers reported the catalytic Wittig reaction of benzaldehyde with methyl bromoacetate in the presence of a 2:1 mixture of diastereomeric phosphine oxides *rac*-**250**,[91] which was obtained by hydrogenation from phosphine oxide *rac*-**231**. A typical example is shown in Scheme 3.3. Benzaldehyde was treated with methyl bromoacetate with 10 mol% of *rac*-**250** in the presence of diphenylsilane and sodium bicarbonate at 100 ºC in toluene to furnish the desired alkene **251** in 75% yield and *trans*:*cis* ratio of > 95:5.

Scheme 3.3: Catalytic Wittig reaction



The catalytic cycle for this Wittig reaction is shown in Scheme 3.4. The reaction first involves the formation of the trialkylphosphine **252** by reduction of the phosphine oxide **249** precursor. The trialkylphosphine **252** then reacts with alkyl halide **253** to generate a phosphonium salt **254**. On deprotonation of phosphonium salt **254**, the resulting phosphonium ylide **255** reacts with aldehyde **256** to afford alkene **257** and phosphine oxide **249**, the latter of which can be reduced to trialkylphosphine **252**.

Scheme 3.4: Proposed catalytic Wittig reaction



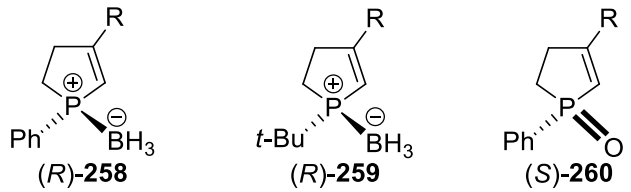
The optimum reducing agent for phosphine oxide *rac*-**249** was found to be diphenylsilane and when triphenylphosphine oxide was used, the reaction was ineffective and only aldehyde **256** was recovered. Preliminary theoretical calculations were carried out to understand the difference in reactivity between phosphine oxide *rac*-**231** and triphenylphosphine oxide. It was shown that the bond length of P=O and P-Ph and the bond angle of O=P-Ph in both compounds

are similar. Therefore, it was suggested that phosphine oxide *rac*-**231** was reduced more easily in the reaction due to the release of ring strain.

3.1.2 Project Outline

Although commercially available phosphine oxide *rac*-**231** was explored in both the catalytic aza-Wittig and Wittig reactions, we became interested in the synthesis of enantioenriched phosphine boranes (*R*)-**258** or (*R*)-**259** (Figure 3.4). These phosphine boranes could easily be transformed into phosphine oxide (*S*)-**260** and other protected phosphines.

Figure 3.4: *P*-Stereogenic phospholenes

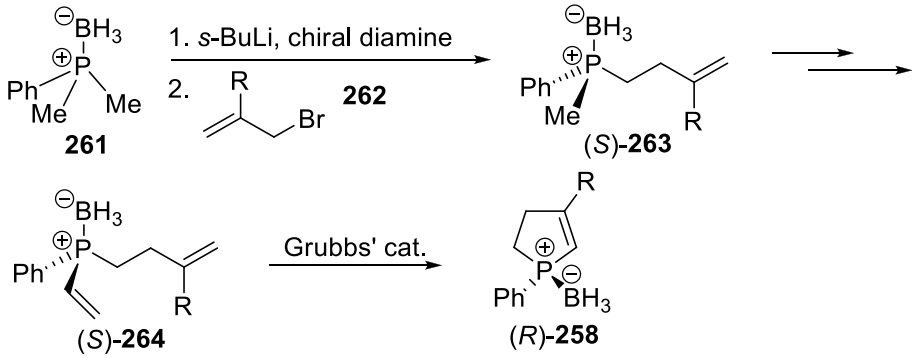


The reasons for the development of a synthetic route to phosphine boranes (*R*)-**258** and (*R*)-**259** are twofold. First, phosphine oxides derived from them could be used as potential catalysts for future developments of catalytic reactions. Although Marsden's heterocycle syntheses generate achiral products, the group has also reported the enantioselective synthesis of β-quaternary azacycles *via* asymmetric aza-Wittig reactions.[92] However, chiral phosphine oxide (*S*)-**231** was not tested as its synthesis was unknown at the time. With the catalytic Wittig reaction, there could be possibilities to further improve the *trans*:*cis* stereoselectivity by using enantioenriched phosphine oxide such as (*R*)-**260**. Secondly, to the best of our knowledge, there are no previous reports on the asymmetric synthesis of *P*-stereogenic phospholenes such as (*R*)-**258** and

(*R*)-**259**. Therefore, we felt that there was a need for the development of synthetic routes to chiral phosphine heterocycles such as (*R*)-**258** and (*R*)-**259**.

We envisioned that the enantioenriched phosphine boranes (*R*)-**258** or (*R*)-**259** could be synthesised *via* asymmetric lithiation/trapping followed by ring-closing metathesis. The proposed synthetic plan is outlined in Scheme 3.5. The stereogenic centre at phosphorus could be created by asymmetric lithiation using *s*-BuLi and a chiral diamine (*e.g.* (–)-sparteine).[93] Electrophilic trapping with an allyl bromide would put the first alkene in place, to give phosphine borane (*S*)-**263**. Then, regioselective lithiation (at the less hindered methyl group)[94] and trapping with paraformaldehyde would give a hydroxy adduct, which could then be transformed into the second alkene, as shown in (*S*)-**264**, ready for the formation of the phosphine heterocycle. Finally, ring-closing metathesis[33] using a Grubbs-type catalyst would furnish the desired vinylic phospholene boranes (*R*)-**258**. We anticipated that the route would be synthetically flexible as substituents other than phenyl and a range of R groups could be introduced.

Scheme 3.5: Proposed route to P-stereogenic phospholene borane (*R*)-258



Although the use of the (+)-sparteine surrogate in the asymmetric lithiation of phosphine boranes produces the opposite enantiomer to that obtained using (–)-sparteine, there is still a need to design and investigate alternative chiral

diamines that would allow access to both enantiomers. Therefore, before we started the development of the asymmetric synthesis of heterocyclic phosphine boranes, we decided to first synthesise and test alternative chiral diamines in the asymmetric lithiation of phosphine boranes. At the time when the project commenced, (−)-sparteine was not commercially available. This further demonstrated the need to develop alternative diamine ligands for the asymmetric lithiation chemistry.

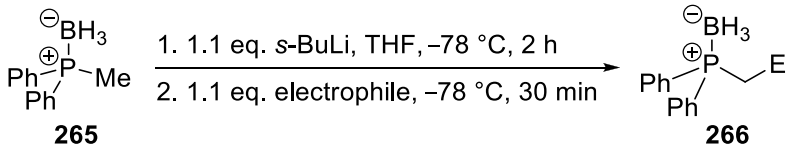
This part of the thesis reports our investigation of chiral diamine ligands for the asymmetric lithiation/trapping of phosphine boranes and the synthesis of enantioenriched vinylic phospholene boranes *via* asymmetric lithiation/trapping and subsequent ring-closing metathesis.

3.2 Asymmetric Lithiation-trapping of Phosphine Boranes

3.2.1 Asymmetric Lithiation Approaches to *P*-Stereogenic Phosphines

In 1985, Imamoto and co-workers reported the lithiation of phosphine borane **265** using *s*-BuLi in THF followed by electrophilic trapping with ketones.[95] Later, an extensive study of this reaction was carried out by the same group.[96] Phosphine borane **265** was lithiated and trapped with a variety of electrophiles to introduce a broad range of functionality. Some examples are shown in Table 3.3.

Table 3.3: Lithiation/trapping with different electrophiles



265 **266**

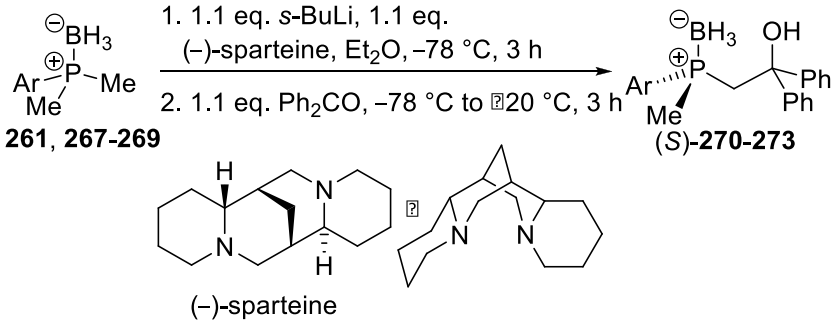
Electrophile	E	Yield (%)[a]
Me_3SiCl	Me_3Si	100
Ph_2CO	$Ph_2C(OH)$	94
$(MeO)_2CO$	(MeO)CO	83
C_4H_9Br	C_4H_9	66

[a] Yield of **266** after purification by chromatography.

The most significant advance was the development of an asymmetric version of Imamoto's reaction. In 1995, Evans and co-workers reported the asymmetric synthesis of phosphine boranes using an enantioselective deprotonation approach.[93] Using the *s*-BuLi/(−)-sparteine complex, a range of dimethyl phosphines **261** and **267**-**269** was lithiated and subsequent electrophilic trapping with benzophenone gave hydroxy phosphine boranes (*S*)-**270**-**273** in >89:11 er (Table 3.4). For example, lithiation/trapping of *ortho*-tolyldimethylphosphine

borane **268** gave hydroxy phosphine borane (*S*)-**272** in 84% yield and 93.5:6.5 er (entry 3).

Table 3.4: Asymmetric lithiation/trapping of dimethyl phosphine boranes

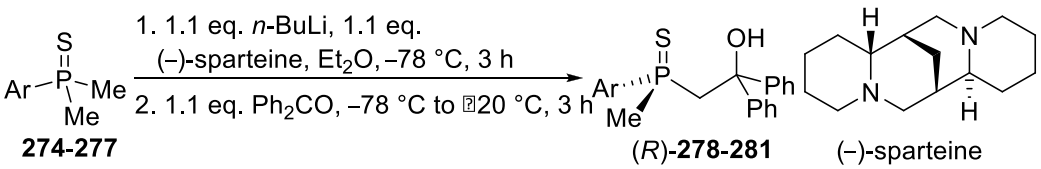


Entry	Compound	Ar	Product	Yield (%)	er (*S*:*R*)[b]
1	**261**	Ph	(*S*)-**270**	88	89.5:10.5
2	**267**	*o*-$MeOC_6H_4$	(*S*)-**271**	81	91.5:8.5
3	**268**	*o*-MeC_6H_4	(*S*)-**272**	84	93.5:6.5
4	**269**	1-Naphthyl	(*S*)-**273**	86	91:9

[a] Yield of (*S*)-**271-274** after purification by chromatography. [b] The er was determined by CSP-HPLC.

Evans and co-workers also studied the asymmetric lithitation/trapping of dimethyl phosphine sulfides. In these cases, higher enantioselectivity was obtained using *n*-BuLi rather than *s*-BuLi. Using the *n*-BuLi/(−)-sparteine complex, hydroxy phosphine sulfides (*R*)-**278-281** were isolated in 79-94% yield with up to 90:10 er (Table 3.5). Evans' work suggested that the phosphine boranes were superior substrates to the analogous phosphine sulfides, generating products with higher enantioselectivity. For example, *ortho*-tolyldimethyl phosphine borane **268** gave hydroxy phosphine borane (*S*)-**272** in 84% yield with 93.5:6.5 er (Table 3.5, entry 3). In comparison, phosphine sulfide adduct (*R*)-**280** was obtained in 79% yield with a lower 89.5:10.5 er (Table 3.5, entry 3).

Table 3.5: Asymmetric lithiation/trapping of dimethyl phosphine sulfides

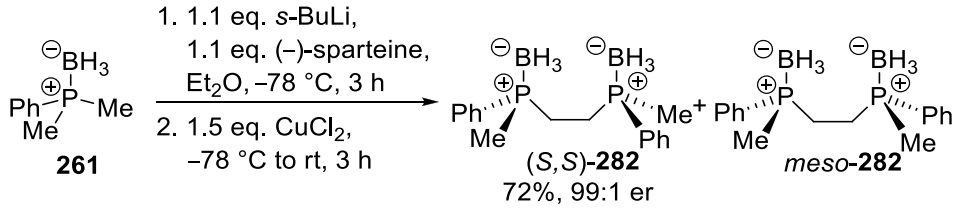


Entry	Compound	Ar	Product	Yield (%)[a]	er (*R*:*S*)[b]
1	**274**	Ph	(*R*)-**278**	94	89:11
2	**275**	*o*-$MeOC_6H_4$	(*R*)-**279**	83	88:12
3	**276**	*o*-MeC_6H_4	(*R*)-**280**	79	89.5:10.5
4	**277**	1-Naphthyl	(*R*)-**281**	80	80:20

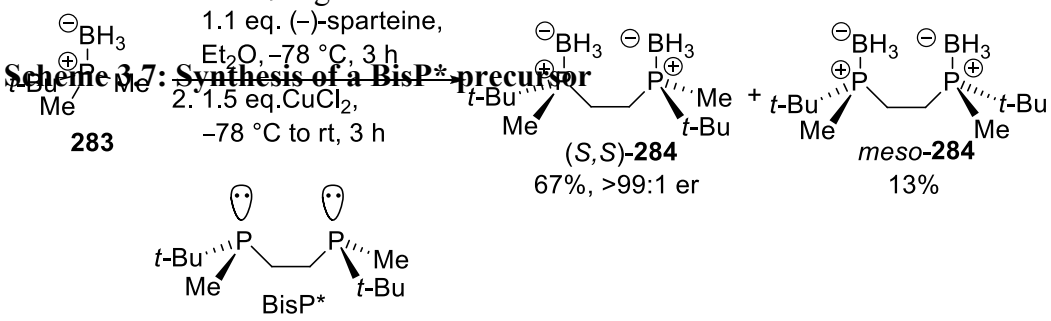
[a] Yield of (*S*)-**278-281** after purification by chromatography. [b] The er was determined by CSP-HPLC.

Evans and co-workers also investigated an oxidative coupling approach for the synthesis of bisphosphines. The original oxidative coupling method was developed by Mislow.[97] Thus, lithiation of phosphine borane **261** using *s*-BuLi/(–)-sparteine, followed by coupling of two lithiated phosphine borane intermediates using a copper(II) salt resulted in the formation of bisphosphine borane (*S*,*S*)-**282** in 72% yield with 99:1 er, together with some *meso*-**282** (Scheme 3.6). As shown in Table 3.4, the lithiation of phosphine borane **261** using *s*-BuLi/(–)-sparteine gives 89.5:10.5 er (Table 3.4, entry 1). The enantioselectivity enhancement upon dimerisation to give (*S*,*S*)-**282** in 99:1 er is due to most of the minor lithiated species being converted into *meso*-**282**.

Scheme 3.6: Oxidative coupling of a lithiated phosphine borane



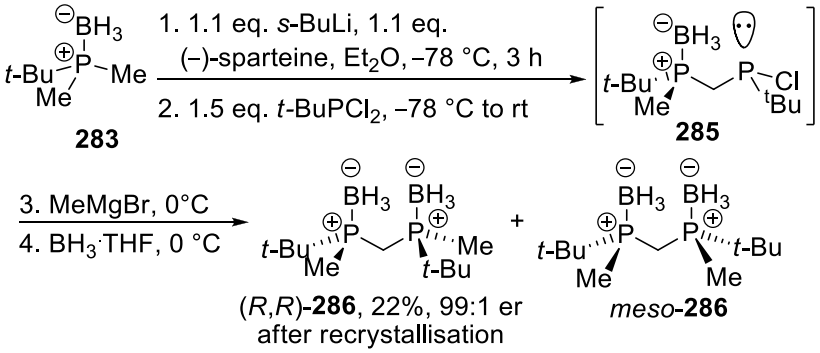
Following Evans' pioneering work, Imamoto and co-workers applied the lithiation-dimerisation procedure to the synthesis of several ethylene-bridged diphosphines known as BISP* ligands.[98,95] These exhibited excellent enantioselectivity in the asymmetric hydrogentaion of α-dehydroamino acid derivatives and other catalytic asymmetric reactions. For example, phosphine borane **283** was lithiated using *s*-BuLi/(−)-sparteine and then dimerised with $CuCl_2$ to give the bisphosphine borane (*S*,*S*)-**284** in 67% yield and >99:1 er together with a 13% yield of *meso*-**284** (Scheme 3.7). Phospine borane (*S*,*S*)-**284** was then treated with excess amine to remove the borane group to give BisP*, a useful chiral bidentate ligand.



Scheme 3.7: Synthesis of a BisP* precursor

Imamoto has also designed and synthesised methylene-bridged diphosphines known as MiniPHOS ligands.[99, 100] For example, phosphine borane **283** was lithiated using *s*-BuLi/(−)-sparteine and trapped with *t*-BuPCl_2 to provide intermediate **285**. Then, nucleophilic displacement of the other chlorine using methylmagnesium bromide and borane protection gave (*R*,*R*)-**286** in 22% yield with 99:1 er after recrystallisation, together with *meso*-**286** (Scheme 3.8).

Scheme 3.8: Synthesis of a MiniPHOS precursor

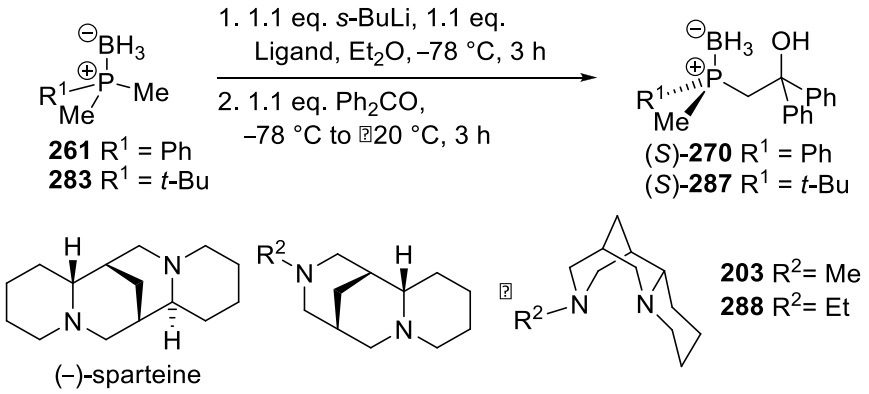


The asymmetric lithiation of phosphine boranes and phosphine sulfides using *s*-BuLi/(–)-sparteine gives phosphines in only one enantiomeric series. Hence, Kann and co-workers investigated the use of other chiral diamine ligands, such as (+)-sparteine surrogate **203** and diamine **288**, in the asymmetric lithiation reaction of phosphine boranes (Table 3.6).[101] Diamine **203** (99:1 er) can be synthesised following a procedure developed by our group, from (–)-cytisine, which was isolated from the seeds of the *Laburnum anagyroides* tree.[102]

Phenyldimethylphosphine borane **261** was lithiated using *s*-BuLi/diamine **203** and trapped with benzophenone to give hydroxy phosphine borane (*R*)-**270** in 89% yield with 84:16 er (Table 3.6, entry 3). In comparison, the corresponding reaction using (–)-sparteine gave (*S*)-**270** in 87% yield with 89:11 er (entry 1). In a similar fashion, *t*-butyldimethylphosphine borane **283** and diamine **203** gave (*R*)-**287** in 78% yield with 96:4 er (entry 4). When (–)-sparteine was used, hydroxy phosphine borane (*S*)-**287** was isolated in 83% yield with 88:12 er (entry 2). Diamine **288** was also synthesised and the enantioselectivity in the corresponding reactions were also measured (entries 5 and 6). It was proposed that increasing the steric bulk of the nitrogen substituent might provide a better mimic for (–)-sparteine, and thus increase the enantioselectivity. Use of *s*-BuLi/*N*-ethyl diamine **288** gave comparable results to that obtained with

(−)-sparteine. It can be concluded that diamine **203** is the best sparteine surrogate for the asymmetric lithiation of phosphine boranes.

Table 3.6: Lithiation of phosphine boranes with different diamine ligands



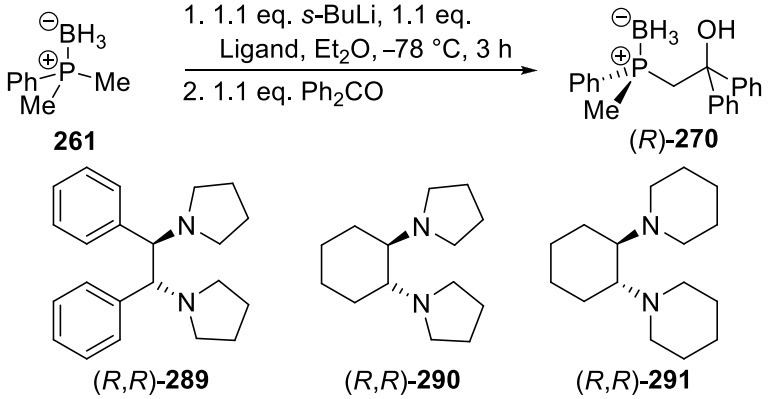
Entry	Ligand	R^1	Yield (%)[a]	er (*S*:*R*)[b]
1	(−)-sparteine	Ph	87	89:11
2	(−)-sparteine	*t*-Bu	83	88:12
3	**203**	Ph	89	16:84
4	**203**	*t*-Bu	78	4:96
5	**288**	Ph	82	28.5:81.5
6	**288**	*t*-Bu	72	12.5:87.5

[a] Yield of (*S*)-**270** and (*S*)-**287** after purification by chromatography. [b] The er was determined by CSP-HPLC.

Kann and co-workers also investigated a series of chiral diamines that are not derived from (−)-cytisine.[101] Representative examples are shown in Table 3.7. Deprotonation of phosphine borane **261** in the presence of *s*-BuLi/diamine (*R*,*R*)-**289** followed by electrophilic trapping with benzophenone gave hydroxy phosphine borane (*R*)-**270** in 58.5:41.5 er (Table 3.7, entry 1). In the case of diamine (*R*,*R*)-**290**, hydroxy phosphine borane (*R*)-**270** was obtained in 76.5:23.5 er with a modest 42% yield (entry 2). This is the best result for a

non-cytisine-derived diamine ligand. In comparison, the related diamine (*R*,*R*)-**291** gave neither high yield nor high enantioselectivity (entry 3).

Table 3.7: Lithiation of phenyl phosphine borane with different diamine ligands

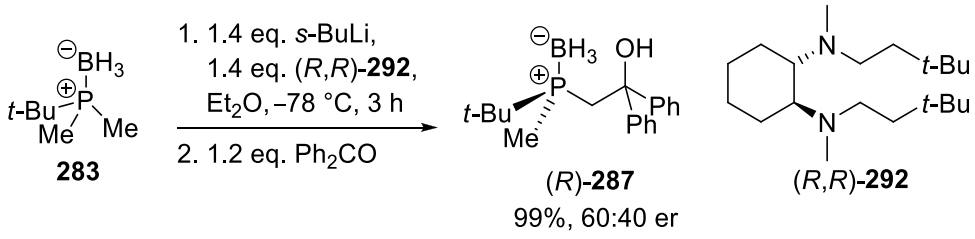


Entry	Ligand	Yield (%)[a]	er (*R*:*S*)[b]
1	(*R*,*R*)-**289**	69	58.5:41.5
2	(*R*,*R*)-**290**	42	76.5:23.5
3	(*R*,*R*)-**291**	28	52.5:47.5

[a] Yield of (*S*)-**270** after purification by chromatography. [b] The er was determined by CSP-HPLC.

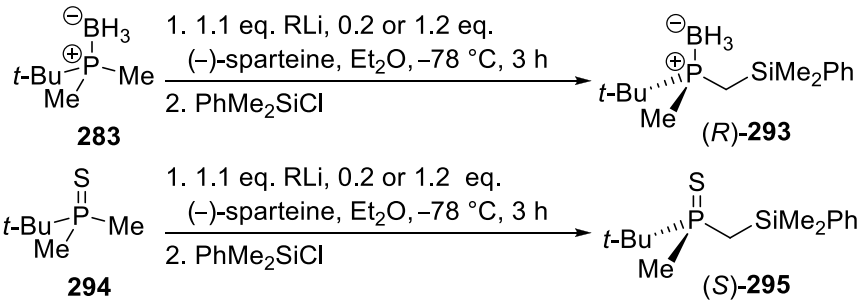
Our group has synthesised a number of cyclohexyl-derived diamines and (*R*,*R*)-**292** was tested in the asymmetric lithiation-trapping of phosphine borane **283**.[103] Thus, phosphine borane **283** was lithiated using *s*-BuLi/(*R*,*R*)-**292** in Et_2O at −78 ºC for 3 h. The intermediate was then trapped with benzophenone to furnish hydroxyl adduct (*R*)-**287** in 99% yield with 60:40 er (Scheme 3.9). Thus, diamine (*R*,*R*)-**292** gives lower enantioselectivity than Kann's best diamine (*R*,*R*)-**290**.

Scheme 3.9: Lithiation/trapping of *t*-butyl phosphine borane



Our group has also investigated the catalytic asymmetric desymmetrisation of phosphine borane **283** and phosphine sulfide **294** as a route to *P*-stereogenic compounds.[104] In this study, the catalytic performance of (–)-sparteine was investigated. A selection of results is shown in Table 3.8. Under stoichiometric conditions, using *s*-BuLi and (–)-sparteine (1.2 eq.) and trapping with phenyldimethylsilyl chloride, silyl phosphine borane (*R*)-**283** was formed in 92:8 er (entry 1). This is a higher enantioselectivity than silyl phosphine sulfide (*S*)-**295** which was formed in 84:16 er (entry 2). Under catalytic conditions (0.2 equiv. of diamine), there is a reduction in enantioselectivity for silyl phosphine borane (*R*)-**293** (entry 3). In contrast, a significant decrease in enantioselectivity for silyl phosphine sulfide (*S*)-**295** (60:40 er) was observed compared to using the stoichiometric conditions (entry 4).

Table 3.8: Deprotonation with different alkyllithum/(−)-sparteine bases



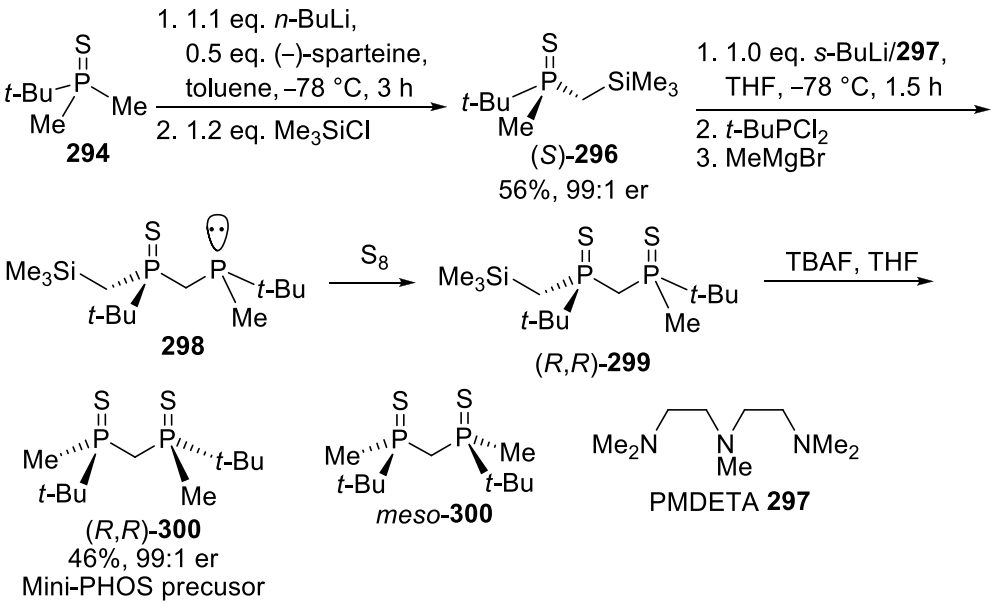
Entry	RLi	Equiv.	Product	Yield (%)[a]	er[b]
1	*s*-BuLi	1.2	(*R*)-**293**	74	92:8
2	*s*-BuLi	1.2	(*S*)-**295**	74	84:16
3	*s*-BuLi	0.2	(*R*)-**293**	76	74:26
4	*s*-BuLi	0.2	(*S*)-**295**	75	60:40
5	*n*-BuLi	1.2	(*R*)-**293**	76	89:11
6	*n*-BuLi	1.2	(*S*)-**295**	88	88:12
7	*n*-BuLi	0.2	(*R*)-**293**	21	84:16
8	*n*-BuLi	0.2	(*S*)-**295**	82	83:17

[a] Yield of (*R*)-**293** and (*S*)-**295** after purification by chromatography. [b] The er was determined by CSP-HPLC.

When the less basic base *n*-BuLi was used under stoichiometric conditions, both phosphine borane **283** and phosphine sulfide **294** were deprotonated and trapped to give products with high yield and good enantioselectivity: (*R*)-**293** (76% yield, 89:11 er, entry 5) and (*S*)-**295** (88% yield, 88:12 er, entry 6) respectively. In the corresponding catalytic reaction, silyl adduct (*R*)-**293** was isolated in similar er, but the yield was significantly lower (entry 7), indicating there was no catalytic turn-over. In contrast, silyl phosphine sulfide (*S*)-**295** was obtained in an impressive 82% yield and 83:17 er in the catalytic reaction (entry 8).

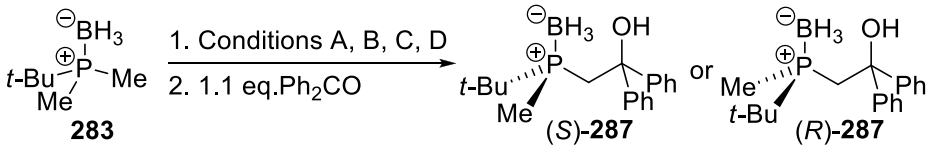
In 2009, our group studied the regioselective lithiation of silyl phosphine sulfides.[94] This methodology allows access to *P*-stereogenic compounds with the opposite configuration to that obtained by direct lithiation-trapping using organolithium reagents and (−)-sparteine. The synthetic utility was demonstrated by the synthesis of (*R*,*R*)-**300**, a Mini-PHOS precursor. First, enantioenriched silyl adduct (*S*)-**296** was prepared using the procedure reported previously.[104] Treatment of phosphine sulfide **294** with *n*-BuLi/(−)-sparteine and subsequent trapping with trimethylsilyl chloride afforded silyl phosphine sulfide (*S*)-**296** in 56% yield and 99:1 er after recrystallization (Scheme 3.10). Next, regioselective lithiation of phosphine sulfide (*S*)-**296** on the less hindered methyl group with *s*-BuLi/PMEDA **297** and subsequent trapping with *t*-butylphosphine dichloride was carried out. Then, displacement of the remaining chloride substituent by addition of methylmagnesium bromide and phosphorus protection with sulfur provided silyl phosphine sulfide (*R*,*R*)-**299**. Finally, TBAF-mediated silyl deprotection yielded (*R*,*R*)-**300** in 46% yield and 99:1 er. *Meso*-**300** was not formed which contrasts with Imamoto's synthesis of the phosphine borane Mini-PHOS precursor.[98, 100]

Scheme 3.10: Regioselective lithiation/trapping of silyl phosphine sulfide



Recently, our group has also developed an alternative one-ligand catalytic asymmetric deprotonation procedure as a route to *P*-steroegenic bisphosphine ligands.[105] This protocol involves using a substoichiometric amount of diamine ligands with sequential additions of *s*-BuLi (Table 3.9). For example, phosphine borane **283** was added to a premixed solution of 0.2 eq. of *s*-BuLi/(–)-sparteine (in Et_2O at –78 ºC). After 36 min, two portions of 0.4 eq. of *s*-BuLi were added at 72 min intervals, which makes up to a total 3 h lithiation time before trapping with Ph_2CO. Hydroxy adduct (*S*)-**287** was isolated in 94% yield and 86:14 er (entry 3), which is comparable to the stoichiometric result (entry 1). A related protocol with 0.3 eq. of ligand gave the same enantioselectivity but a lower yield (entry 4).

Table 3.9: Asymmetric lithiation/trapping of phosphine borane 283



Conditions: A: 1.1 eq. *s*-BuLi, 1.0 eq. diamines, Et_2O, −78 ºC, 3 h

B: 1.1 eq. *s*-BuLi, 0.2 eq. diamines, Et_2O, −78 ºC, 3 h

C: (i) 0.2 eq. *s*-BuLi, 0.2 eq. diamines, Et_2O, −78 ºC, 36 min; (ii) 0.4 eq. *s*-BuLi, −78 ºC, 72 min; (iii) 0.4 eq. *s*-BuLi, −78 ºC, 72 min

D: (i) 0.3 eq. *s*-BuLi, 0.3 eq. diamines, Et_2O, −78 ºC, 36 min; (ii) 0.35 eq. *s*-BuLi, −78 ºC, 72 min; (iii) 0.35 eq. *s*-BuLi, −78 ºC, 72 min

Entry	Diamine	Equiv. of	Conditions	Yield	er (*S*:*R*)[b]
1	(−)-sparteine	1.0	A	72	95:5
2	(−)-sparteine	0.2	B	64	80:20
3	(−)-sparteine	0.2	C	94	86:14
4	(−)-sparteine	0.3	D	89	86:14
5	Diamine **203**	1.0	A	75	8:92
6	Diamine **203**	0.3	D	83	9:91

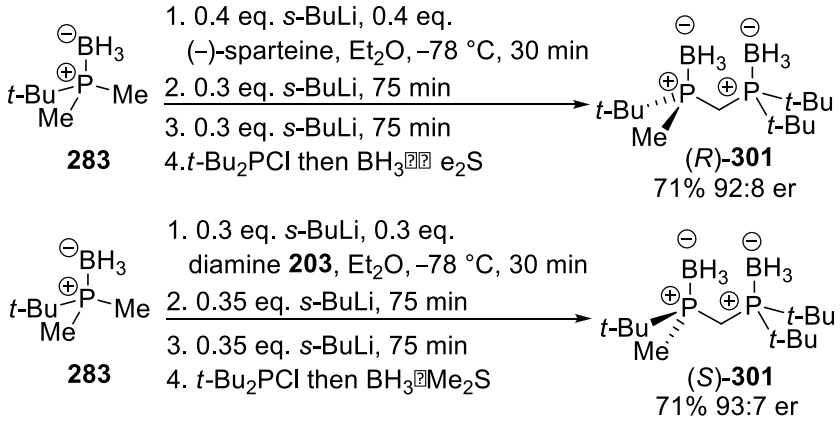
[a] Yield of (*S*)-**287** and (*R*)-**287** after purification by chromatography. [b] The er was determined by CSP-HPLC.

The reaction procedure was also performed with diamine **203**. Since *s*-BuLi/diamine **203** deprotonates phosphine borane **283** faster than *s*-BuLi/(−)-sparteine,[106] use of 0.3 eq. of diamine **203** with 0.3 eq. of *s*-BuLi, followed by sequential addition of two portions of 0.35 eq. of *s*-BuLi before trapping with benzophenone gave hydroxy adduct (*R*)-**287** in 91:9 er (entry 6).

This is almost the same result as that obtained with a stoichiometric amount of diamine **203** (entry 5).

Finally, the sequential catalytic lithiation-trapping procedure was applied to the synthesis of some *P*-stereogenic ligands. As an example, phosphine borane **283** was lithiated using 0.4 eq. of *s*-BuLi/(–)-sparteine and sequential addition of *s*-BuLi, followed by trapping with di-*t*-butylphosphine chloride and then borane protection gave 'trichickenfootphos' precursor (*R*)-**301** in 71% yield and an excellent 92:8 er (Scheme 3.11). In the same way, the opposite enantiomer (*S*)-**301** was obtained in 71% yield and 93:7 er by using 0.3 eq. of diamine **203**.

Scheme 3.11: Syntheses of 'trichikenfootphos' precursors



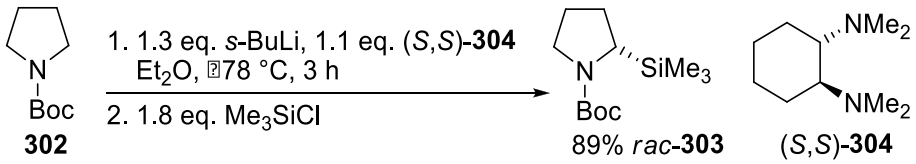
In summary, desymmetrisation followed by electrophilic trapping of tertiary dimethyl phosphines has been employed as a route to a range of *P*-stereogenic phosphines. Both (–)-sparteine and diamine **203** are efficient chiral diamine ligands and they facilitate access to *P*-stereogenic phosphines with opposite configuration.

3.2.2 Selection and Synthesis of Suitable Chiral Diamines

To study the asymmetric lithiation of phosphine boranes, three chiral diamine ligands were prepared. The cyclohexyl-derived diamine ligand, (*S*,*S*)-TMCDA

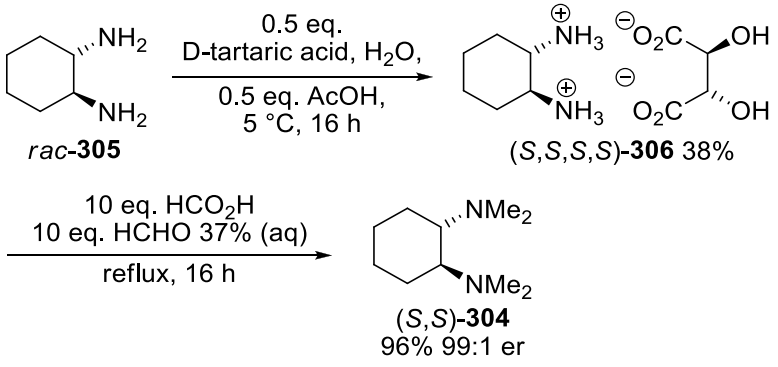
(*S*,*S*)-**304**, was chosen as one of the ligands because it is easily synthesised and its use in the lithiation-trapping of *N*-Boc pyrrolidine **302** is known.[107] Although TMCDA (*S*,*S*)-**304** resulted in racemic silyl product *rac*-**303** when used in the lithiation of *N*-Boc pyrrolidine **302**, it had not previously been tested in the asymmetric lithiation of phosphine boranes (Scheme 3.12).

Scheme 3.12: Lithiation/trapping of *N*-Boc pyrrolidine 302



Starting from racemic *trans*-cyclohexane-1,2-diamine **305**, resolution using D-tartaric acid and acetic acid gave salt (*S*,*S*,*S*,*S*)-**306**, which was isolated in 38% yield (maximum 50%) by filtration. Then, Eshweiler-Clarke methylation of salt (*S*,*S*,*S*,*S*)-**306** using formic acid and formaldehyde gave (*S*,*S*)-**304** in 96% yield. In this way, 3 g of TMCDA (*S*,*S*)-**304** was prepared in 36% yield over the two steps (Scheme 3.13).

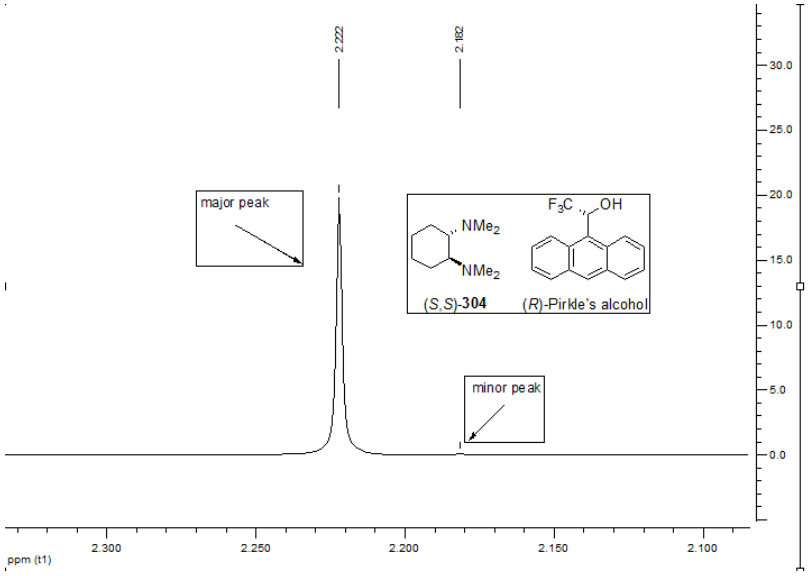
Scheme 3.1:3 Synthesis of diamine (*S*,*S*)-304



The enantiomeric ratio of TMCDA (*S*,*S*)-**304** was determined by chiral shift ^{1}H NMR spectroscopy in the presence of 2,2,2-trifluoro-1-(9-anthryl)ethanol (Pirkle's alcohol).[103] This works by the formation of diastereomeric complexes

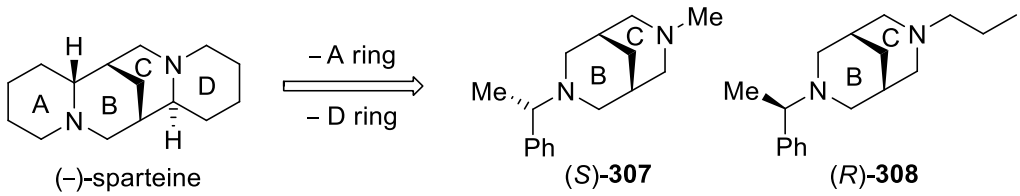
between the amine and the alcohol. As a result, two peaks in the ^{1}H NMR spectrum are observed for the diastereomeric complexes. The key peak for chiral shift ^{1}H NMR analysis of TMCDA is the NMe singlet observed at 2.22 ppm (major) and at 2.18 ppm (minor). Integration of the major and minor peaks gives a ratio which is indicative of the enantiomeric ratio of the product. In this way, the enantiomeric ratio of TMCDA (*S*,*S*)-**304** with (*R*)-Pirkle's alcohol was found to be 99:1 er (Figure 3.5).

Figure 3.5: ^{1}H NMR spectral analysis of (*S*,*S*)-304



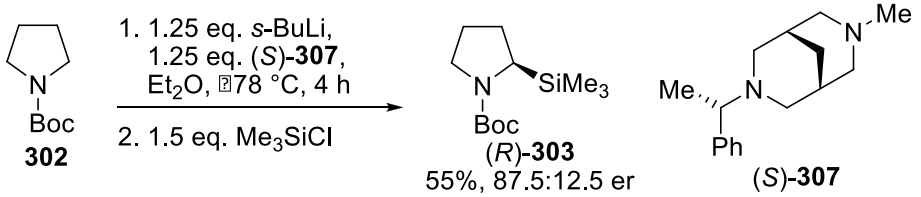
Bispidines contain the core diaza [3.3.1] ring system of (−)-sparteine and bispidines such as (*S*)-**307** and (*R*)-**308** derived from α-methylbenzylamine (Figure 3.6) were also an interesting class of ligands for our study in the asymmetric lithiation. It was hoped that the [3.3.1] ring structure would introduce rigidity and reduce the conformational variability in the transition state. The bispidine structure in (*S*)-**307** and (*R*)-**308** mimic the B and C rings in (−)-sparteine. Therefore, it was thought that this type of diamine ligand could also prove to be reactive and enantioselective when used in Evans' procedure.

Figure 3.6: Structures of diamines (*S*)-307 and (*R*)-308



Bispidine (*S*)-**307** has previously been used in the lithiation of *N*-Boc pyrrolidine **302** and high enantioselectivity of the product was obtained (Scheme 3.14).[107] Asymmetric deprotonation of *N*-Boc pyrrolidine **302** using *s*-BuLi/(*S*)-**307** and subsequent trapping with tetramethylsilyl chloride afforded silyl adduct (*R*)-**303** in 55% yield and 87.5:12.5 er. It would be interesting to discover whether diamines (*S*)-**307** and (*R*)-**308** (previously unstudied) would introduce high enantioselectivity in the lithiation-trapping of phosphine boranes. Hence, diamines (*S*)-**307** and (*R*)-**308** became target ligands.

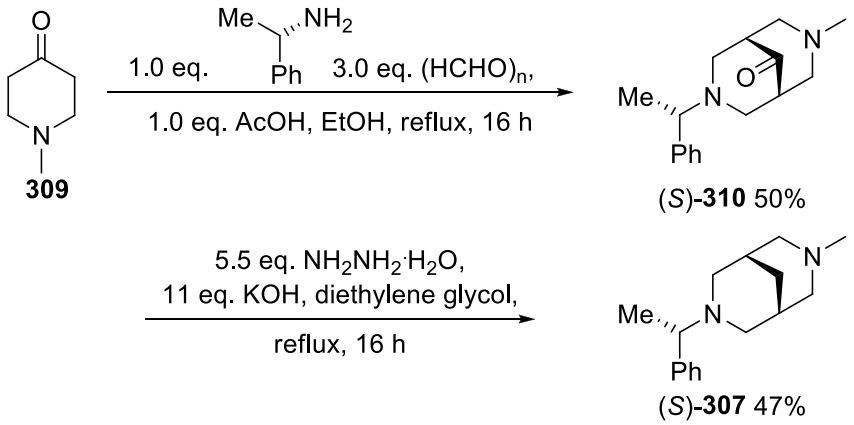
Scheme 3.14: Lithiation/trapping of *N*-Boc pyrrolidine 302



Following a procedure reported by Beak, a double Mannich reaction using freshly distilled *N*-Me-piperidone **309**, (*S*)-α-methylbenzylamine and formaldehyde gave bispidone (*S*)-**310** in 50% yield after Kugelrohr distillation (Scheme 3.15). A modified Wolff-Kishner reduction procedure was then used to produce bispidine (*S*)-**307**.[108] Bispidone (*S*)-**310** was refluxed with hydrazine monohydrate and 50% aqueous KOH solution in diethylene glycol to give bispidine (*S*)-**307** in 47% yield (Scheme 3.15). During the work-up, it was important to note that the reaction mixture was cooled to ~60 ºC and then transferred to a separation funnel before water was added. This is because a

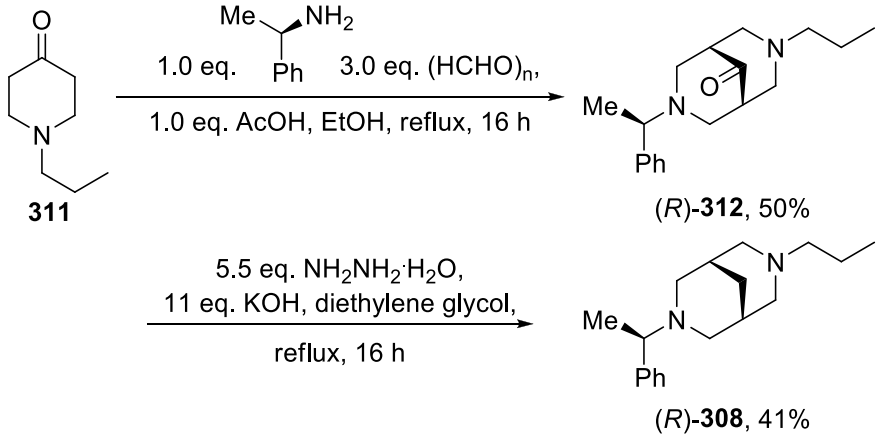
lower temperature results in a viscous reaction mixture which would be very difficult to handle when performing the work-up.

Scheme 3.15: Synthesis of diamine (*S*)-307



In the same way, the *n*-propyl analogue, bispidone (*R*)-**312**, was prepared in 50% yield from *N*-*n*-propyl-piperidone **311** and (*R*)-α-methylbenzylamine. Bispidine (*R*)-**308** was then prepared in 41% yield by Wolff-Kishner reduction of bispidone (*R*)-**312** (Scheme 3.16).

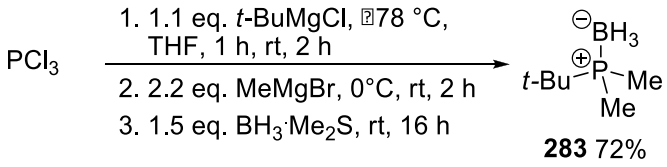
Scheme 3.16: Synthesis of diamine (*R*)-308



3.2.3 Investigation of Chiral Diamines in the Lithiation-Trapping of a Phosphine Borane

Since some of the best *P*-stereogenic ligands such as Mini-PHOS[99, 109] and QuinoxP*[110] contain *t*-Bu and Me groups on the phosphorus atom, *t*-butyldimethyl phosphine borane **283** was selected as a suitable substrate for an investigation of asymmetric lithiation using *s*-BuLi and new chiral diamines. *t*-Butyldimethyl phosphine borane **283** was synthesised using a method reported by Imamoto and co-workers.[98] Sequential nucleophilic addition of *t*-butyl magnesium chloride and methyl magnesium bromide to phosphorus trichloride gave the crude trialkyl phosphine. Subsequent treatment with borane dimethyl sulfide complex gave phosphine borane **283** in 72% yield on a 5 g scale (Scheme 3.17).

Scheme 3.17: Synthesis of *t*-butyl phosphine borane



To investigate the reactivity and enantioselectivity of the chiral diamine ligands in the *s*-BuLi/diamine-mediated lithiation/trapping of phosphine borane **283**, it was first necessary to identify a suitable electrophile which would give a product that could be easily purified by column chromatography. In addition, the electrophile should also introduce a strong chromophore into the molecule which would facilitate the determination of er using chiral stationary phase HPLC (CSP-HPLC) equipped with a UV/Vis diode array detector.

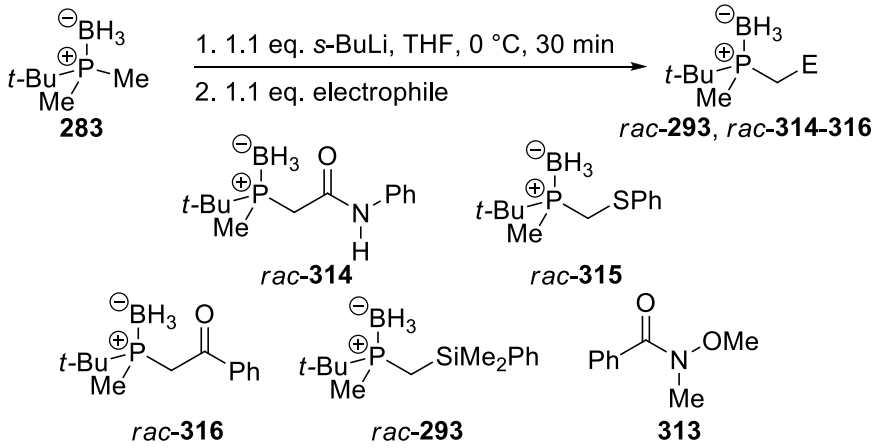
In Evans' procedure, benzophenone was used as the electrophile to give hydroxy phosphine borane (*S*)-**270** in 88% yield and 89.5:10.5 er (See Table 3.4, entry 1).

However, Kann and co-workers have found that benzophenone could also be reduced in the reaction to give benzhydrol, which cannot be easily separated from the desired products. It also co-elutes on CSP-HPLC with one of the enantiomers of hydroxy phosphine borane **270**. Hence, determination of the enantioselectivity from lithiation/trapping with benzophenone by CSP-HPLC is potentially unreliable.[101] We therefore decided not to use benzophenone for our studies.

Indentification of the best electrophile was carried out using a racemic lithiation protocol. To start with, the lithiation/trapping of phosphine borane **283** using phenyl isocyanate, diphenyl disulfide, Weinreb amide **313** and dimethylphenylsilyl chloride were investigated. Thus, racemic lithiation of phosphine borane **283** was carried out using 1.1 eq. of *s*-BuLi in THF at 0 ºC for 30 min. This was followed by trapping with different electrophiles (Table 3.10). Using phenyl isocyanate and diphenyl disulfide as electrophiles, none of the desired products *rac*-**314** and *rac*-**315** were formed (Table 3.10, entries 1 and 2). On inspection of the ^{1}H NMR spectra of the crude products, both reactions resulted in decomposition. It was not clear why these electrophiles failed to give any product.

Lithiation and trapping with Weinreb amide **313** gave phosphine ketone *rac*-**316** in 67% yield after purification by column chromatography (entry 3). The enantiomers of ketone *rac*-**316** were successfully resolved on CSP-HPLC using chiral OD column. Dimethylphenylsilyl chloride was also used as an electrophile for the lithiation of phosphine borane **283** and silyl adduct *rac*-**293** was isolated in 60% yield (entry 4). However, the separation of silyl phosphine borane *rac*-**293** on CSP-HPLC was poor and the peaks overlapped. Therefore, Weinreb amide **313** was chosen as the electrophile.

Table 3.10: Lithiation/trapping with different electrophiles

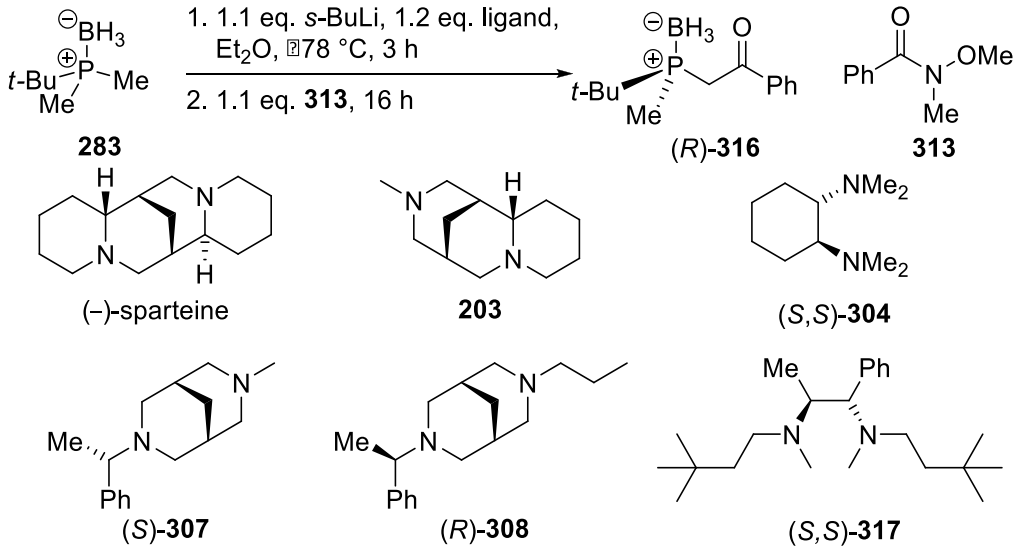


Entry	Electrophile	Product	Yield (%)[a]
1	PhNCO	*rac*-**314**	--
2	PhSSPh	*rac*-**315**	--
3	**313**	*rac*-**316**	67
4	$Me_2PhSiCl$	*rac*-**293**	60

[a] Yield after purification by chromatography.

Having indentified a suitable electrophile for the racemic lithiation of phosphine borane **283** using *s*-BuLi in THF, we then investigated the asymmetric lithiation using different chiral diamines. Lithiation of phosphine borane **283** was carried out using 1.1 eq. of *s*-BuLi in the presence of 1.2 eq. of the chiral diamine ligands in Et_2O at −78 ºC. In general, phosphine borane was lithiated for 3 h before electrophilic quenching with Weinreb amide **313**. The crude product was purified by column chromatography and the enantiomer ratio of the product was determined by CSP-HPLC on chiral OD column. The results of this study are presented in Table 3.11.

Table 3.11: Lithiation/trapping with different diamine ligands



Entry	Diamine	Yield (%)[a]	er (*R*:*S*)[b]
1	(−)-sparteine	56	9:91
2	**203**	65	91:9
3	(*S*,*S*)-**304**	50	78:22
4	(*S*)-**307**	41	61:39
5	(*R*)-**308**	33	45:55
6	(*S*,*S*)-**317**[c]	67	45:55

[a] Yield after purification by chromatography. [b] er determined by CSP-HPLC on Daicel Chiracel OD column. [c] (*S*,*S*)-**317** was synthesised by a member of the group.

Lithiation of phosphine borane **283** using *s*-BuLi/(−)-sparteine and trapping with Weinreb amide **313** gave ketone adduct (*S*)-**316** in 56% yield and 91:9 er (Table 3.11, entry 1). Similarly, with diamine **203** as a chiral ligand, ketone adduct (*R*)-**316** was isolated in 65% yield and 91:9 er (entry 2). The asymmetric lithiation of phosphine borane **283** with (−)-sparteine and diamine **203** is well-studied and our ers are consistent with those previously reported.[16,21] These two results provided the benchmark for the new chiral diamines investigated in this project.

In the corresponding reaction using *s*-BuLi/diamine (*S*,*S*)-**304**, phosphine borane **283** was lithiated and trapped to furnish (*R*)-**316** in 50% yield and 78:22 er (entry 3). This reaction was repeated several times to show that it was reproducible. The er is slightly higher than that shown by Kann and co-workers with diamine (*R*,*R*)-**290** (76.5:23.5 er), which is also a cyclohexyl-based diamine ligand and trapping with benzophenone (see Table 3.7, entry 2). In contrast, when *s*-BuLi/(*S*,*S*)-**304** was used in the lithiation of *N*-Boc pyrrolidine **302**, silyl adduct **303** was formed with 90% conversion, but no enantioselectivity in the product was observed (See Scheme 3.12).[107]

The deprotonation of phosphine borane **283** using *N*-Me bispidine (*S*)-**307** afforded phosphine ketone (*R*)-**316** in 41% yield and 61:39 er (entry 4). In contrast, Beak showed that *s*-BuLi/(*S*)-**307** provided silyl adduct (*R*)-**303** in 87.5:12.5 er (See Scheme 3.14).[107] With *N*-Pr diamine (*R*)-**308**, both the yield and enantioselectivity were disappointing: 33% yield of (*S*)-**316** with 55:45 er (entry 5). The enantiomeric induction of phosphine ketone (*R*)-**316** is the same using (*S*,*S*)-**317** as the chiral ligand, but with a higher yield (67%) compared with diamine (*R*)-**308** (entry 6).

In summary, it was shown that using (−)-sparteine or diamine **203** as a ligand in the asymmetric lithiation of phosphine borane **283**, ketone adduct **316** can be accessed with high enantioselectivity (91:9 er) in both configurations. Diamine (*S*,*S*)-**304** was found to function as an effective (+)-sparteine surrogate and lithiation of phosphine borane **283** using *s*-BuLi/diamine (*S*,*S*)-**304** gave ketone adduct (*R*)-**316** in 78:22 er, the best result of the non-sparteine-like ligands that were tested. Although diamine ligand (*S*,*S*)-**304** provided substantial enantioselectivity in the lithiation of phosphine borane **283** and trapping with

Weinreb amide **313**, (−)-sparteine or diamine **203** are still the best ligandsgiving both high yield and high enantioselectivity.

3.3 Asymmetric Lithiation and Ring-Closing Metathesis Route to *P*-Stereogenic Phosphine Heterocycles

3.3.1 Strategies for the Synthesis of *P*-Stereogenic Vinyl Phosphine Heterocycles

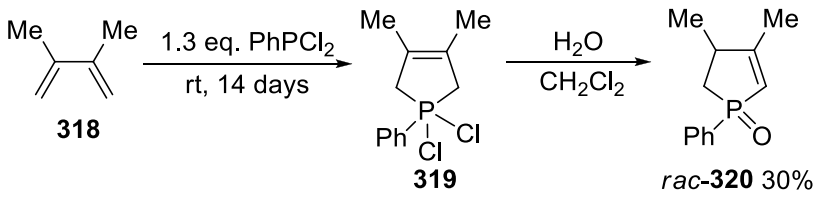
There are a number of methods for the synthesis of electronically and sterically diverse acyclic phosphine compounds.[111, 112] However, the development of synthetic routes to *P*-stereogenic phosphine heterocycles is not well-studied. To the best of our knowledge, there are no previous reports on the asymmetric synthesis of *P*-stereogenic vinyl heterocycles such as (*R*)-**258** and (*R*)-**259** (Figure 3.7).

Figure 3.7: *P*-Stereogenic phospholene boranes

(*R*)-**258** (*R*)-**259**

There are a limited number of routes for the synthesis of vinylic phospholenes in a racemic fashion. For example, 1,3-diene **318** and phenylphosphorus dichloride underwent a McCormac reaction[113] to provide cyclic phosphine intermediate **319**. Then, hydrolysis of **319** furnished the desired vinyl phospholene *rac*-**320** in 30% yield (Scheme 3.18).[114]

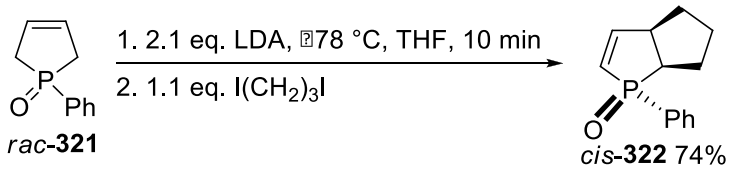
Scheme 3.18: Example of McCormac reaction



318 **319** *rac*-**320** 30%

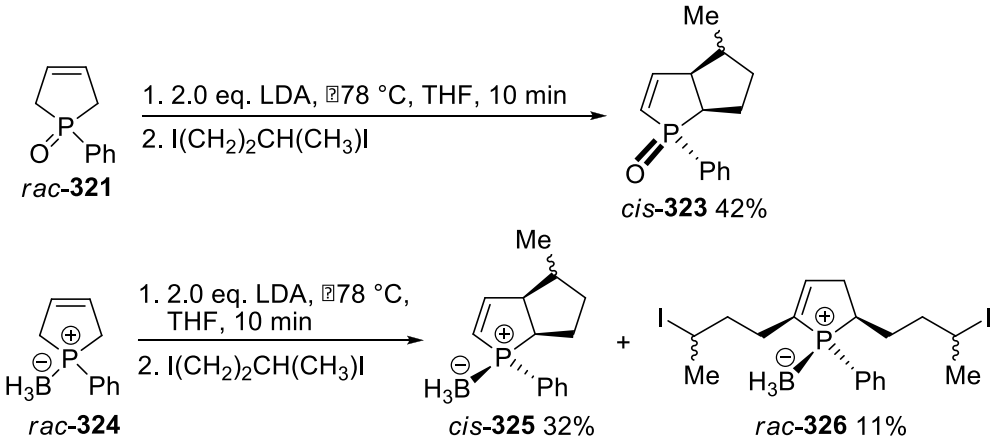
Pietrusiewicz and co-workers studied cyclopentannulation and alkylation of phospholene derivatives which led to the formation of vinylic phospholenes.[115, 116] For example, deprotonation of phosphine oxide *rac*-**321** (which could be made from diallylphenylphosphine oxide *via* ring-closing metathesis) using 2.0 eq. of LDA followed by trapping with diiodopropane furnished bicyclic vinyl phospholene *cis*-**322** in 74% yield (Scheme 3.19). Stereochemical assignment was made on the basis of nOe experiments and this indicated that the *cis*-fused ring system was formed exclusively.

Scheme 3.19: Alkylation of phosphine oxide *rac*-321



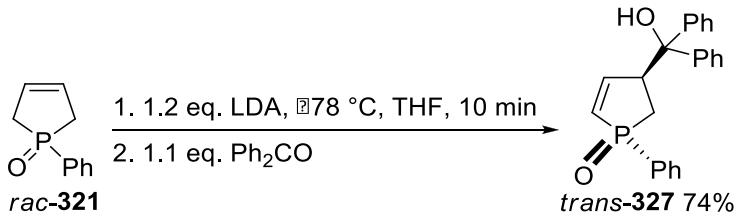
When 1,3-diiodobutane was used as the electrophile to diversify the substitution pattern of the annulated products, the reaction became less selective and monocyclic alkylated products were also observed (Scheme 3.20). With phosphine oxide *rac*-**321**, vinyl phospholene *cis*-**323** was formed in 42% yield. Under the same reaction conditions, the desired phosphine borane *cis*-**325** was formed in 32% yield, together with 11% of the dialkylated product *rac*-**326**. In addition, the bicyclic product could not be separated from the corresponding dialkylated derivatives by chromatography.

Scheme 3.20: Alkylations of phospholene derivatives



During the course of investigating the alkylation of phospholene derivatives, Pietrusiewicz and co-workers found that when benzophenone was used as an electrophile for the lithiated species obtained from phosphine oxide *rac*-**321**, the trapping was directed to the 3-position. Thus, phosphine oxide *rac*-**321** was treated with LDA and trapping with benzophenone afforded vinyl phospholene *trans*-**327** in 74% yield (Scheme 3.21). The stereochemical assignment was carried out using nOe experiments, and it indicated that the electrophile was added *trans* to the P-Ph group. Although this approach provided the desired vinylic phospholene structure, it is limited by substrate scope since when alkyl halides were used, the trapping occurred α to the phosphorus.

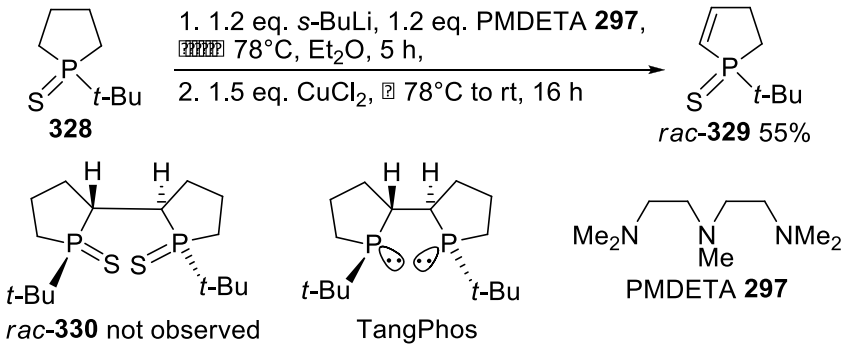
Scheme 3.21: Alkylation of phosphine oxide *rac*-321



The ligand TangPhos has been synthesised *via* the asymmetric lithiation of phospholene sulfide **328** and subsequent oxidative dimerisation using $CuCl_2$.[87]

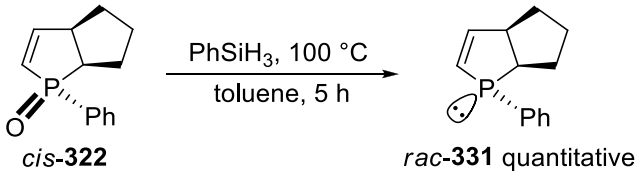
Our group investigated the dimerization process. On one single attempt, phospholene sulfide **328** was lithiated in a racemic fashion using *s*-BuLi/PMDETA at −78 ºC in Et_2O for 5 h, followed by the addition of $CuCl_2$ at −78 ºC. The reaction was allowed to warm to rt over 16 h. The desired dimerised product *rac*-**330** was not observed, but a vinylic phosphine sulfide *rac*-**329** was isolated in 55% yield (Scheme 3.22).[117] It was suggested that the formation of phospholene *rac*-**329** might arise from either an organocuprate-mediated process or a radical mechanism.

Scheme 3.22: Attempted Cu(II)-mediated dimerisation



There are two examples of the preparation of enantioenriched cyclic vinyl phosphines similar in structure to (*R*)-**258** and (*R*)-**259**, both of which were reported by Pietrusiewicz and co-workers.[118, 119] The first approach to obtain enantiomerically enriched bicyclic phospholene oxide used the classical resolution method.[118] Vinyl phosphine oxide *rac*-**322** was first synthesised using the pentannulation procedure described previously (See Scheme 3.19). Then, reduction of phosphine oxide *cis*-**322** with phenylsilane gave vinyl phosphine *rac*-**331** in quantitative yield (Scheme 3.23).

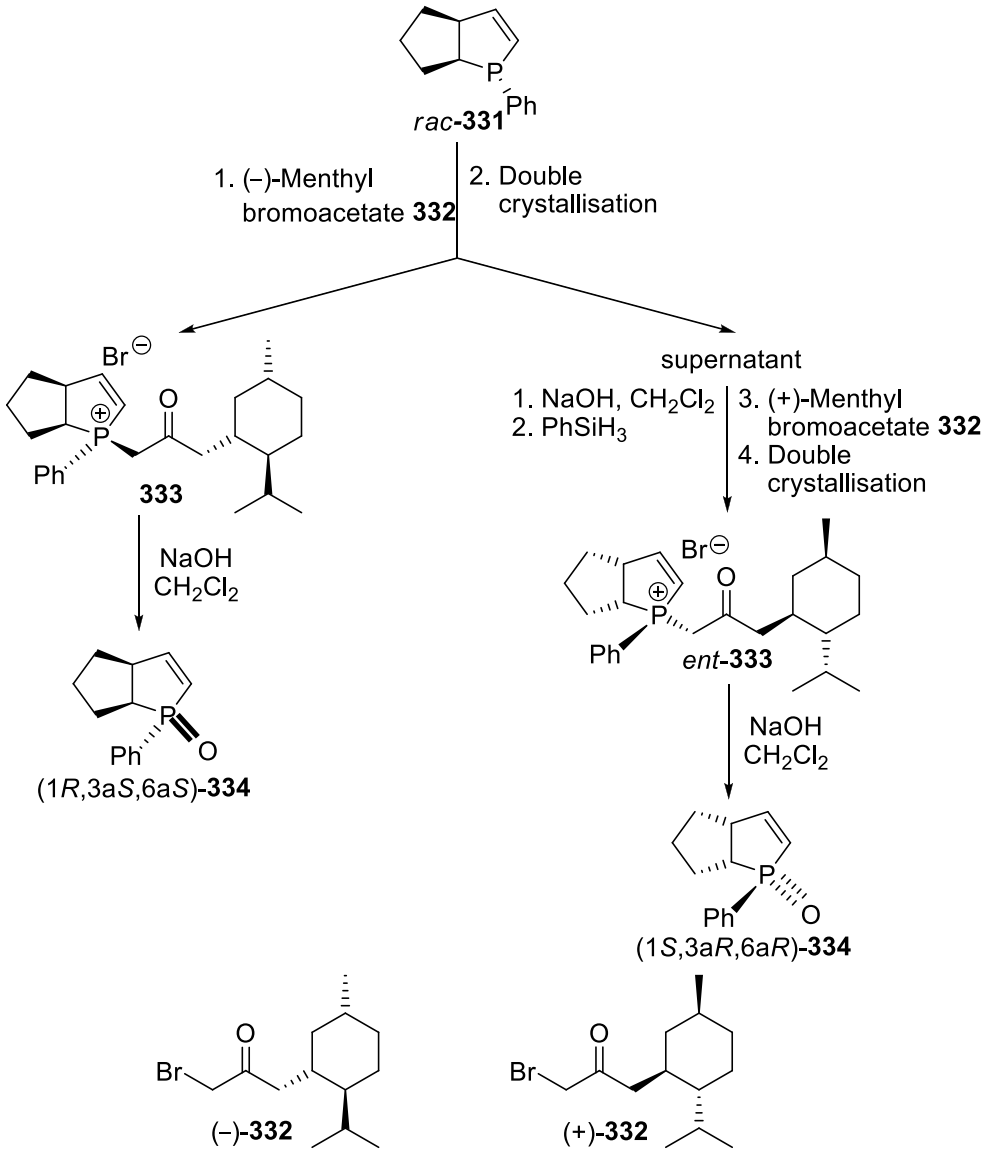
Scheme 3.23: Formation of phosphine heterocycle *rac*-331 *via* reduction



cis-**322** *rac*-**331** quantitative

For the resolution procedure, a solution of cyclic phosphine *rac*-**331** in ethyl acetate was treated with a solution of (−)-menthyl bromoacetate (−)-**332** in ethyl acetate to produce crystalline phosphonium bromides. Recrystallisation gave phosphonium bromide **333** as a single diastereoisomer. Phosphonium bromide **333** was then hydrolysed using sodium hydroxide to give phosphine oxide (1*R*,3a*S*,6a*S*)-**334** in 25% yield (out of a possible 50%) with >99:1 er. To access the enantiomer, phosphine oxide (1*S*,3a*R*,6a*R*)-**334**, the supernatant was hydrolysed to the phosphine oxide and reduced to the free phosphine. Resolution using (+)-menthyl bromoacetate gave phosphonium bromide *ent*-**333** in 37% yield with >99:1 er. This resolution procedure for isolating enantioenriched phosphine oxides allows access to both enantiomers. However, the methodology is inefficient as a number of steps are required and the overall yield is moderate.

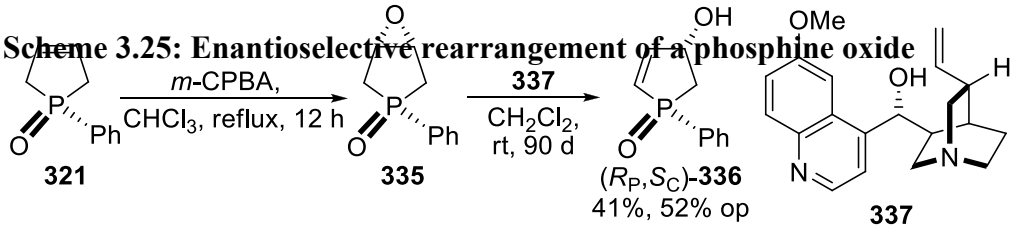
Scheme 3.24: Formation of enantiomeric phosphine oxide 334 *via* resolution



Pietrusiewicz and co-workers also investigated the chiral base-promoted enantioselective rearrangement of organophosphorus epoxides as an asymmetric route to phosphine heterocycles.[119] An extensive study of this reaction was carried out on phosphine oxide **321** and phosphine borane **338** using various chiral base systems such as *s*-BuLi/(–)sparteine and *Cinchona* alkaloids. It was found that the rearrangement generally afforded the desired hydroxy phospholene **336** or **339** in good yield but with moderate enantioselectivity. For

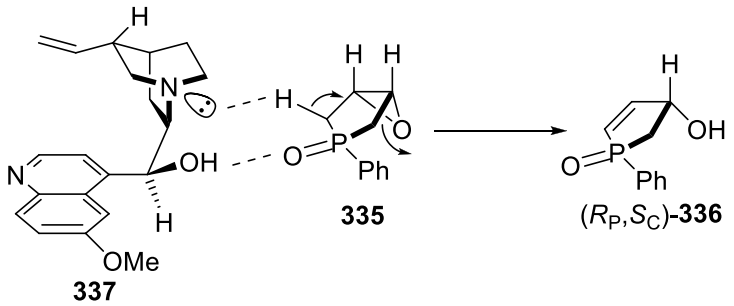
example, epoxide **335** was synthesised by diastereoselective epoxidation of phosphine oxide **321** using *m*-CPBA. Then, treatment of phosphine oxide **335** with quinidine at 20 ºC for 90 days(!) gave hydroxy phospholene oxide (R_P,S_C)-**336** in 41% yield, with 52% optical purity (Scheme 3.25).

Scheme 3.25: Enantioselective rearrangement of a phosphine oxide



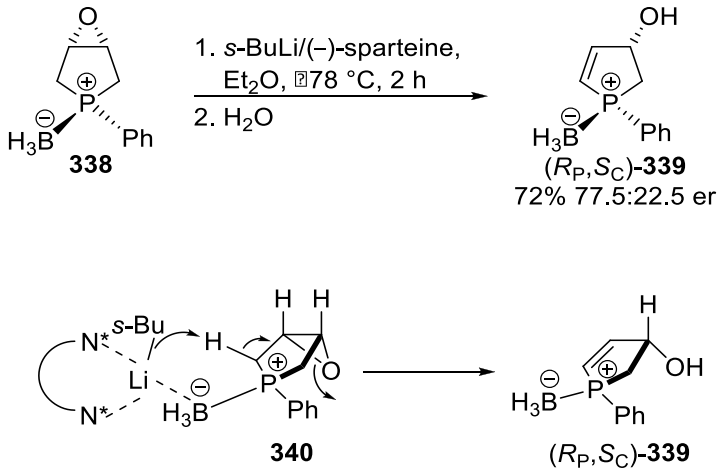
The proposed reaction mechanism for the weak base-mediated epoxide rearrangement using quinidine is shown in Scheme 3.26. It was shown that the abstraction of the proton adjacent to phosphorus occurred *syn* to the oxygen of the phosphine oxide. In addition, the oxygen in a phosphine oxide is an efficient lone pair donor to protons and metal cations. Therefore, it was assumed the rearrangement process begins with the coordination of quinidine **337** to epoxide **335** through hydrogen bonding. Then, the base abstracts the more accessible enantiotopic proton, which in this case is *anti* to the epoxide oxygen to give phosphine oxide (R_P,S_C)-**336**.

Scheme 3.26: Proposed mechanism for epoxide rearrangement



With a strong organolithium base, the enantioselective rearrangement of phosphine borane **338** using *s*-BuLi/(−)-sparteine in Et_2O at −78 ºC resulted in hydroxy phospholene borane (R_P, S_C)-**339** in 72% yield with 77.5:22.5 er (Scheme 3.27). The rearrangement utilising *s*-BuLi/(−)-sparteine proceeds *via* a different reaction mechanism. The complex-induced proximity effect, in which coordination of the borane group to the lithium directs the incoming organolithium reagent, is shown in **340**. Then, one of the enantiotopic protons is abstracted preferentially to afford phosphine oxide (R_P, S_C)-**339**. Although both procedures allow access to the enantioenriched hydroxy phospholenes, the methodology is hampered by a narrow substrate scope.

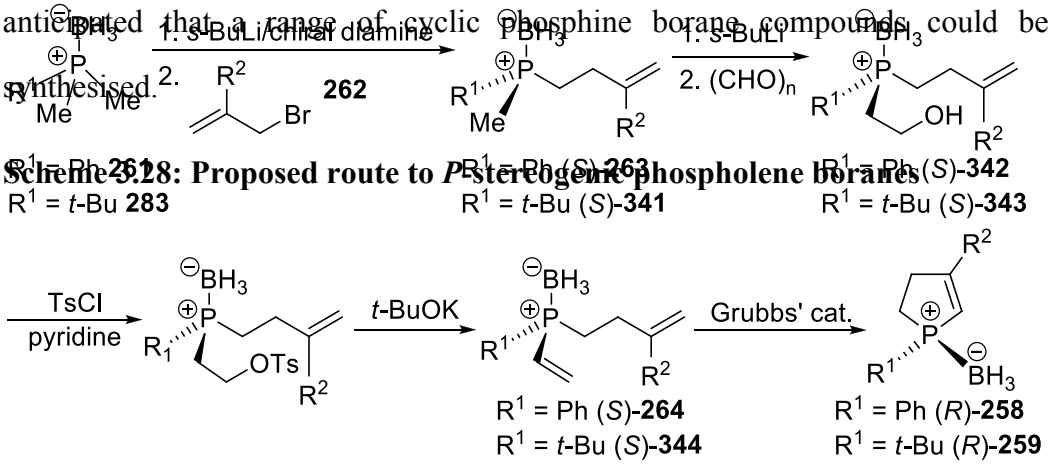
Scheme 3.27: Enantioselective rearrangement of a phosphine borane



To summarise, only two strategies have been developed for the synthesis of enantioenriched *P*-stereogenic phospholenes. The resolution approach suffers from multiple steps and low yield, while the desymmetrisation method is restricted in substrate scope and exhibits only moderate enantioselectivity. Therefore, the pursuit of an efficient and general approach to *P*-stereogenic phospholenes remains a significant and important synthetic challenge.

3.3.2 Synthesis of Enantioenriched Phospholenes

As outlined in Section 3.1.2, we envisioned that the synthesis of cyclic phosphine compounds such as phosphine boranes (*R*)-**258** or (*R*)-**259** could be achieved using an asymmetric lithiation approach (Scheme 3.28). Thus, treatment of phosphine boranes **261** or **283** with *s*-BuLi/chiral diamine followed by trapping with allyl bromides **262** would afford alkene phosphine boranes (*S*)-**263** and (*S*)-**341**. The employment of a chiral diamine ligand would set up the configuration at phosphorus. Then, regioselective lithiation and trapping with paraformaldehyde would give (*S*)-**342** and (*S*)-**343**. Subsequent tosylation and elimination would then put in the second alkene in (*S*)-**264** and (*S*)-**344**. Finally, ring-closing metathesis would deliver enantioenriched cyclic phosphine boranes (*R*)-**258** and (*R*)-**259**. Notably, by varying the substituent in the dimethyl phosphine borane starting materials as well as in allyl bromides **262**, we anticipated that a range of cyclic phosphine borane compounds could be synthesised.

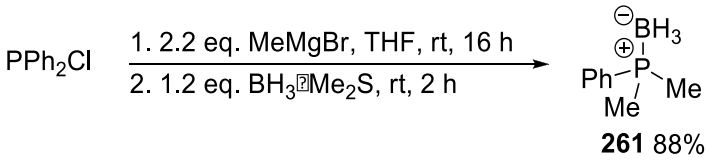


Scheme 3.28: Proposed route to *P*-stereogenic phospholene boranes

First, the synthesis of cyclic phosphine compounds in a racemic fashion was investigated. We chose cyclic phosphine borane *rac*-**258** as the target molecule

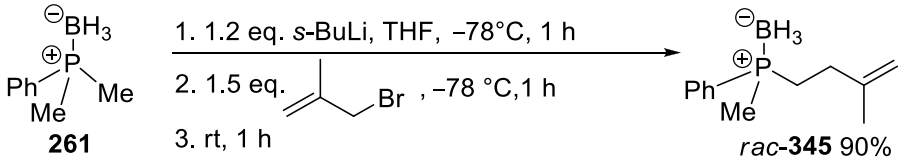
as it is the precursor of the ligand used in the catalytic Wittig reaction by O'Brien and co-workers.[91] Phosphine borane **261** was synthesised using a known procedure (Scheme 3.29).[98] Nucleophilic displacement of diphenylchlorophosphine with methylmagnesium bromide gave the crude trialkyl phosphine. Subsequent treatment with borane dimethyl sulfide complex gave phosphine borane **261** in 88% yield.

Scheme 3.29: Synthesis of phenyl phosphine borane



Then, phosphine borane **261** was lithiated using *s*-BuLi in THF at –78 °C. After 1 h, methallyl bromide was added and the allylated phosphine borane *rac*-**345** was obtained in an excellent 90% yield after purification by column chromatography (Scheme 3.30). The ^{1}H NMR spectrum of *rac*-**345** showed a characteristic doublet at δ_H 1.58 (J_{PH} = 10.5 Hz) corresponding to one of the methyl group and two sets of broad singlets at δ_H 4.73 and δ_H 4.69, assigned to the terminal alkene protons.

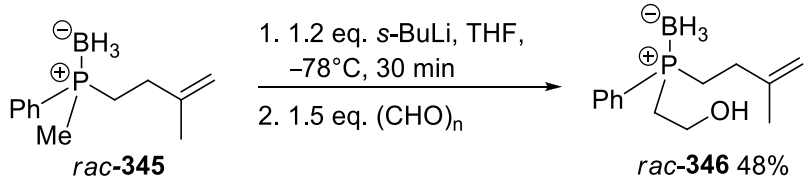
Scheme 3.30: Lithiation/trapping of phosphine borane 261



Next, the formation of the hydroxy adduct *rac*-**346** was investigated (Scheme 3.31). Phosphine borane *rac*-**345** was lithiated using *s*-BuLi in THF at –78 ºC for 30 min. Trapping the lithiated intermediate with paraformaldehyde gave hydroxy adduct *rac*-**346** in 67% yield after purification by column chromatography.

However, this high isolated yield could not be reproduced despite several attempts. Hence, we prefer to quote a reproducible yield of 48% for this reaction. We speculate that the presence of the hydroxy group in *rac*-**346** could increase the polarity of the molecule leading to a difficult purification by column chromatography, which could explain the variable yields obtained. There was no evidence of the other regioisomeric trapped product from this reaction on inspection of the ^{1}H NMR spectrum of the crude product. Thus, this reaction showed complete regioselectivity for lithiation at the less sterically hindered methyl group compared to the methylene group. The ^{1}H NMR spectrum of *rac*-**346** revealed a multiplet at δ_H 3.96-3.78 with relative integration of 2H for the protons α to the hydroxy group. Crucially, there was no evidence for the *P*-methyl group in the ^{1}H NMR spectrum of the crude product.

Scheme 3.31: Lithiation/trapping with paraformaldehyde

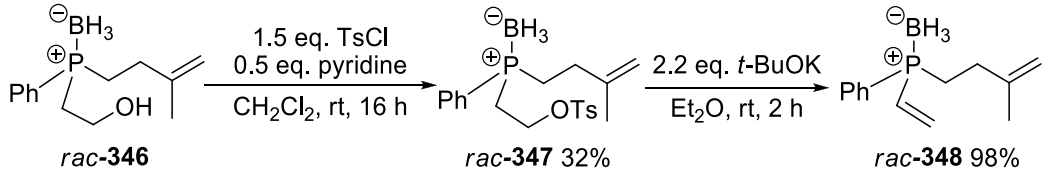


rac-**345** *rac*-**346** 48%

Next, we needed to develop a method for elimination of the hydroxy group. For this, we planned to use tosylation and base-mediated elimination. Thus, hydroxy adduct *rac*-**346** was subjected to tosylation using tosyl chloride and pyridine (Scheme 3.32). Despite > 90% conversion on inspection of the ^{1}H NMR spectrum of the crude mixture, we were only able to isolate tosylate *rac*-**347** in 32% yield after chromatography. We suspected that instability of tosylate *rac*-**347** on silica gel could be the reason for the low isolated yield. Indeed, decomposition to an unknown by-product was shown by TLC analysis. Pleasingly, tosylate *rac*-**347** was readily converted into diene *rac*-**348** in 98% yield when treated with potassium *t*-butoxide in Et_2O at rt for 2 h. The ^{1}H NMR

spectrum of *rac*-**348** showed the presence of three new alkene protons compared to *rac*-**346**. A 1H doublet of triplets at δ_H 6.40 (J = 18.0, 13.0 Hz) was assigned to the alkene proton α to the phosphorus. A multiplet at δ_H 6.27-6.14 was due to the two terminal alkene protons.

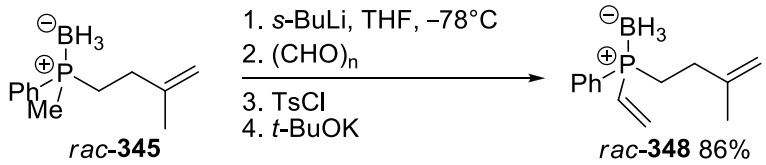
Scheme 3.32: Tosylation and elimination of phosphine borane *rac*-346



rac-**346** *rac*-**347** 32% *rac*-**348** 98%

Since there were isolation issues with both hydroxy phosphine borane *rac*-**346** and tosylate *rac*-**347**, it was decided that the regioselective lithiation and trapping with paraformaldehyde, tosylation and elimination would be carried out using the crude mixture from the previous step without any purification. In this way, only diene *rac*-**348** would be purified by chromatography. Using this telescoped procedure, diene *rac*-**348** was obtained from allylated phosphine borane *rac*-**345** in 86% yield over 3 steps (Scheme 3.33). The impressive yield from this three-step process supports the idea that purification issues were the source of the problems in obtaining high yields of hydroxy adduct *rac*-**346** and tosylate *rac*-**347**.

Scheme 3.33: Telescoped procedure to diene *rac*-348

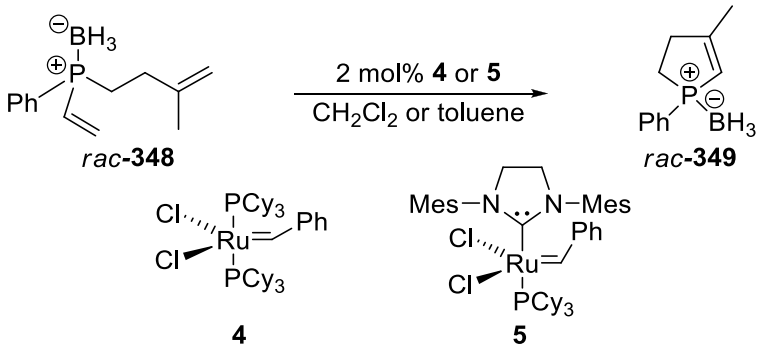


rac-**345** *rac*-**348** 86%

With diene *rac*-**348** in hand, the formation of cyclic phosphine borane *rac*-**349** was investigated using ring-closing metathesis and a range of Grubbs' catalysts were evaluated. Although there are many examples of cyclic phosphine borane

synthesis using this approach (see Section 1.2), there are no reported examples of ring-closing metathesis approaches to vinylic phospholene boranes such as *rac*-**349**. Grubbs' 1st generation catalyst **4** (2 mol %) was investigated first. None of the desired product *rac*-**349** was detected in the ^{1}H NMR spectrum of the crude mixture and only the starting material *rac*-**348** was present (Table 3.12, entry 1). Hence, a more reactive Grubbs' 2nd generation catalyst **5** (2 mol %), was employed.

Table 3.12: Ring-closing metathesis using catalysts 4 and 5



Entry	Catalyst	Solvent	Temp	Time (h)	*rac*-**348**:*rac*-**349**[a]
1	**4**	CH_2Cl_2	rt	16	100:0
2	**5**	CH_2Cl_2	rt	72	77:23
3	**5**	CH_2Cl_2	reflux	16	83:17[b]
4	**5**	toluene	reflux	16	78:22[c]

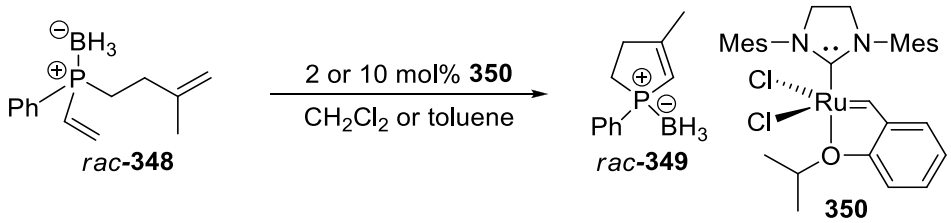
[a] Ratio of *rac*-**348**:*rac*-**349** determined from the ^{1}H NMR spectrum of the crude product. [b] Crude product from entry 2 was used as starting material. [c] Crude product from entry 3 was used as starting material.

After stirring at rt for 72 h, 23% conversion to diene *rac*-**349** was observed (entry 2). The conversion was identified by a signal at δ_H 5.70, which was assigned to the alkene proton in the product *rac*-**349**. Encouraged by this enhanced reactivity, the reaction temperature was then increased and the crude mixture from entry 2 was refluxed with Grubbs' 2nd generation catalyst **5** (2 mol %) in CH_2Cl_2 for 16 h.

However, a similar result was observed compared to stirring at rt: 17% conversion into phospholene *rac*-**349** (entry 3). Disappointingly, when the crude mixture from entry 3 was heated to reflux in toluene for 16 h, no further conversion was observed (entry 4).

Phosphine-free isopropoxy-chelated complexes, such as **350**, a group of catalysts introduced by Hoveyda, show an expanded application with enhanced reactivity in ring-closing metathesis reactions.[120] Therefore, such a catalyst was explored next. Ring-closing metathesis of diene *rac*-**348** using Hoveyda-Grubbs 2nd generation catalyst **350** (2 mol %) in CH_2Cl_2 at rt for 16 h gave 13% conversion to phospholene *rac*-**349** (Table 3.13, entry 1). Then, the catalyst loading was increased to 10 mol% and the crude mixture from entry 1 was stirred in CH_2Cl_2 at rt for 16 h. On inspection of the ^{1}H NMR spectrum of the crude mixture, 50% conversion into phospholene *rac*-**349** was observed (entry 2). This is a significantly better result compared to Grubbs' 2nd generation catalyst **5**.

Table 3.13: Ring-closing metathesis using catalyst 350



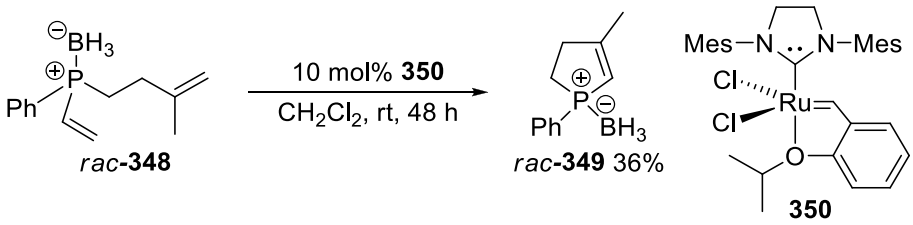
Entry	Catalyst	Solvent	Temp	Time (h)	*rac*-**348**:*rac*-**349**[a]
1	**350**[b]	CH_2Cl_2	rt	16	87:13
2	**350**[c]	CH_2Cl_2	rt	16	50:50[d]
3	**350**[c]	CH_2Cl_2	rt	48	40:60[d]
4	**350**[c]	CH_2Cl_2	rt	72	40:60[d]
5	**350**[c]	CH_2Cl_2	reflux	16	n.d.[e]

[a] Ratio of *rac*-**348**:*rac*-**349** determined from the ^{1}H NMR spectrum of the crude product. [b] 2 mol% of Hoveyda-Grubbs II **5** catalyst was used. [c] 10 mol% of Hoveyda-Grubbs II **350** catalyst was used. [d] Crude product from previous entry was used as starting material. [e] Ratio of *rac*-**348**:*rac*-**349** could not be determined.

The crude mixture from the previous ring-closing metathesis study was used for the following reactions. Satisfyingly, when the reaction time was extended to 48 h, the conversion improved to 60% (entry 3). With a prolonged reaction time of 72 h, no further improvement of conversion was observed (entry 4). Finally, increasing the reaction temperature to reflux in CH_2Cl_2 for 16 h with Hoveyda-Grubbs 2nd generation catalyst **350** (10 mol %) gave a complex mixture with only a trace of the desired product *rac*-**349** presents (entry 5). It is possible that heating the reaction mixture with Hoveyda-Grubbs type catalyst could lead to product decomposition and/or a cross-metathesis side reaction. Thus, the ring-closing metathesis showed that the highest conversion of diene *rac*-**348** into cyclic phosphine borane *rac*-**349** was 60% after stirring at rt for 80 h in total.

Therefore, a separate reaction was carried out using 10 mol% of Hoveyda-Grubbs 2nd generation catalyst **350** at rt. After 48 h, the crude product was purified and *rac*-**349** was isolated in 36% yield, together with 40% recovered diene *rac*-**348** (Scheme 3.34). The ^{1}H NMR spectrum of the desired product *rac*-**349** showed a new signal at δ_H 5.70 (ddd, J = 32.0, 3.0, 1.5 Hz), corresponding to the alkene proton next to the phosphorus. A 3H singlet at δ_H 2.09 is assigned to the methyl group.

Scheme 3.34: Formation of phospholene borane *rac*-349



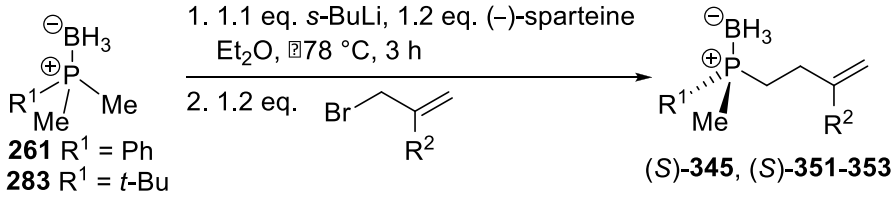
The highest conversion for the transformation of *rac*-**349** from *rac*-**348** is 60% using 10 mol% of Hoveyda-Grubbs 2nd generation catalyst **350**. This indicates that, in this case, the Hoveyda-Grubbs catalyst **350** is superior to the Grubbs-type catalysts. Therefore, use of Hoveyda-Grubbs 2nd generation catalyst **350** (10 mol %) in CH_2Cl_2 at rt for 48 h was our best conditions for formation of cyclic phosphine borane *rac*-**349**. Based on these results and more details discussed later, we conclude that the steric hindrance around the disubstituted alkene leads to inefficient ring-closing metathesis.

Although the yield for the final ring-closing metathesis was low, a viable route for the synthesis of vinyl phospholene boranes has been developed. Therefore, we turned our attention to the asymmetric synthesis of cyclic phosphine boranes. Since (−)-sparteine and diamine **203** were the best diamine ligands amongst the six ligands tested in the lithiation of phosphine borane **283** (see Section 3.2.3),

we decided to investigate the synthesis of enantioenriched cyclic phosphine boranes using (–)-sparteine as the ligand. To demonstrate the versatility of this methodology, examples starting from *t*-butyl phosphine boranes were also synthesised. We also planned to vary the allyl bromide in order to show the synthetic utility of our proposed route.

Lithiation of phosphine boranes **261** and **283** was carried out using *s*-BuLi/(–)-sparteine in Et_2O at –78 ºC following the Evans' procedure.[93] After trapping with methallyl bromide, allylated phosphine (*S*)-**345** was obtained in 73% yield and 89:11 er by CSP-HPLC (Table 3.14, entry 1). Using allyl bromide as an electrophile, allylated phosphine (*S*)-**351** was isolated in 57% yield with a similar 88:12 er (entry 2).

Table 3.14: Asymmetric lithiation/trapping of phosphine boranes



Entry	R^1	R^2	Product	Yield (%)[a]	er
1	Ph	Me	(*S*)-**345**	73	89:11[b]
2	Ph	H	(*S*)-**351**	57	88:12[b]
3	*t*-Bu	Me	(*S*)-**352**	57	96:4[c]
4	*t*-Bu	H	(*S*)-**353**	58	93:7[c]

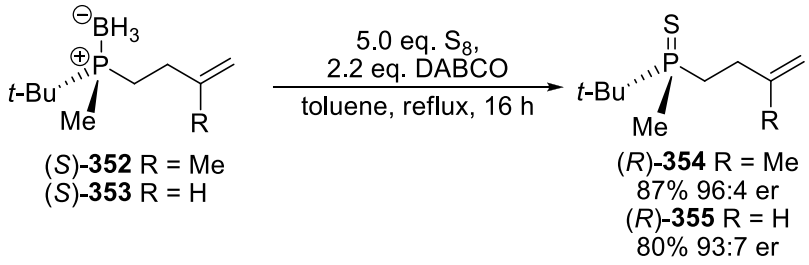
[a] Yield of (*S*)-**345** and (*S*)-**351**-**353** after purification by chromatography. [b] Enantiomeric ratio determined by CSP-HPLC and Daicel Chiracel AD-H column. [c] Enantiomeric ratio determined by CSP-HPLC of the corresponding phosphine sulfides on a Daicel Chiracel AD-H column.

In contrast, the lithiation-alkylation of *t*-butyl phosphine borane **283** gave allyl phosphine adducts (*S*)-**352** and (*S*)-**353** in 57% yield with 96:4 er (entry 3) and 58% yield with 93:7 er (entry 4) respectively. The enantioselectivity is generally

higher for the *t*-butyl phosphine borane than for the phenyl substituted analogue **261**. This may be due to the enhanced steric bulk between the *t*-butyl and methyl groups compared to the phenyl and methyl substituents.[93, 98]

The enantiomeric ratios of (*S*)-**345** and (*S*)-**351** were determined directly by CSP-HPLC. However, there is no UV chromophore in phosphine boranes (*S*)-**352** and (*S*)-**353** that would allow the determination of er using CSP-HPLC. Thus, phosphine boranes (*S*)-**352** and (*S*)-**353** were transformed into phosphine sulfides (*R*)-**354** and (*R*)-**355** respectively for the determination of the enantioselectivity in the asymmetric lithiation step. It is known in our group that the P=S group provides a suitable UV chromophore. Phosphine borane (*S*)-**352** was treated with sulfur and DABCO in refluxing toluene for 16 h to afford phosphine sulfide (*R*)-**354** in 87% yield (Scheme 3.35). The same procedure was also carried out on phosphine borane (*S*)-**353** to obtain phosphine sulfide (*R*)-**355** in 80% yield. The ers of phosphine sulfides (*R*)-**354** and (*R*)-**355** were determined to be 96:4 and 93:7 respectively.

Scheme 3.35: Formation of phosphine sulfides



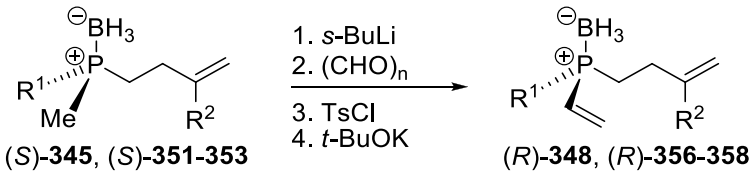
(*S*)-**352** R = Me
(*S*)-**353** R = H

(*R*)-**354** R = Me
87% 96:4 er
(*R*)-**355** R = H
80% 93:7 er

The preparation of dienes (*R*)-**348** and (*R*)-**356-358** was then performed from the enantioenriched allylated phosphine boranes (*S*)-**345** and (*S*)-**351-353** using the optimised telescoped procedure. The results are presented in Table 3.15. Regioselective lithiation of phenyl phosphine boranes (*S*)-**345** and (*S*)-**351** followed by trapping with paraformaldehyde gave the crude hydroxy phosphine

boranes. The crude hydroxy adducts were then used in the tosylation and elimination reactions. Diene phenyl phosphine boranes (*R*)-**348** and (*R*)-**356** were obtained in 71% and 58% yield respectively after purification by column chromatography (entries 1 and 2). Under the same reaction conditions, *t*-butyl phosphine boranes (*S*)-**352** and (*S*)-**353** were transformed into dienes (*R*)-**357** and (*R*)-**358** and isolated in 56% and 60% yield respectively (entries 3 and 4).

Table 3.15: Synthesis of phosphine dienes using the telescoped procedure



(*S*)-**345**, (*S*)-**351-353** → (*R*)-**348**, (*R*)-**356-358**

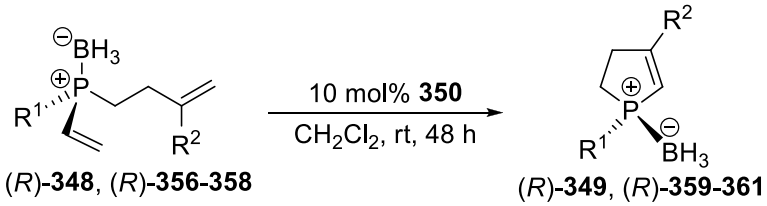
Entry	SM	R^1	R^2	Product	Yield (%)[a]
1	(*S*)-**345**	Ph	Me	(*R*)-**348**	58
2	(*S*)-**351**	Ph	H	(*R*)-**356**	71
3	(*S*)-**352**	*t*-Bu	Me	(*R*)-**357**	56
4	(*S*)-**353**	*t*-Bu	H	(*R*)-**358**	60

[a] Yield of (*R*)-**348** and (*R*)-**356-358** after purification by chromatography.

Finally, ring-closing metathesis was carried out on dienes (*R*)-**348** and (*R*)-**356-358** and the results are presented in Table 3.16. Using the optimised conditions (10 mol% Hoveyda-Grubbs 2nd generation catalyst **350** in CH_2Cl_2 at rt for 48 h), dienes (*R*)-**348** and (*R*)-**357** afforded the desired substituted cyclic phenyl phosphine borane (*R*)-**349** and cyclic *t*-butyl phosphine borane (*R*)-**360** in 46% yield and 41% yield respectively (entries 1 and 3). Notably, a significantly higher yield of cyclic phosphine boranes (*R*)-**359** and (*R*)-**361** (71% and 85% respectively) were achieved using a low loading of 1 mol% of Hoveyda-Grubbs 2nd generation catalyst **350** (entries 2 and 4).

When there is a methyl group attached to the alkene, the ring-closing metathesis gave moderate yield. With monosubstituted alkenes, the reaction proceeded smoothly and provided the desired products in high yield with low loading of the catalyst. This further indicates the steric effect of the methyl substituent which reduces the formation of the cyclic phosphine boranes.

Table 3.16: *P*-Stereogenic phospholene boranes *via* ring-closing metathesis



(*R*)-**348**, (*R*)-**356-358** → (*R*)-**349**, (*R*)-**359-361**

Entry	SM	R^1	R^2	Catalyst loading	Product	Yield (%)[a]
1	(*R*)-**348**	Ph	Me	10	(*R*)-**349**	46
2	(*R*)-**356**	Ph	H	1	(*R*)-**359**	71
3	(*R*)-**357**	*t*-Bu	Me	10	(*R*)-**360**	41
4	(*R*)-**358**	*t*-Bu	H	1	(*R*)-**361**	85

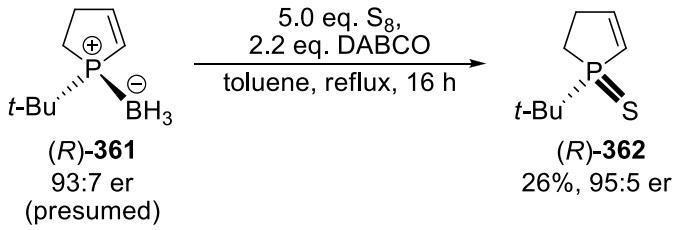
[a] Yield of (*R*)-**349** and (*R*)-**359**-**361** after purification by chromatography.

To confirm that the enantiomeric ratio of phosphine borane (*S*)-**351** (88:12 er) did not change throughout the reaction sequence, the enantioselectivity of cyclic phosphine borane (*R*)-**359** was obtained using CSP-HPLC. The er of 87:13 for cyclic phosphine borane (*R*)-**359** confirmed that the reactions proceeded without loss of enantiomer ratio.

To demonstrate that the functional group at phosphorus can undergo transformation with retention of configuration, phosphine borane (*R*)-**361** was converted into phosphine sulfide (*R*)-**362** (Scheme 3.36). Thus, treating phosphine borane (*R*)-**361** with sulfur and DABCO, phosphine sulfide (*R*)-**362** was isolated in 26% yield. The enantioselectivity of phosphine sulfide (*R*)-**362**

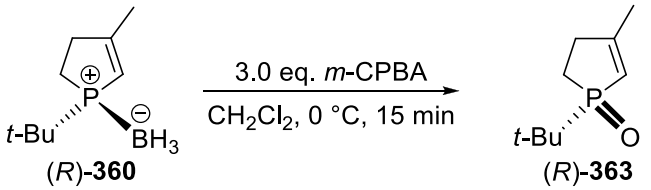
was determined to be 95:5 er using CSP-HPLC, while the enantiomer ratio of phosphine borane (*R*)-**361** was presumed to be 93:7 er, as it was derived from phosphine borane (*S*)-**353** of 93:7 er. These results confirmed the expected retention of configuration at phosphorus through the oxidation reaction.

Scheme 3.36: Transformation of phosphine sulfide (*R*)-362 from phosphine borane (*R*)-361

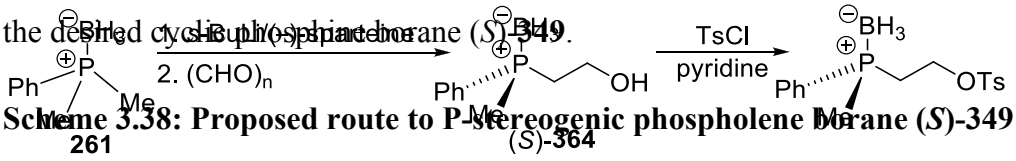


In order to synthesise an enantioenriched version of phosphine oxide **231** used in the catalytic Wittig and aza-Wittig reactions, described by O'Brien and Marsden respectively, the phosphine borane functional group would need to be converted into a phosphine oxide. As a test reaction, phosphine borane (*R*)-**360** was treated with *m*-CPBA in CH_2Cl_2 at 0 ºC for 15 min (Scheme 3.37).[121] Pleasingly, the ^{31}P NMR spectrum of the crude product revealed that the phosphine borane (*R*)-**360** had fully converted into phosphine oxide (*R*)-**363**: the signal at δ_P 68.2 corresponding to the phosphine borane (*R*)-**360** had disappeared and a new siganl at δ_P 87.1 indicated the presence of phosphine oxide (*R*)-**363**. Unfortunately, it was extremely difficult to purify phosphine oxide (*R*)-**363** by column chromatography probably due to its highly polar nature. Therefore, we were unable to isolate phosphine oxide (*R*)-**363** as a pure compound.

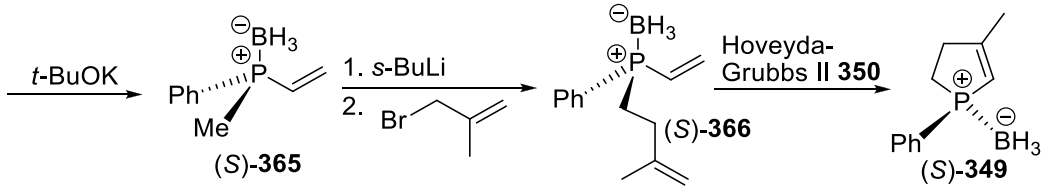
Scheme 3.37: Attempted synthesis of phosphine oxide (*R*)-363



Next, we wondered whether it would be possible to synthesise the enantiomeric cyclic phosphine borane, (*S*)-**349**, without employment of the (+)-sparteine surrogate **203**. The opposite configuration at phosphorus would be obtained by reversing the order of two of the steps in the synthetic sequence. Our proposed plan is shown in Scheme 3.38. Thus, lithiation of phosphine borane **261** using *s*-BuLi/(–)-sparteine and trapping with paraformaldehyde would give hydroxyl adduct (*S*)-**364**. Tosylation followed by elimination would then provide vinyl phosphine borane (*S*)-**365**. Regioselective lithiation of vinyl phosphine borane (*S*)-**365** would introduce the second alkene to give (*S*)-**366**. Finally, ring-closing metathesis using the Hoveyda-Grubbs 2nd generation catalyst **350** would furnish the desired cyclic phosphine borane (*S*)-**349**.



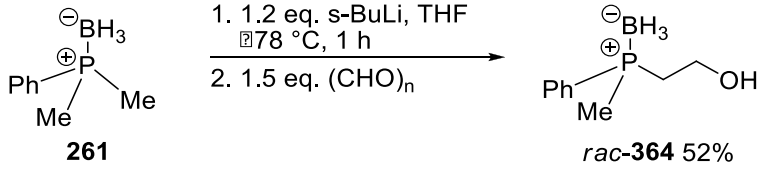
Scheme 3.38: Proposed route to P-stereogenic phospholene borane (*S*)-349



First, we started the synthesis by investigating the lithiation/trapping with phosphine borane **261** in a racemic fashion (Scheme 3.39). Thus, phosphine borane **261** was lithiated using *s*-BuLi in THF at –78 °C for 1 h followed by

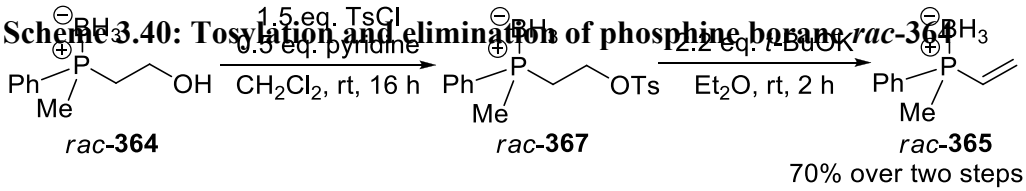
trapping with paraformaldehyde. Pleasingly, hydroxy adduct *rac*-**364** was isolated in 52% yield and a 24% yield of phosphine borane **261** was also recovered.

Scheme 3.39: Lithiation/trapping with paraformaldehyde



Next, hydroxy adduct *rac*-**364** was transformed into tosylate *rac*-**367** using tosyl chloride and pyridine (Scheme 3.40). After stirring at rt for 16 h, tosylate *rac*-**367** was formed with good conversion on inspection of the ^{1}H NMR spectrum of the crude product. Since we experienced purification issues when isolating tosylate *rac*-**347**, tosylate *rac*-**367** was used without any further purification. Vinylic phosphine borane *rac*-**365** was prepared by the elimination of tosylate *rac*-**367** using potassium *t*-butoxide. After purification by column chromatography, vinyl phosphine borane *rac*-**365** was isolated in 70% yield over two steps (Scheme 3.40).

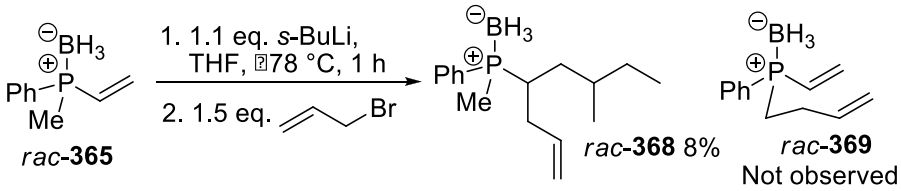
Scheme 3.40: Tosylation and elimination of phosphine borane *rac*-364



With vinyl phosphine borane *rac*-**365** in hand, regioselective lithiation was next explored. Thus, vinyl phosphine borane *rac*-**365** was treated with *s*-BuLi in THF at −78 ºC for 1 h. Then, allyl bromide was added (Scheme 3.41). On inspection of the ^{1}H NMR spectrum of the crude product, diene *rac*-**369** was not observed.

Instead, alkylated phosphine borane *rac*-**368** was isolated in 8% yield after chromatography, along with some unidentified by-products.

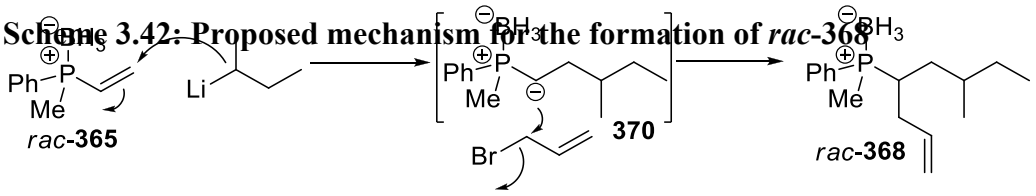
Scheme 3.41: Lithiation/trapping with allyl bromide



On inspection of the ^{1}H NMR spectrum of the isolated product, an *s*-butyl group was clearly incorporated since there were multiplet signals at δ_H 0.87-0.61 (6H) corresponding to the two methyl groups. There are three stereogenic centres in *rac*-**368** which would result in four diastereoisomers. The ^{1}H NMR spectrum revealed the presence of four diastereoisomers in approximately equal amounts. This is evident from the four sets of doublets at δ_H 1.59 (J = 10.0 Hz), 1.58 (J = 10.0 Hz), 1.57 (J = 9.5 Hz) and 1.56 (J = 10.0 Hz), with equal integrations, corresponding to the methyl group α to the phosphorus. The mass spectrometry result further confirmed the molecular formula to be consistent with phosphine borane *rac*-**368**.

A mechanism to account for the formation of *rac*-**368** is shown in Scheme 3.42. Instead of reacting as a strong base and abstracting a proton from the methyl group in phosphine borane *rac*-**365**, *s*-BuLi attacks the terminal alkene as a nucleophile to afford the anion intermediate **370**. On addition of allyl bromide, intermediate **370** undergoes nucleophilic substitution to give alkylated phosphine borane *rac*-**368**.

Scheme 3.42: Proposed mechanism for the formation of *rac*-368



Unfortunately, at this stage, initial attempts to carry out the lithiation of phosphine borane *rac*-**365** were unsuccessful, producing only a small amount of alkylated phosphine borane *rac*-**368**. Hence, we decided not to pursue the synthesis of phospholene (*S*)-**349** with the other configuration any further.

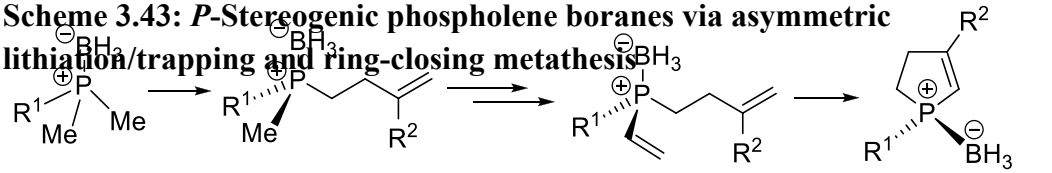
In summary, the first examples of asymmetric synthesis of *P*-stereogenic vinylic phospholene boranes such as (*R*)-**349** and (*R*)-**359**-**361** have been accomplished. The route involves asymmetric lithiation of dimethyl phosphine borane **261** and **283**, followed by electrophilc trapping with methyl allyl bromide and allyl bromide. Crucially, a telescoped regioselective deprotonation, paraformaldehyde trapping and hydroxy group elimination procedure was developed, to give enantioenriched alkylated phosphine boranes (*R*)-**348** and (*R*)-**356**-**358**. Finally, ring-closing metathesis using Hoveyda-Grubbs 2nd generation catalyst **350** afforded the desired phosphine heterocycles (*R*)-**349** and (*R*)-**359**-**361**.

3.4 Conclusions and Future Work

In conclusion, we have designed and synthesised three chiral diamine ligands and evaluated their utility in the asymmetric lithiation/trapping of phosphine borane **283**. (−)-Sparteine and diamine **203** remain the best ligands in the reaction, providing ketone adduct (*R*)-**316** in 91:9 er and 9:91 er respectively, while diamine (*S*,*S*)-**304** was found to function as an effective (+)-sparteine surrogate and gave ketone adduct (*R*)-**316** in 78:22 er.

In a separate study, we have developed a general route for the synthesis of enantioenriched vinyl phospholenes *via* asymmetric lithiation/trapping and ring-closing metathesis (Scheme 3.43). The *s*-BuLi/(−)-sparteine-mediated asymmetric lithiation-trapping of phenyl phosphine borane **261** gave alkylated products (*S*)-**345** and (*S*)-**351** in 73% yield with 89:11 er and 57% yield with 96:4 er respectively. With *t*-butyl phosphine borane **283**, alkylated phosphine boranes (*S*)-**352** and (*S*)-**353** were obtained in 57% yield with 96:4 er and 58% yield with 93:7 er respectively.

Scheme 3.43: *P*-Stereogenic phospholene boranes via asymmetric lithiation/trapping and ring-closing metathesis



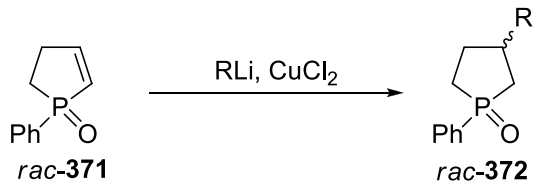
R^1 = Ph **261** R^1 = Ph (*S*)-**263** R^1 = Ph (*S*)-**264** R^1 = Ph (*R*)-**258**
R^1 = *t*-Bu **283** R^1 = *t*-Bu (*S*)-**341** R^1 = *t*-Bu (*S*)-**344** R^1 = *t*-Bu (*R*)-**259**

A telescoped procedure was developed for the synthesis of dienes (*R*)-**348** and (*R*)-**356**-**358**. This includes regioselective lithiation of the phosphine boranes, trapping with paraformaldehyde to give hydroxy adducts, followed by tosylation and elimination. This three-step telescoped protocol allows access to

enantioenriched dienes (*R*)-**348** and (*R*)-**356**-(*R*)-**358** in 56-71% yield, with only chromatographic purification in the last step. Finally, ring-closing metathesis using Hoveyda-Grubbs 2nd generation catalyst **350** afforded the desired vinyl phospholenes (*R*)-**349** and (*R*)-**359**-**361** in moderate to good yield. This approach has been published.[122]

Future work could study the regioselective addition of organocuprate reagents to phospholene oxide *rac*-**371**, which would need to be synthesised (Scheme 3.44). Since organocuprate reagents are soft nucleophiles, the reaction should take place *via* conjugate addition to give *rac*-**372**. The diastereoselectivity should also be investigated. This would provide an alternative route to the synthesis of cyclic phosphine oxides *rac*-**372** and an understanding of the reactivity of cyclic phosphine oxide *rac*-**371**.

Scheme 3.44: Regioselective addition to a phosphine oxide

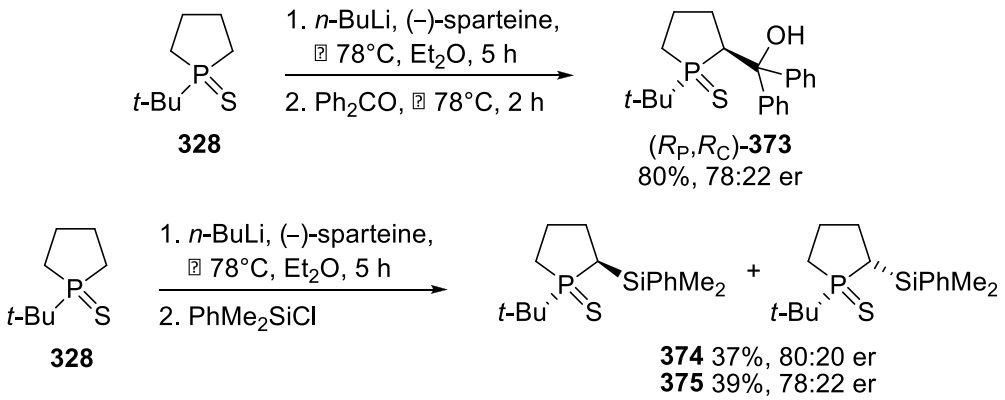


rac-**371** *rac*-**372**

Future work could also include an asymmetric lithiation/trapping approach to the synthesis of cyclic phosphine sulfides such as (R_P,R_C)-**373** (Scheme 3.45). By introducing a chiral centre α to the phosphine, this type of cyclic phosphorus compound could be used to explore the diastereoselectivity of the catalytic Wittig reactions. Initial investigations on the asymmetric lithiation/trapping of phospholene sulfide **328** have been carried out in our group.[117] The stereoselective lithiation of phospholene sulfide **328** was explored by trapping with both fast-trapping electrophiles and less reactive electrophiles. For example, phospholene sulfide **328** was lithiated using *n*-BuLi/(−)-sparteine. Trapping with

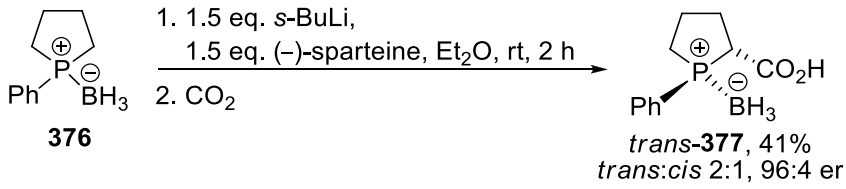
benzophenone afforded (R_P,R_C)-**373** in 80% and 78:22 er as a single diastereomeric product. In contrast, when the lithiated intermediate was trapped with a less reactive electrophile such as phenyldimethylsilyl chloride, two diastereomeric phosphine sulfides **374** and **375** were formed in similar enantioselectivity (Scheme 3.45).

Scheme 3.45: Asymmetric lithiation/trapping of a cyclic phosphine sulfide



In 2001, Kobayashi and co-workers reported the asymmetric lithiation and trapping with 5- and 6-membered cyclic phosphine boranes.[123] An example is shown in Scheme 3.46. Cyclic phosphine borane **376** was treated with *s*-BuLi/(–)-sparteine followed by trapping with dry-ice to afford *trans*-**377** in 41% yield and 96:4 er. Therefore, a more detailed study on the asymmetric lithiation of phosphine borane **376** could be carried out. Investigation on the stereoselectivity by trapping with various electrophiles and the temperature at which the electrophiles were added could be explored.

Scheme 3.46: Asymmetric lithiation/trapping of a cyclic phosphine borane



Chapter 4. Experimental

4.1 General

All non-aqueous reactions were carried out under oxygen free Ar using flame-dried glassware. Et_2O and THF were dried on a Pure Solv MD-7 solvent purification system or distilled from sodium and benzophenone. Alkyllithiums were titrated against *N*-benzylbenzamide before use.[124] All diamines used in lithiations were distilled over CaH_2 before use. Petrol refers to the fraction of petroleum ether boiling in the range of 40-60 ºC and was purchased in Winchester quantities. Brine refers to a saturated solution. Water is distilled water.

Flash chromatography was carried out using Fluka Chemie GmbH silica (220-440 mesh). Thin layer chromatography was carried out using commercially available Merck F_{254} aluminium backed silica plates. Proton (400 MHz), carbon (100.6 MHz) and phosphine (109 MHz) NMR spectra were recorded in $CDCl_3$, chemical shifts are quoted in parts per million relative to $CHCl_3$ (δ_H 7.27) and $CDCl_3$ (δ_C 77.0, central line of triplet). Carbon NMR spectra were recorded with broad band proton decoupling and assigned using DEPT experiments. Coupling constants (*J*) are quoted in Hertz. Infrared spectra were recorded on an ATI Mattson Genesis FT-IR spectrometer. Electrospray high and low resonance mass spectra were recorded at room temperature on a Jasco DIP-370 polarimeter (using sodium D line; 259 nm) and $[\alpha]_D$ given in units of 10^{-1} deg cm^3 g^{-1}. Chiral stationary phase HPLC was performed on an Agilent 1200 series chromatography.

4.2 General Procedures

General Procedure A: Addition of allyl magnesium bromide to aldehydes

Allyl magnesium bromide (100 mL of 1 M solution in Et_2O, 100.0 mmol, 1.1 eq.) was added dropwise to a stirred solution of the aldehyde (91.0 mmol, 1.0 eq.) in Et_2O (100 mL) at 0 ºC under Ar. The resulting solution was stirred at 0 ^oC for 1 h and then stirred at rt for 1 h. Saturated $NH_4Cl_{(aq)}$ (200 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure B: *O*-Alkylation of homoallylic alcohols

A solution of the alcohol (2.93 mmol, 1.0 eq) in THF (5 mL) was added dropwise to a stirred suspension of NaH (60% wt dispersion in mineral oil, 8.79 mmol, pre-washed with Et_2O (3 × 2 mL), 3.0 eq.) in THF (10 mL) at rt under Ar. The resulting mixture was stirred at rt for 15 min. Then, 3-bromo-2-methylprop-1-ene (3.52 mmol, 1.2 eq.) was added and the resulting mixture was stirred and heated at reflux for 16 h. After being allowed to cool to rt, the solution was poured into saturated $NH_4Cl_{(aq)}$ (15 mL) and extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure C: Cyclic ether formation *via* ring-closing metathesis

Grubbs' 2nd generation catalyst **5** (0.06 mmol, 0.01 eq.) was added in one portion to a stirred solution of the diene (5.94 mmol, 1.0 eq.) in CH_2Cl_2 (50 mL) at rt. The resulting mixture was stirred at rt for 3 h. The solvent was evaporated under reduced pressure to give the crude product.

General Procedure D: Hydrogenation using Pd/C

Pd/C (5% wt on carbon, 0.14 mmol, 0.1 eq.) was added to a stirred solution of the alkene (1.42 mmol, 1.0 eq.) in MeOH (5 mL) at rt under N_2. The flask was evacuated and back-filled with N_2 three times and finally evacuated and back-filled with H_2. Then, the mixture was stirred at rt for 1 h. Et_2O (10 mL) was added and the solids were removed by filtration through a pad of Celite® and the filter-cake was washed with Et_2O (3 × 10 mL). The combined organic washings were evaporated under reduced pressure to give the crude product.

General Procedure E: Asymmetric lithiation of phosphine borane **261** or **283** and trapping with methyallyl bromide/allyl bromide

s-BuLi (1.63 mL of a 1.3 M solution in hexane, 2.12 mmol, 1.1 eq.) was added dropwise to a stirred solution of (−)-sparteine (2.32 mmol, 1.2 eq.) in Et_2O (8 mL) at −78 ºC under Ar. After stirring for 15 min, a solution of phosphine borane **261** or **283** (1.93 mmol, 1.0 eq.) in Et_2O (2 mL) was added dropwise. The resulting solution was stirred at −78 ºC for 2 h. Then, methallyl bromide or allyl bromide (2.32 mmol, 1.2 eq.) was added dropwise and the mixture was allowed to warm to rt over 1 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure F: Lithiation and trapping with paraformaldehyde, tosylation and elimination

s-BuLi (2.62 mL of a 1.3 M solution in hexane, 3.41 mmol, 1.2 eq.) was added dropwise to a stirred solution of phosphine borane (*S*)-**345** (2.84 mmol, 1.0 eq.) in THF (10 mL) at −78 ºC under Ar. The resulting mixture was stirred at −78 ºC for 2 h. Then, a solution of paraformaldehyde (3.41 mmol, 1.2 eq.) in THF (5 mL) was added dropwise and the mixture was allowed to warm to rt over 16 h.

Saturated $NH_4Cl_{(aq)}$ (5 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude hydroxy phosphine borane. A solution of *p*-toluenesulfonyl chloride (2.86 mmol, 1.5 eq.) in CH_2Cl_2 (5 mL) was added dropwise to a stirred solution of the crude hydroxy phosphine borane and pyridine (2.86 mmol) in CH_2Cl_2 (5 mL) at rt under Ar. The resulting mixture was stirred at rt for 16 h. 2 M $HCl_{(aq)}$ (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude tosylate. KO*t*-Bu (4.51 mmol) was added in one portion to a stirred solution of the crude tosylate in Et_2O (10 mL) at rt under Ar. The resulting mixture was stirred at rt for 2 h. Then, the solid was removed by filtration through Celite®. The solid was washed with Et_2O (3 × 5 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure G: Cyclic phosphine formation *via* ring-closing metathesis

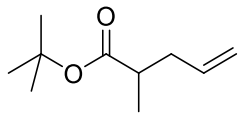
Grubbs-Hoveyda 2nd generation catalyst **350** (0.01-0.1 eq.) was added in one portion to a stirred solution of vinyl phosphine borane (*R*)-**348** (0.23 mmol, 1.0 eq.) in CH_2Cl_2 (2 mL) at rt. The resulting mixture was stirred at rt for 16 h. The solvent was evaporated under reduced pressure to give the crude product.

General Procedure H: Formation of phosphine sulfide using DABCO

A suspension of phosphine sulfide (*S*)-**352** (0.11 mmol, 1.0 eq.), DABCO (0.24 mmol, 2.2 eq.) and sulfur (0.54 mmol, 5.0 eq.) in toluene (5 mL) was stirred and heated at 80 ºC under Ar for 16 h. Then, 1 M $HCl_{(aq)}$ (10 mL) was added and the mixture was stirred for 30 min. The layers were separated and the aqueous layer

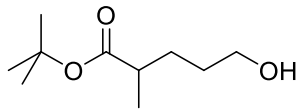
was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

4.3 Experimental for Chapter 2



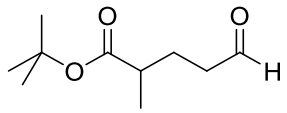
***t*-Butyl 2-methylpent-4-enoate 95**

LDA (5.8 mL of a 2 M solution in THF, 11.52 mmol, 1.0 eq.) was added dropwise to a stirred solution of *t*-butyl propionate (1.5 g, 11.52 mmol, 1.0 eq.) in THF (25 mL) at −78 ºC under Ar. After stirring at −78 ºC for 1 h, allyl bromide (1.0 mL, 11.52 mmol, 1.0 eq.) was added dropwise. The reaction mixture was allowed to warm to rt over 2 h and then stirred at rt for 16 h. Saturated $NH_4Cl_{(aq)}$ (25 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 95:5 petrol-EtOAc as eluent gave alkylated ester **95** (1.68 g, 84%) as a colourless oil, R_F (95:5 petrol-EtOAc) 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (ddt, J = 14.0, 10.0, 7.0 Hz, 1H, =CH), 5.09-5.01 (m, 2H, $=CH_2$), 2.42-2.35 (m, 2H, CH), 2.20-2.12 (m, 1H, CH), 1.45 (s, 9H, CMe_3), 1.11 (d, J = 7.0 Hz, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.6 (C=O), 135.9 (=CH), 116.6 ($=CH_2$), 80.1 ($OCMe_3$), 40.1 (CH), 38.1 (CH_2), 28.2 (CMe_3), 16.7 (Me); MS (ESI) *m/z* 194 [$(M + Na)^+$, 29], 126 (100); HRMS (ESI) *m/z* calcd for $C_{10}H_{20}O_3$ $(M + Na)^+$ 193.1199, found 193.9730 (−5.9 ppm error). Spectroscopic data consistent with those reported in the literature.[125] Alkylated ester **95** is volatile and should be used immediately after purification.



***t*-Butyl 5-hydroxy-2-methylpentanoate 96**

BH_3·THF complex (3.44 mL of a 1 M solution in THF, 3.44 mmol, 1.2 eq.) was added dropwise to a stirred solution of alkylated ester **95** (488 mg, 2.86 mmol, 1 eq.) in THF (25 mL) at 0 ºC under Ar. The resulting solution was allowed to warm to rt and stirred at rt for 16 h. $NaOH_{(aq)}$ (2.15 mL of a 2 M solution, 4.30 mmol, 1.5 eq.) and H_2O_2 (2.75 mL of a 35 wt% solution in water, 31.46 mmol, 11.0 eq.) were added and the mixture was stirred for 3.5 h. Then, brine (5 mL) and water (10 mL) were added. The aqueous layer was extracted with EtOAc (3 × 10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 95:5 CH_2Cl_2-EtOAc as eluent gave alcohol **96** (227 mg, 42%) as a colourless oil, R_F (95:5 CH_2Cl_2-EtOAc) 0.7; IR (film) 3422 (OH), 2976, 2936, 2876, 1728 (C=O), 1460, 1368, 1255, 1223, 1155, 1067, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.60 (td, J = 6.0, 3.0 Hz, 2H, CH_2OH), 2.37-2.28 (m, 1H, CH), 1.71-1.50 (m, 4H, CH), 1.43 (s, 9H, CMe_3), 1.10 (d, J = 7.0 Hz, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 176.3 (C=O), 80.1 (O*C*Me_3), 62.8 (CH_2OH), 40.3 (CH), 30.5 (CH_2), 30.0 (CH_2), 28.2 (C*Me*$_3$), 17.5 (Me); MS (ESI) *m/z* 211 [$(M + Na)^+$, 100], 155 [$(M - OCMe_3)^+$, 25]; HRMS (ESI) *m/z* calcd for $C_{10}H_{20}O_3$ $(M + Na)^+$ 211.1305, found 211.1305 (0.0 ppm error).



***t*-Butyl 2-methyl-5-oxopentanoate 97**

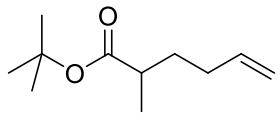
Dess-Martin periodinane (676 mg, 1.59 mmol, 1.2 eq.) was added in one portion to a stirred solution of alcohol **96** (250 mg, 1.33 mmol, 1.0 eq.) in CH_2Cl_2 (10 mL) at rt under Ar. The resulting suspension was stirred at rt for 1 h. Then, a

solution of $Na_2S_2O_3 \cdot 5H_2O$ (3.2 g, 9.21 mmol, 8.0 eq.) in 5% $NaHCO_{3(aq)}$ (10 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product (229 mg, 93%) which was sufficiently pure for use in the next step.

A solution of alcohol **96** (74 mg, 0.41 mmol, 1.0 eq.) in CH_2Cl_2 (1 mL) was added dropwise to a stirred solution of pyridinium chlorochromate (175 mg, 0.82 mmol, 2.0 eq.) in CH_2Cl_2 (1 mL) at rt under Ar. The resulting mixture was stirred at rt for 1 h before Et_2O (5 mL) was added and the solids were removed by filtration through Celite®. The filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 petrol-EtOAc as eluent gave aldehyde **97** (14 mg, 20%) as a colourless oil, R_F (4:1 petrol-EtOAc) 0.3; IR (film) 2976, 2936, 2878, 1727 (C=O), 1714 (C=O), 1459, 1392, 1368, 1279, 1155, 1074, 1033, 987, 916, 848 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.78 (br t, J = 2.0 Hz, 1H, CHO), 2.51-2.46 (m, 2H, CH_2CHO), 2.41-2.33 (m, 1H, CHMe), 1.96-1.87 (m, 1H, C$H$$CH_2$), 1.80-1.71 (m, 1H, C$H$$CH_2$), 1.45 (s, 9H, CMe_3), 1.14 (d, J = 7.0 Hz, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 202.0 (C=O, CHO), 178.0 (C=O, ester), 80.4 (O$C$$Me_3$), 41.6 ($C$$H_2$CHO), 39.6 (CH), 28.5 (C$Me_3$), 25.8 ($CH_2$), 17.2 (Me); MS (ESI) *m/z* 211 [(M + Na)$^+$, 100], 155 [(M – *t*-BuO)$^+$, 25]; HRMS (ESI) *m/z* calcd for $C_{10}H_{20}O_3$ (M + Na)$^+$ 209.1148, found 209.1150 (–0.5 ppm error).

LDA (5.2 mL of a 2 M solution in THF, 10.44 mmol, 1.1 eq.) was added dropwise to a stirred solution of *t*-butyl propionate (1.2 g, 9.49 mmol, 1.0 eq.) in THF (25 mL) at –78 °C under Ar. After stirring at –78 °C for 1 h, allyl bromide (1.1 mL, 10.44 mmol, 1.1 eq.) was added dropwise. The reaction mixture was allowed to warm to rt over 2 h and then stirred at rt for 16 h. Saturated $NH_4Cl_{(aq)}$

(25 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Then, the crude alkylated ester was dissolved in THF (25 mL) at 0 ºC under Ar and $BH_3{\cdot}THF$ complex (10.71 mL of a 1 M solution in THF, 10.71 mmol, 1.2 eq.) was added dropwise. The resulting solution was allowed to warm to rt and stirred at rt for 4 h. $NaOH_{(aq)}$ (6.7 mL of a 2 M solution, 13.40 mmol, 1.5 eq.) and H_2O_2 (8.72 mL of a 35 wt% solution in water, 99.55 mmol, 11.0 eq.) were added and the mixture was stirred for 30 min. Then, brine (15 mL) and water (20 mL) were added. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude alcohol. Then, the crude alcohol was dissolved in CH_2Cl_2 (40 mL) at rt under Ar. Dess-Martin periodinane (3.71 g, 8.76 mmol, 1.5 eq.) was added in one portion. The resulting suspension was stirred at rt for 16 h. Then, a solution of $Na_2S_2O_3{\cdot}5H_2O$ (11.6 g, 46.72 mmol, 8.0 eq.) in 5% $NaHCO_{3(aq)}$ (50 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 EtOAc-petrol as eluent gave aldehyde **97** (241 mg, 14%) as a colourless oil.



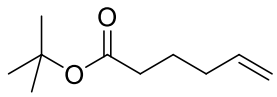
***t*-Butyl 2-methylhex-5-enoate 100**

n-BuLi (12.0 mL of a 2.05 M solution in hexane, 24.71 mmol, 1.4 eq.) was added dropwise to a stirred solution of di-*i*-propylamine (2.5 g, 24.71 mmol, 1.4 eq.) in THF (35 mL) at −78 ºC under Ar. The resulting solution was warmed to 0 ºC for 10 min and then cooled to −78 ºC. A solution of *t*-butyl propionate (3.5 g, 26.46

mmol, 1.5 eq.) in THF (5 mL) was added dropwise. After stirring at –78 ºC for 1 h, 4-bromobutene (1.8 mL, 17.64 mmol, 1.0 eq.) was added dropwise followed by DMPU (4.0 mL, 33.28 mmol, 2.0 eq.). The reaction mixture was stirred at –78 ºC for 1 h before allowed to warm to at –45 ºC and stirred for 1.5 h. Saturated $NH_4Cl_{(aq)}$ (35 mL) and water (15 mL) were added at this temperature and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 95:5 petrol-EtOAc as eluent gave alkylated ester **100** (2.01 g, 62%) as a colourless oil, R_F (95:5 petrol-EtOAc) 0.7; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (ddd, J = 17.0, 10.0, 7.0 Hz, 1H, =CH), 5.15 (dq, J = 17.0, 2.0 Hz, 1H, =CH), 5.00-4.95 (m, 1H, =CH), 2.33 (sextet, J = 7.0 Hz, 1H, CH), 2.09-2.04 (m, 2H, CH_2CH=), 1.78-1.68 (m, 1H, CH_AH$_B$CHMe), 1.56-1.47 (m, 1H, CH$_A$$H_B$CHMe), 1.45 (s, 9H, CMe_3), 1.10 (d, J = 7.0 Hz, 3H, Me). Spectroscopic data consistent with those reported in the literature.[126]

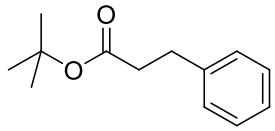
n-BuLi (0.79 mL of a 2.05 M solution in hexane, 1.62 mmol, 1.4 eq.) was added dropwise to a stirred solution of di-*i*-propylamine (164 mg, 1.62 mmol, 1.4 eq.) in THF (5 mL) at –78 ºC under Ar. The resulting solution was warmed to 0 ºC for 10 min and then cooled to –78 ºC. A solution of ester **109** (200 mg, 1.18 mmol, 1.0 eq.) in THF (1 mL) was added dropwise. After stirring at –78 ºC for 1 h, methyl iodide (0.14 mL, 2.21 mmol, 1.5 eq.) was added dropwise. The reaction mixture was allowed to warm to rt over 2 h and then stirred at rt for 16 h. Saturated $NH_4Cl_{(aq)}$ (5 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 95:5

petrol-EtOAc as eluent gave alkylated ester **100** (182 mg, 67%) as a colourless oil.



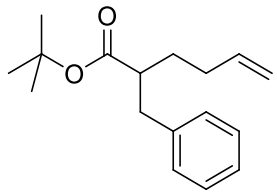
***t*-Butyl hex-5-enoate 109**

n-BuLi (1.70 mL of a 2.05 M solution in hexane, 4.02 mmol, 1.4 eq.) was added dropwise to a stirred solution of di-*i*-propylamine (429 mg, 4.02 mmol, 1.4 eq.) in THF (5 mL) at –78 ºC under Ar. The resulting solution was warmed to 0 ºC for 10 min and then cooled to –78 ºC. A solution of *t*-butyl acetate (500 mg, 4.30 mmol, 1.5 eq.) in THF (1 mL) was added dropwise. After stirring at –78 ºC for 1 h, 4-bromobutene (0.31 mL, 3.09 mmol, 1.0 eq.) was added dropwise followed by DMPU (2.5 mL, 20.68 mmol, 6.7 eq.). The reaction mixture was stirred at –78 ºC for 1 h before being allowed to warm to –45 ºC and stirred for 1.5 h. Saturated $NH_4Cl_{(aq)}$ (5 mL) and water (1 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 95:5 petrol-EtOAc as eluent gave alkylated ester **109** (297 mg, 55%) as a colourless oil, R_F (95:5 petrol-EtOAc) 0.7; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddd, J = 17.0, 10.0, 8.0 Hz, 1H, =CH), 5.09-5.01 (m, 2H, =CH_2), 2.23 (t, J = 8.0 Hz, 2H, CH_2CO), 2.08 (q, J = 8.0 Hz, 2H, CH_2CH=), 1.69 (quintet, J = 8.0 Hz, 2H, C$H_2$$CH_2CO$), 1.45 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (one CH_2 signal not resolved) δ 172.4 (C=O), 137.0 (=CH), 115.2 (=CH_2), 80.2 (O*C*Me_3), 34.7 (CH_2), 29.1 (CH_2), 28.1 (C*Me*$_3$). Spectroscopic data consistent with those reported in the literature.[127]



_t_-Butyl 3-phenylpropanoate 110

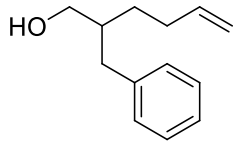
_n_-BuLi (6.37 mL of a 2.5 M solution in hexane, 15.92 mmol, 1.2 eq.) was added dropwise to a stirred solution of di-_i_-propylamine (1.46 g, 15.92 mmol, 1.2 eq.) in THF (30 mL) at –78 ºC under Ar. The resulting solution was warmed to 0 ºC for 10 min and then cooled to –78 ºC. A solution of _t_-butyl acetate (1.54 g, 13.26 mmol, 1.0 eq.) in THF (5 mL) was added dropwise. After stirring at –78 ºC for 1 h, benzyl bromide (3.40 g, 19.89 mmol, 1.5 eq.) was added dropwise. The reaction mixture was allowed to warmed to rt over 16 h. Saturated $NH_4Cl_{(aq)}$ (40 mL) and water (20 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 99:1 petrol-Et_2O as eluent gave alkylated ester **110** (1.96 g, 72%) as a colourless oil, R_F (99:1 petrol-Et_2O) 0.7; IR (film) 2979, 2932, 1730 (C=O), 1455, 1392, 1367, 1297, 1255, 1148, 911, 735, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.27 (m, 2H, Ph), 7.22-7.20 (m, 3H, Ph), 2.92 (t, J = 8.0 Hz, 2H, CH_2CO), 2.55 (t, J = 8.0 Hz, 2H, CH_2Ph), 1.43 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.2 (C=O), 140.7 (_ipso_-Ph), 128.4 (Ph), 128.3 (Ph), 126.1 (Ph), 80.2 (O_C_Me_3), 37.0 (CH_2), 31.1 (CH_2), 28.0 (C_Me_$_3$); MS (ESI) _m/z_ 229 [$(M + Na)^+$, 100], 105 (96), 151 (70), 133 (67); HRMS (ESI) _m/z_ calcd for $C_{13}H_{18}O_2S$ $(M + Na)^+$ 229.1199, found 229.1199 (–0.1 ppm error). Spectroscopic data consistent with those reported in the literature.[128]



_t_-Butyl 2-benzylhex-5-enoate 111

_n_-BuLi (4.10 mL of a 2.5 M solution in hexane, 10.24 mmol, 1.3 eq.) was added dropwise to a stirred solution of di-_i_-propylamine (1.04 g, 9.45 mmol, 1.2 eq.) in THF (50 mL) at –78 ºC under Ar. The resulting solution was warmed to 0 ºC for 10 min and then cooled to –78 ºC. A solution of ester **110** (1.95 g, 9.45 mmol, 1.2 eq.) in THF (15 mL) was added dropwise. After stirring at –78 ºC for 1 h, 4-bromobutene (0.80 mL, 7.88 mmol, 1.0 eq.) was added dropwise followed by DMPU (5.0 mL, 11.82 mmol, 1.5 eq.). The reaction mixture was stirred at –78 ºC for 1 h before being allowed to warm to –45 ºC and stirred for 1.5 h. Saturated $NH_4Cl_{(aq)}$ (50 mL) and water (15 mL) were added at –45 ºC and the mixture was allowed to warm to rt. The two layers were separated. The aqueous layer was extracted with Et_2O (3 × 50 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 95:5 petrol-EtOAc as eluent gave alkylated ester **111** (96 mg, 5%) as a colourless oil, R_F (95:5 petrol-EtOAc) 0.7; IR (film) 2978, 2930, 1726 (C=O), 1454, 1391, 1284, 1254, 1228, 1150, 912, 848, 737, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.25 (m, 2H, Ph), 7.21-7.17 (m, 3H, Ph), 5.78 (ddt, J = 17.0, 10.0, 7.0 Hz, 1H, =CH), 5.05-4.96 (m, 2H, $=CH_2$), 2.88 (dd, J = 14.0, 9.0 Hz, 1H, $PhCH_AH_B$), 2.73 (dd, J = 14.0, 9.0 Hz, 1H, $PhCH_AH_B$), 2.62-2.55 (m, 1H, CHCO), 2.17-2.01 (m, 2H, CH), 1.79-1.70 (m, 1H, CH), 1.59-1.50 (m, 1H, CH), 1.34 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.7 (C=O), 139.4 (Ph), 137.9 (_ipso_-Ph), 129.0 (Ph), 128.2 (Ph), 126.1 (=CH), 115.0 ($=CH_2$), 80.2 ($OCMe_3$), 47.6 (CH), 38.7 (CH_2), 31.5 (CH_2), 31.4 (CH_2), 28.0 (CMe_3); MS (ESI) _m/z_ 283 [$(M + Na)^+$,

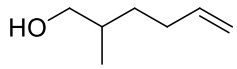
100]; HRMS (ESI) *m/z* calcd for $C_{17}H_{24}O_2S$ $(M + Na)^+$ 283.1664, found 283.1664 (+1.6 ppm error).



2-Benzylhex-5-en-1-ol 112

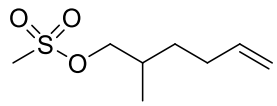
n-BuLi (3.73 mL of a 2.5 M solution in hexane, 8.09 mmol, 1.2 eq.) was added dropwise to a stirred solution of di-*i*-propylamine (819 mg, 8.09 mmol, 1.2 eq.) in THF (40 mL) at –78 ºC under Ar. The resulting solution was warmed to 0 ºC for 10 min and then cooled to –78 ºC. A solution of ester **110** (1.53 g, 7.42 mmol, 1.1 eq.) in THF (15 mL) was added dropwise. After stirring at –78 ºC for 1 h, 4-bromobutene (0.68 mL, 6.74 mmol, 1.0 eq.) was added dropwise followed by DMPU (3.5 mL, 8.09 mmol, 1.2 eq.). The reaction mixture was stirred at –78 ºC for 1 h before being allowed to warm to –45 ºC and stirred for 1.5 h. Saturated $NH_4Cl_{(aq)}$ (50 mL) and water (15 mL) were added at –45 ºC and the mixture was allowed to warm to rt. The two layers were separated. The aqueous layer was extracted with Et_2O (3 × 50 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. A solution of crude ester **111** (940 mg, 3.61 mmol, 1.0 eq.) in THF (20 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (686 mg, 18.05 mmol, 5.0 eq.) in THF (15 mL) at 0 ºC under Ar. The resulting mixture was stirred at 0 ºC for 1 h and then stirred at rt for 1 h. 1 M $NaOH_{(aq)}$ (10 mL) was added dropwise and the solids were removed by filtration through Celite®. The filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 petrol-Et_2O as eluent gave alcohol **112** (447 mg, 40%) as a colourless oil, R_F (4:1 petrol-Et_2O) 0.3; IR (film) 3367 (OH), 3027, 2926, 1640 (C=C), 1495, 1453, 1030, 996, 910, 735, 700 cm^{-1}; ^1H NMR (400

MHz, $CDCl_3$) δ 7.32-7.28 (m, 2H, Ph), 7.22-7.18 (m, 3H, Ph), 5.80 (ddt, J = 17.0, 10.0, 7.0 Hz, 1H, =CH), 5.03 (dq, J = 17.0, 2.0 Hz, 1H, =CH), 4.98-4.96 (m, 1H, =CH), 3.59-3.51 (m, 2H, CH_2OH), 2.66 (d, J = 7.0 Hz, 2H, CH_2Ph), 2.17-2.11 (m, 2H, CH_2CH=), 1.90-1.80 (m, 1H, CH), 1.57-1.38 (m, 2H, CH_2CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 140.5 (Ph), 138.6 (*ipso*-Ph), 129.1 (Ph), 128.2 (Ph), 125.6 (=CH), 114.5 (=CH_2), 64.3 (OCH_2), 41.7 (CH), 37.4 (CH_2), 31.0 (CH_2), 29.7 (CH_2); MS (ESI) *m/z* 191 [M^+, 90], 213 [$(M + Na)^+$, 100], 191 (70); HRMS (ESI) *m/z* calcd for $C_{13}H_{19}O$ M^+ 191.1410, found 191.1433 (⁻1.5 ppm error).



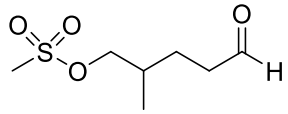
2-Methylhex-5-en-1-ol 113

A solution of ester **100** (540 mg, 2.96 mmol, 1.0 eq.) in THF (5 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (138 mg, 3.55 mmol, 1.5 eq.) in THF (5 mL) at 0 ºC under Ar. The resulting mixture was stirred at 0 ºC for 1 h and then stirred at rt for 1 h. 1 M $NaOH_{(aq)}$ (5 mL) was added dropwise and the solids were removed by filtration throught Celite®. The filtrate was evaporated under reduced pressure to give crude alcohol **113** (224 mg, 66%) as a colourless oil, which was sufficiently pure for use in the next step, ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (ddd, J = 17.0, 10.0, 7.0 Hz, 1H, =CH), 5.03 (dq, J = 17.0, 2.0 Hz, 1H, =CH), 4.97-4.95 (m, 1H, =CH), 3.52 (dd, J = 10.0, 6.0 Hz, 1H, C$H_A$$H_B$OH), 3.45 (dd, J = 10.0, 6.0 Hz, 1H, C$H_A$$H_B$OH), 2.20-2.01 (m, 2H, C$H_2$CH=), 1.72-1.61 (m, 1H, OH), 1.57-1.49 (m, 1H, C*H*Me), 1.27-1.18 (m, 2H, CH_2CH), 0.94 (d, J = 7.0 Hz, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.9 (=CH), 114.4 (=CH_2), 68.2 (CH_2OH), 35.2 (CH), 32.3 (CH_2), 31.2 (CH_2), 16.4 (Me). Spectroscopic data consistent with those reported in the literature.[129]



2-Methyl-5-oxopentyl methanesulfonate 101

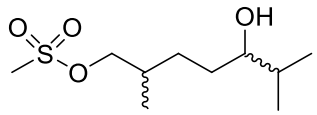
Et_3N (0.37 mL, 2.48 mmol, 1.3 eq.) was added dropwise to a stirred solution of alcohol **113** (218 mg, 1.91 mmol, 1.0 eq.) in CH_2Cl_2 (5 mL) at 0 ºC under Ar. Methanesulfonyl chloride (0.15 mL, 1.91 mmol, 1.0 eq.) was added dropwise. The resulting mixture was stirred at 0 ºC for 1 h. Water (5 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with 2 M $HCl_{(aq)}$ (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 petrol-EtOAc as eluent gave mesylate **101** (352 mg, 96%) as a colourless oil, R_F (4:1 petrol-EtOAc) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddt, J = 17.0, 10.0, 7.0 Hz, 1H, =CH), 5.04 (dq, J = 17.0, 2.0 Hz, 1H, =CH), 5.02-4.98 (m, 1H, =CH), 4.11 (dd, J = 10.0, 7.0 Hz, 1H, CH_AH$_B$O), 4.05 (dd, J = 10.0, 7.0 Hz, 1H, CH$_A$$H_B$O), 3.01 (s, 3H, $MeSO_2$), 2.21-2.20 (m, 2H, CH_2CH=), 1.98-1.89 (m, 1H, CHMe), 1.60-1.51 (m, 1H, CH_AH$_B$CHMe), 1.35-1.26 (m, 1H, CH$_A$$H_B$CHMe), 1.00 (d, J = 7.0 Hz, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.0 (=CH), 115.0 (=CH_2), 47.3 (OCH_2), 37.2 ($MeSO_2$), 32.4 (CH), 31.8 (CH_2), 30.8 (CH_2), 16.3 (Me).



2-Methyl-5-oxopentyl methanesulfonate 103

OsO_4 (0.21 mL of 2.5 %wt solution in *t*-butanol, 0.021 mmol, 0.02 eq.), $NaIO_4$ (890 mg, 4.16 mmol, 4.0 eq.) and 2,6-lutidine (0.24 mL, 2.08 mmol, 2.0 eq.) were added to a stirred solution of mesylate **101** (200 mg, 1.04 mmol, 1.0 eq.) in a 3:1 mixture of dioxane-water (8 mL) at rt. The resulting mixture was stirred at

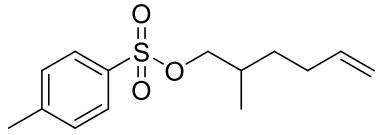
rt for 1 h. Water (10 mL) and CH_2Cl_2 (20 mL) were added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give crude aldehyde **103** (100 mg, 50%)as a colourless oil which was sufficiently pure for use in the next step, ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H, CHO), 4.09-4.07 (m, 2H, CH_2O), 3.03 (s, 3H, Me), 2.62-2.47 (m, 2H, CH), 1.99-1.79 (m, 2H, C*H*$_2$CH), 1.60-1.51 (m, 3H, CH), 1.01 (d, J = 7.0 Hz, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 201.6 (C=O), 73.7 (OCH_2), 40.9 (CH_2), 37.1 ($MeSO_2$), 32.3 (CH), 24.7 (CH_2), 16.0 (Me); MS (ESI) *m/z* 217 [(M + Na)$^+$, 100]; HRMS (ESI) *m/z* calcd for $C_7H_{14}NaO_4$ (M + Na)$^+$ 217.0505, found 217.0504 (0.5 ppm error).



5-Hydroxy-2,6-dimethylheptyl methanesulfonate 116

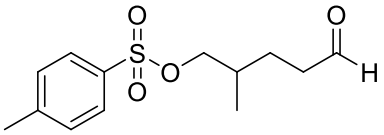
i-PrMgCl (0.29 mL of a 2 M solution in THF, 0.29 mmol, 1.2 eq.) was added dropwise to a stirred solution of aldehyde **103** (95 mg, 0.49 mmol, 1.0 eq.) in THF (5 mL) at 0 ºC under Ar. The resulting mixture was stirred at 0 ºC for 1 h and then stirred at rt for 3 h. Saturated $NH_4Cl_{(aq)}$ (5 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 Et_2O-CH_2Cl_2 as eluent gave a 50:50 mixture (by ^{1}H NMR spectroscopy) of alcohol **116** (18 mg, 15%) as a colourless oil, R_F (9:1 Et_2O-CH_2Cl_2) 0.7; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13-4.02 (m, 4H, CH_2O), 3.36-3.32 (m, 2H, C*H*OH), 3.01 (s, 6H, $MeSO_2$), 1.78-1.31 (m, 14H, CH, OH), 1.01 (d, J = 7.0 Hz, 1.5H, Me), 1.00 (d, J = 7.0 Hz, 1.5H, Me), 0.90 (d, J = 7.0

Hz, 1.5H, Me), 0.89 (d, J = 7.0 Hz, 1.5H, Me), 0.88 (d, J = 7.0 Hz, 1.5H, Me), 0.87 (d, J = 7.0 Hz, 1.5H, Me).



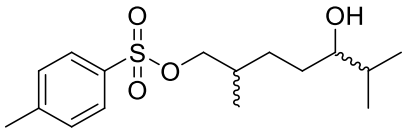
2-Methylhex-5-enyl 4-methylbenzenesulfonate 102

p-Toluenesulfonyl chloride (864 mg, 4.54 mmol, 1.5 eq.) was added dropwise to a stirred solution of alcohol **113** (345 mg, 3.02 mmol, 1.0 eq.) in pyridine (10 mL) at 0 ºC under Ar. The resulting mixture was stirred at rt for 16 h. Water (5 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were washed with 2 M $HCl_{(aq)}$ (80 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 petrol-EtOAc as eluent gave tosylate **102** (578 mg, 71%) as a colourless oil, R_F (4:1 petrol-EtOAc) 0.3; IR (film) 2972, 2928, 2856, 1641 (C=C), 1599, 1495, 1462, 1360, 1307, 1292, 1188, 1177, 970, 939, 734, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.0 Hz, 2H, *o*-$C_6H_4SO_2$), 7.74 (d, J = 8.0 Hz, 2H, *m*-$C_6H_4SO_2$), 5.71 (ddt, J = 17.0, 10.0, 7.0 Hz, 1H, =CH), 4.97-4.90 (m, 2H, $=CH_2$), 3.89 (dd, J = 9.0, 6.0 Hz, 1H, $CH_AH_BOSO_2$), 3.82 (dd, J = 9.0, 6.0 Hz, 1H, $CH_AH_BOSO_2$), 2.44 (s, 3H, MeC_6H_4), 2.05-1.90 (m, 2H, $CH_2CH=$), 1.84-1.76 (m, 1H, CH), 1.48-1.39 (m, 1H, CH_AH_BCH), 1.25-1.15 (m, 1H, CH_AH_BCH), 0.88 (d, J = 6.0 Hz, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.6 (*ipso*-Ar), 138.0 (=CH), 132.9 (*ipso*-Ar), 129.7 (Ar), 127.8 (Ar), 114.7 ($=CH_2$), 74.8 (OCH_2), 32.1 (CH), 31.6 (CH_2), 30.6 (CH_2), 21.5 (C_6H_4Me), 16.1 (Me); MS (ESI) *m/z* 291 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{14}H_{20}O_3S$ $(M + Na)^+$ 291.1025, found 291.1032 (–2.0 ppm error). Spectroscopic data consistent with those reported in the literature.[130]



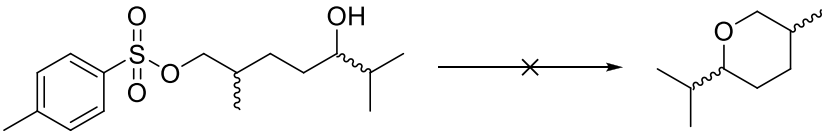
4-Methyl-5-(((4-methylbenzene)sulfonyl)oxy)pentanal 104

OsO_4 (0.56 mL of 2.5 %wt solution in *t*-butanol , 0.055 mmol, 0.02 eq.), $NaIO_4$ (2.34 g, 10.96 mmol, 4.0 eq.) and 2,6-lutidine (0.64 mL, 5.48 mmol, 2.0 eq.) were added to a stirred solution of tosylate **102** (568 mg, 1.65 mmol, 1.0 eq.) in a 3:1 mixture of dioxane-water (16 mL) at rt. The resulting mixture was stirred at rt for 1 h. Water (20 mL) and CH_2Cl_2 (40 mL) were added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (6 × 10 mL). The combined organic layers were washed with brine (80 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 petrol-EtOAc as eluent gave aldehyde **104** (654 mg, 88%) as a colourless oil, R_F (4:1 petrol-EtOAc) 0.3; IR (film) 2967, 2828, 1723 (C=O), 1598, 1463, 1358, 1188, 1176, 1098, 968, 816, 792, 733, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.74 (s, 1H, CHO), 7.79 (d, J = 8.0 Hz, 2H, *o*-$C_6H_4SO_2$), 7.36 (d, J = 8.0 Hz, 2H, *m*-$C_6H_4SO_2$), 3.88-3.86 (m, 2H, CH_2OSO_2), 2.45 (s, 3H, MeC_6H_4), 2.45-2.40 (m, 2H, CH_2CHO), 1.88-1.80 (m, 1H, CH), 1.77-1.68 (m, 1H, CH_AH$_B$CH), 1.52-1.42 (m, 1H, CH$_A$$H_B$CH), 0.91 (d, J = 7.0 Hz, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 201.6 (C=O), 144.8 (Ar), 132.6 (*ipso*-Ar), 129.8 (Ar), 127.7 (Ar), 74.2 (OCH_2), 40.8 (CH_2), 32.1 (CH), 24.6 (CH_2), 21.5 (C_6H_4*Me*), 16.0 (Me); MS (ESI) *m/z* 293 [$(M + Na)^+$, 41], 288 (100); HRMS (ESI) *m/z* calcd for $C_{13}H_{18}O_4S$ $(M + Na)^+$ 293.0818, found 293.0824 (−2.2 ppm error).



5-Hydroxy-2,6-dimethylheptyl 4-methylbenzenesulfonate 117

i-PrMgCl (1.30 mL of a 2 M solution in THF, 2.60 mmol, 1.2 eq.) was added dropwise to a stirred solution of aldehyde **104** (585 mg, 2.16 mmol, 1.0 eq.) in THF (10 mL) at 0 ºC under Ar. The resulting mixture was stirred at 0 ºC for 1 h and then stirred at rt for 1 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 petrol-Et_2O as eluent gave a 50:50 mixture (by ^{13}C NMR spectroscopy) of alcohol **117** (596 mg, 88%) as a colourless oil, R_F (4:1 petrol-Et_2O) 0.3; IR (film) 3566 (OH), 2962, 1465, 1359, 1176, 1121, 1098, 966, 835, 815, 667, 555 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.0 Hz, 2H, *o*-$C_6H_4SO_2$), 7.32 (d, J = 8.0 Hz, 2H, *m*-$C_6H_4SO_2$), 3.88-3.76 (m, 2H, CH_2OSO_2), 3.25-3.22 (m, 1H, C*H*OH), 2.41 (s, 3H, MeC_6H_4), 1.94 (s, 1H, OH), 1.80-1.01 (m, 6H, CH), 0.88-0.83 (m, 9H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.6 (*ipso*-Ar), 132.9 (*ipso*-Ar), 129.7 (Ar), 127.7 (Ar), 76.5 (CHOH), 76.3 (CHOH), 74.9 (OCH_2), 74.8 (OCH_2), 32.4 (CH), 33.2 (CH), 32.8 (CH), 32.7 (CH), 30.9 (CH_2), 30.8 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 21.5 (C_6H_4*Me*), 18.7 (Me), 18.6 (Me), 17.0 (Me), 16.8 (Me), 16.4 (Me), 16.2 (Me); MS (ESI) *m/z* 315 [(M^+, 13], 332 (100); HRMS (ESI) *m/z* calcd for $C_{16}H_{27}O_4S$ M^+ 315.1624, found 315.1624 (+0.1 ppm error).



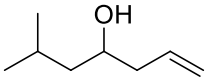
Attempted synthesis of 2-*i*-propyl-5-methyltetrahydro-2H-pyran 115

K_2CO_3 (264 mg, 1.91 mmol, 3.0 eq.) was added to a stirred solution of alcohol **117** (200 mg, 0.64 mmol, 1.0 eq.) in MeOH (5 mL) under Ar. The resulting mixture was stirred at rt for 16 h. H_2O (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. No evidence of the desired product was observed in the ^1H NMR spectrum of the crude product.

K_2CO_3 (264 mg, 1.91 mmol, 3.0 eq.) was added to a stirred solution of alcohol **117** (200 mg, 0.64 mmol, 1.0 eq.) in MeOH (5 mL) under Ar. The resulting mixture was stirred and heated to reflux for 16 h. After being allowed to cool to rt, the solution was poured into saturated $NH_4Cl_{(aq)}$ (10 mL) and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. No evidence of the desired product was observed in the ^1H NMR spectrum of the crude product and starting material alcohol **117** was still present.

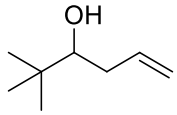
A solution of alcohol **117** (130 mg, 0.41 mmol, 1.0 eq.) in THF (2 mL) was added dropwise to a stirred suspension of NaH (33 mg of 60% wt dispersion in mineral oil, 0.82 mmol, pre-washed with Et_2O (3 × 2 mL), 2.0 eq.) in THF (3 mL) under Ar. The resulting mixture was stirred and heated to reflux for 16 h. After being allowed to cool to rt, the solution was poured into saturated $NH_4Cl_{(aq)}$ (10 mL) and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and

evaporated under reduced pressure to give the crude product. No evidence of the desired product was observed in the ^{1}H NMR spectrum of the crude product.



6-Methylhept-1-en-4-ol 122

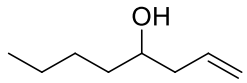
Using general procedure A, allyl magnesium bromide (100 mL of 1 M solution in Et_2O, 100.0 mmol, 1.1 eq.) and 3-methylbutanal (7.8 g, 90.9 mmol, 1.0 eq.) in Et_2O (100 mL) gave the crude product. Purification by flash column chromatography with 4:1 petrol-Et_2O as eluent gave alcohol **122** (10.5 g, 90%) as a colourless oil, R_F (4:1 petrol-Et_2O) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89-5.78 (m, 1H, =CH), 5.16-5.11 (m, 2H, =CH_2), 3.76-3.70 (m, 1H, C*H*OH), 2.32-2.26 (m, 1H, =CHCH_AH_B), 2.16-2.09 (m, 1H,=CHCH_AH_B), 1.83-1.76 (m, 1H, C*H*Me_2), 1.56 (br s, 1H, OH), 1.42 (ddd, J = 13.0, 9.0, 5.0 Hz, 1H, CH_AH_BCHOH), 1.25 (ddd, J = 13.0, 9.0, 5.0 Hz, 1H, CH_AH_BCHOH), 0.93 (d, J = 7.0 Hz, 3H, Me), 0.91 (d, J = 7.0 Hz, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 134.9 (=CH), 118.1 (=CH_2), 68.6 (CHO), 46.0 (CH_2), 42.5 (CH_2), 24.6 (CH), 23.4 (Me), 22.1 (Me). Spectroscopic data consistent with those reported in the literature.[131]



2,2-Dimethylhex-5-en-3-ol 123

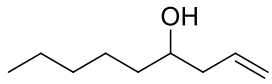
Using general procedure A, allyl magnesium bromide (100 mL of 1 M solution in Et_2O, 100.0 mmol, 1.1 eq.) and pivalaldehyde (7.8 g, 90.9 mmol, 1.0 eq.) in Et_2O (100 mL) gave the crude product. Purification by flash column chromatography with 4:1 petrol-Et_2O as eluent gave alcohol **123** (6.5 g, 56%) as a colourless oil, R_F (4:1 petrol-Et_2O) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90-5.80 (m, 1H, =CH), 5.15-5.11 (m, 2H, =CH_2), 3.24 (dd, J = 11.0, 10.0 Hz,

1H, C*H*OH), 2.38-2.33 (m, 1H, =CHCH_AH_B), 2.01-1.93 (m, 1H, =CHCH_AH_B), 1.67 (s, 1H, OH), 0.91 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 136.6 (=CH), 117.7 (=CH_2), 78.1 (CHO), 36.5 (CH_2), 34.5 (*C*Me_3), 25.7 (C*Me*$_3$). Spectroscopic data consistent with those reported in the literature. [132]



Oct-1-en-4-ol 124

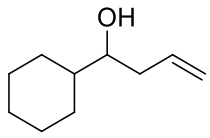
Using general procedure A, allyl magnesium bromide (100 mL of 1 M solution in Et_2O, 100.0 mmol, 1.1 eq.) and pentanal (7.8 g, 90.9 mmol, 1.0 eq.) in Et_2O (100 mL) gave the crude product. Purification by flash column chromatography with 4:1 petrol-Et_2O as eluent gave alcohol **124** (11.0 g, 94%) as a colourless oil, R_F (4:1 petrol-Et_2O) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88-5.78 (m, 1H, =CH), 5.15-5.11 (m, 2H, =CH_2), 3.67-3.61 (m, 1H, C*H*OH), 2.33-2.09 (m, 2H, =CHC*H*$_2$), 1.75 (s, 1H, OH), 1.49-1.30 (m, 6H, CH), 0.91 (t, *J* = 7.0 Hz, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 134.9 (=CH), 118.0 (=CH_2), 70.6 (CHO), 41.9 (CH_2), 36.5 (CH_2), 27.8 (CH_2), 22.7 (CH_2), 14.0 (Me). Spectroscopic data consistent with those reported in the literature.[133]



Non-1-en-4-ol 125

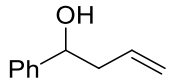
Using general procedure A, allyl magnesium bromide (100 mL of 1 M solution in Et_2O, 100.0 mmol, 1.1 eq.) and hexanal (9.1 g, 90.9 mmol, 1.0 eq.) in Et_2O (100 mL) gave the crude product. Purification by flash column chromatography with 4:1 petrol-Et_2O as eluent gave alcohol **125** (12.2 g, 98%) as a colourless oil, R_F (4:1 petrol-Et_2O) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88-5.78 (m, 1H, =CH), 5.15-5.11 (m, 2H, =CH_2), 3.67-3.61 (m, 1H, C*H*OH), 2.33-2.27 (m, 1H, =CHCH_AH_B), 2.17-2.10 (m, 1H, =CHCH_AH_B), 1.72 (s, 1H, OH), 1.47-1.29 (m, 8H, CH), 0.89 (t, *J* = 7.0 Hz, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 134.9

(=CH), 118.0 (=CH_2), 70.8 (CHO), 42.0 (CH_2), 36.9 (CH_2), 31.8 (CH_2), 25.4 (CH_2), 22.7 (CH_2), 14.1 (Me). Spectroscopic data consistent with those reported in the literature.[132]



1-Cyclohexylbut-3-en-1-ol 126

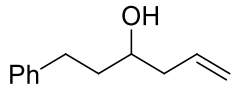
Using general procedure A, allyl magnesium bromide (19.61 mL of 1 M solution in Et_2O, 19.61 mmol, 1.1 eq.) and cyclohexanecarbaldehyde (2.0 g, 90.9 mmol, 1.0 eq.) in Et_2O (50 mL) gave the crude product. Purification by flash column chromatography with 4:1 petrol-Et_2O as eluent gave alcohol **126** (2.3 g, 82%) as a colourless oil, R_F (4:1 petrol-Et_2O) 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90-5.78 (m, 1H, =CH), 5.17-5.13 (m, 2H, =CH_2), 3.42-3.38 (m, 1H, C*H*OH), 2.38-2.37 (m, 1H, =CHCH_AH$_B$), 2.32-2.09 (m, 1H, =CHCH$_A$$H_B$), 1.89-1.65 (m, 5H), 1.56 (s, 1H, OH), 1.42-0.98 (m, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 135.5 (=CH), 118.0 (=CH_2), 74.7 (CHO), 43.1 (CH), 38.8 (CH_2), 29.1 (CH_2), 28.1 (CH_2), 26.5 (CH_2), 26.3 (CH_2), 26.1 (CH_2). Spectroscopic data consistent with those reported in the literature.[132]



1-Phenylbut-3-en-1-ol 127

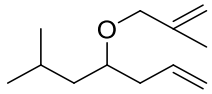
Using general procedure A, allyl magnesium bromide (100 mL of 1 M solution in Et_2O, 100.0 mmol, 1.1 eq.) and benzaldehyde (9.6 g, 90.9 mmol, 1.0 eq.) in Et_2O (100 mL) gave the crude product. Purification by flash column chromatography with 4:1 petrol-Et_2O as eluent gave alcohol **127** (11.0 g, 90%) as a colourless oil, R_F (4:1 petrol-Et_2O) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.34 (m, 5H, Ph), 5.88-5.78 (m, 1H, =CH), 5.21-5.15 (m, 2H, =CH_2), 3.55 (ddd, J = 8.0, 5.0, 3.0 Hz, 1H, C*H*OH), 2.59-2.47 (m, 2H, =CHCH_2), 2.06-2.04

(m, 1H, OH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.8 (*ipso*-Ph), 134.4 (Ph), 128.4 (Ph), 127.5 (Ph), 125.8 (=CH), 118.3 (=CH_2), 73.2 (CHO), 43.8 (CH_2); MS (ESI) *m/z* 171 [$(M + Na)^+$, 75], 131 (100); HRMS (ESI) *m/z* calcd for $C_{10}H_{12}O$ $(M + Na)^+$ 171.0786, found 171.0780 (⁻3.5 ppm error). Spectroscopic data consistent with those reported in the literature.[134]



1-Phenylhex-5-en-3-ol 128

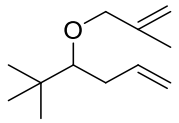
Using general procedure A, allyl magnesium bromide (41.0 mL of 1 M solution in Et_2O, 41.0 mmol, 1.1 eq.) and 3-phenylpropanal (5.0 g, 37.23 mmol, 1.0 eq.) in Et_2O (100 mL) gave the crude product. Purification by flash column chromatography with 4:1 petrol-Et_2O as eluent gave alcohol **128** (3.4 g, 51%) as a colourless oil, R_F (4:1 petrol-Et_2O) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.28 (m, 2H, Ph), 7.23-7.18 (m, 3H, Ph), 5.88-5.78 (m, 1H, =CH), 5.18-5.14 (m, 2H, =CH_2), 3.72-3.66 (m 1H, C*H*OH), 2.86-2.79 (m, 1H, =CHCH_AH_B), 2.74-2.67 (m, 1H, =CHCH_AH_B), 2.37-2.31 (m, 1H, CH_AH_BOH), 2.23-2.16 (m, 1H, CH_AH_BOH), 1.83-1.77 (m, 2H, CH_2), 1.62 (m, 1H, OH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 142.0 (*ipso*-Ph), 134.6 (Ph), 128.4 (Ph), 128.3 (Ph), 125.8 (=CH), 118.4 (=CH_2), 69.9 (CHO), 42.1 (CH_2), 38.4 (CH_2), 32.0 (CH_2). Spectroscopic data consistent with those reported in the literature.[135]



6-Methyl-4-(2-methylallyloxy)hept-1-ene 129

Using general procedure B, alcohol **122** (3.0 g, 23.40 mmol, 1.0 eq.), NaH (3.4 g of 60% wt dispersion in mineral oil, 70.20 mmol, pre-washed with Et_2O (3 × 10 mL), 3.0 eq.) and 3-bromo-2-methylprop-1-ene (2.81 mL, 28.08 mmol, 1.2 eq.) in THF (60 mL) gave the crude product. Purification by flash column

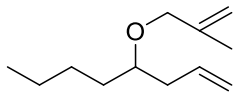
chromatography with 99:1 petrol-Et_2O as eluent gave ether **129** (3.9 g, 90%) as a colourless oil, R_F (99:1 petrol-Et_2O) 0.5; IR (film) 2956, 2926, 2869, 1464, 1368, 1347, 1085, 992, 899, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.84 (ddt, J = 17.0, 10.0, 7.0 Hz, 1H, =CH), 5.10-5.04 (m, 2H, $=CH_2$), 4.97-4.87 (m, 2H, $=CH_2$), 3.95 (d, J = 12.0 Hz, 1H, OCH_AH_B), 3.83 (d, J = 12.0 Hz, 1H, OCH_AH_B), 3.45-3.40 (m, 1H, CHO), 2.30-2.27 (m, 2H, $=CHCH_2$), 1.83-1.78 (m, 1H, $CHMe_2$), 1.76 (s, 3H, =CMe), 1.50 (ddd, J = 14.0, 8.0, 6.0 Hz, 1H, CH_AH_BCHO), 1.24 (ddd, J = 14.0, 8.0, 6.0 Hz, 1H, CH_AH_BCHO), 0.93 (d, J = 7.0 Hz, 3H, CH*Me*), 0.90 (d, J = 7.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 142.8 (=*C*Me), 135.0 (=CH), 116.8 ($=CH_2$), 112.0 ($=CH_2$), 76.6 (CHO), 72.9 (OCH_2), 43.4 (CH_2), 38.5 (CH_2), 24.5 (CH), 23.3 (Me), 22.3 (Me), 19.8 (Me); MS (APCI) *m/z* 183 [$(M + H)^+$, 30], 179 (100); HRMS (APCI) *m/z* calcd for $C_{12}H_{22}O$ $(M + H)^+$ 183.1746, found 183.1743 (1.4 ppm error).



5,5-Dimethyl-4-[(2-methylprop-2-en-1-yl)oxy]hex-1-ene 130

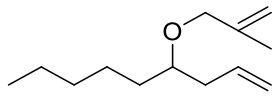
Using general procedure B, alcohol **123** (3.0 g, 23.40 mmol, 1.0 eq.), NaH (3.4 g of 60% wt dispersion in mineral oil, 70.20 mmol, pre-washed with Et_2O (3 × 10 mL), 3.0 eq.) and 3-bromo-2-methylprop-1-ene (2.81 mL, 28.08 mmol, 1.2 eq.) in THF (60 mL) gave the crude product. Purification by flash column chromatography with 99:1 petrol-Et_2O as eluent gave ether **130** (4.1 g, 94%) as a colourless oil, R_F (99:1 petrol-Et_2O) 0.5; IR (film) 2955, 2867, 1640 (C=C), 1480, 1462, 1392, 1363, 1335, 1113, 1090, 1058, 987, 898 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.94 (ddt, J = 17.0, 10.0, 7.0 Hz, 1H, =CH), 5.12-5.06 (m, 1H, $=CH_AH_B$), 5.01-4.83 (m, 3H, $=CH_2$, $=CH_AH_B$), 4.02 (d, J = 12.0 Hz, 1H, OCH_AH_B), 3.83 (d, J = 12.0 Hz, 1H, OCH_AH_B), 2.93 (dd, J = 8.5, 8.0 Hz, 1H, CHO), 2.37-2.30 (m, 1H, $=CHCH_AH_B$), 2.25-1.16 (m, 1H, $=CHCH_AH_B$), 1.75 (s,

3H, =CMe), 0.93 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 142.9 (=*C*Me), 137.5 (=CH), 115.8 ($=CH_2$), 111.2 ($=CH_2$), 87.9 (CHO), 76.3 (OCH_2), 36.0 (*C*Me_3), 35.8 (CH_2), 26.3 (C*Me*$_3$), 19.9 (Me); MS (ESI) *m/z* 183 [$(M + H)^+$, 90], 61 (100), 126 (70); HRMS (ESI) *m/z* calcd for $C_{12}H_{22}O$ $(M + H)^+$ 183.1737, found 183.1743 (+3.4 ppm error).



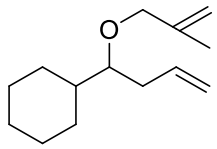
4-[(2-Methylprop-2-en-1-yl)oxy]oct-1-ene 131

Using general procedure B, alcohol **124** (2.0 g, 23.40 mmol, 1.0 eq.), NaH (2.3 g of 60% wt dispersion in mineral oil, 70.20 mmol, pre-washed with Et_2O (3 × 10 mL), 3.0 eq.) and 3-bromo-2-methylprop-1-ene (1.87 mL, 18.72 mmol, 1.2 eq.) in THF (60 mL) gave the crude product. Purification by flash column chromatography with 99:1 petrol-Et_2O as eluent gave ether **131** (2.8 g, 98%) as a colourless oil, R_F (99:1 petrol-Et_2O) 0.4; IR (film) 2957, 2928, 2859, 1456, 1375, 1342, 1107, 992, 911, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H, =CH), 5.10-5.04 (m, 2H, $=CH_2$), 4.98-4.87 (m, 2H, $=CH_2$), 3.93 (d, *J* = 12.0 Hz, 1H, OC*H*$_A$H$_B$), 3.86 (d, *J* = 12.0 Hz, 1H, OCH$_A$*H*$_B$), 3.38-3.32 (m, 1H, CHO), 2.30-2.27 (m, 2H, =CHC*H*$_2$), 1.76 (s, 3H, =CMe), 1.53-1.26 (m, 6H, 6 × CH), 0.91 (t, *J* = 7.0 Hz, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 142.8 (=*C*Me), 135.1 (=CH), 116.6 ($=CH_2$), 111.9 ($=CH_2$), 78.4 (CHO), 72.9 (OCH_2), 38.2 (CH_2), 33.4 (CH_2), 27.5 (CH_2), 22.8 (CH_2), 19.7 (Me), 14.1 (Me); MS (APCI) *m/z* 183 [$(M + H)^+$, 100], 165 (80); HRMS was not obtained successfully by either ESI or APCI.



4-[(2-Methylprop-2-en-1-yl)oxy]non-1-ene 132

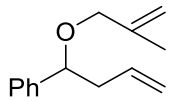
Using general procedure B, alcohol **125** (2.0 g, 14.06 mmol, 1.0 eq.), NaH (2.0 g of 60% wt dispersion in mineral oil, 44.4 mmol, pre-washed with Et_2O (3 × 10 mL), 3.0 eq.) and 3-bromo-2-methylprop-1-ene (1.69 mL, 16.87 mmol, 1.2 eq.) in THF (60 mL) gave the crude product. Purification by flash column chromatography with 99:1 petrol-Et_2O as eluent gave ether **132** (2.7 g, 98%) as a colourless oil, R_F (99:1 petrol-Et_2O) 0.5; IR (film) 2928, 2857, 1641, 1456, 1375, 1343, 1086, 993, 910, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.83 (ddt, J = 17.0, 10.0, 7.0 Hz, 1H, =CH), 5.11-5.03 (m, 2H, $=CH_2$), 4.98-4.85 (m, 2H, $=CH_2$), 3.92 (d, J = 12.0 Hz, 1H, OCH_AH_B), 3.86 (d, J = 12.0 Hz, 1H, OCH_AH_B), 3.38-3.32 (m, 1H, CHO), 2.34-2.23 (m, 2H, $=CHCH_2$), 1.76 (s, 3H, =CMe), 1.51-1.46 (m, 2H, CH_2), 1.35-1.26 (m, 6H, CH), 0.89 (t, J = 7.0 Hz, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 142.8 (=*C*Me), 135.1 (=CH), 116.6 ($=CH_2$), 111.8 ($=CH_2$), 78.4 (CHO), 72.8 (OCH_2), 38.2 (CH_2), 33.7 (CH_2), 32.0 (CH_2), 25.0 (CH_2), 22.6 (CH_2), 19.6 (Me), 14.0 (Me); MS (ESI) *m/z* 197 [$(M + H)^+$, 20], 61 (100), 126 (70), 83 (65); HRMS (ESI) *m/z* calcd for $C_{13}H_{24}O$ $(M + H)^+$ 197.1907, found 197.1900 (−3.5 ppm error).



(1-(2-Methylallyloxy)but-3-enyl)cyclohexane 133

Using general procedure B, alcohol **126** (5.0 g, 32.40 mmol, 1.0 eq.), NaH (4.7 g of 60% wt dispersion in mineral oil, 44.4 mmol, pre-washed with Et_2O (3 × 10 mL), 3.0 eq.) and 3-bromo-2-methylprop-1-ene (3.89 mL, 16.87 mmol, 1.2 eq.) in THF (80 mL) gave the crude product. Purification by flash column chromatography with 99:1 petrol-Et_2O as eluent gave ether **133** (2.7 g, 98%) as a

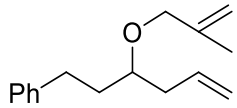
colourless oil, R_F (99:1 petrol-Et_2O) 0.4; IR (film) 2880, 2809, 1427, 1352, 1324, 1094, 1016, 983, 884 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.92-5.82 (m, 1H, =CH), 5.10-5.03 (m, 2H, $=CH_2$), 4.98-4.86 (m, 2H, $=CH_2$), 3.93 (d, J = 12.0 Hz, 1H, OCH_AH_B), 3.82 (d, J = 12.0 Hz, 1H, OCH_AH_B), 3.12-3.08 (m, 1H, CHO), 2.31-2.26 (m, 2H, $=CHCH_2$), 1.76 (s, 3H, =CMe), 1.26-0.87 (m, 11H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 142.9 (=*C*Me), 135.7 (=CH), 116.4 ($=CH_2$), 111.8 ($=CH_2$), 83.3 (CHO), 73.9 (OCH_2), 41.0 (CH), 35.2 (CH_2), 28.9 (CH_2), 28.6 (CH_2), 26.6 (CH_2), 26.4 (CH_2), 26.3 (CH_2), 19.8 (Me); MS (ESI) *m/z* 1231 [$(M + Na)^+$, 30], 137 (100); HRMS (ESI) *m/z* calcd for $C_{14}H_{24}O$ $(M + Na)^+$ 231.1727, found 231.1719 (-2.7 ppm error).



(1-(2-Methylprop-2-en-1-yloxy)but-3-en-1-yl)benzene 12

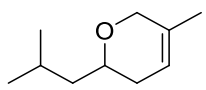
Using general procedure B, alcohol **127** (1.4 g, 9.65 mmol, 1.0 eq.), NaH (463 mg of 60% wt dispersion in mineral oil, 44.4 mmol, pre-washed with Et_2O (3 × 10 mL), 1.2 eq.) and 3-bromo-2-methylprop-1-ene (1.17 mL, 11.58 mmol, 1.2 eq.) in THF (45 mL) gave the crude product. Purification by flash column chromatography with 9:1 petrol-Et_2O as eluent gave ether **12** (1.8 g, 93%) as a colourless oil, R_F (9:1 petrol-Et_2O) 0.3; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.29 (m, 5H, Ph), 5.80 (ddt, J = 17.0, 10.0, 7.0 Hz, 1H, =CH), 5.08-5.01 (m, 2H, $=CH_2$), 4.95 (br s, 1H, $=CH_AH_BCMe$), 4.89 (br s, 1H, $=CH_AH_BCMe$), 4.32 (dd, J = 7.0, 6.0 Hz, 1H, C*H*OH), 3.83 (d, J = 12.0 Hz, 1H, OCH_AH_B), 3.66 (d, J = 12.0 Hz, 1H, OCH_AH_B), 2.61 (dt, J = 14.0, 7.0 Hz, 1H, CH_AH_BCH), 2.42 (dt, J = 14.0, 6.0 Hz, 1H, CH_AH_BCH), 1.74 (s, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 142.2 (*ipso*-Ph), 141.9 (=*C*Me), 134.9 (Ph), 128.2 (Ph), 127.5 (Ph), 126.7 (=CH), 116.8 ($=CH_2$), 111.9 ($=CH_2$), 80.8 (CHO), 72.2 (OCH_2), 42.7 (CH_2), 19.6 (Me); MS (ESI) *m/z* 225 [$(M + Na)^+$, 40], 131 (100), 222 (63); HRMS (ESI) *m/z*

calcd for $C_{14}H_{18}O$ $(M + Na)^+$ 225.1258, found 225.1250 (−3.8 ppm error). Spectroscopic data consistent with those reported in the literature.[136]



(3-(2-Methylallyloxy)hex-5-enyl)benzene 134

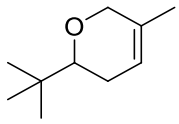
Using general procedure B, alcohol **128** (3.0 g, 17.03 mmol, 1.0 eq.), NaH (2.0 g of 60% wt dispersion in mineral oil, 51.09 mmol, pre-washed with Et_2O (3 × 10 mL), 3.0 eq.) and 3-bromo-2-methylprop-1-ene (1.87 mL, 18.73 mmol, 1.2 eq.) in THF (80 mL) gave the crude product. Purification by flash column chromatography with 99:1 petrol-Et_2O as eluent gave ether **134** (3.4 g, 86%) as a colourless oil, R_F (99:1 petrol-Et_2O) 0.4; IR (film) 3029, 2980, 2930, 2875, 2816, 1473, 1432, 1323, 1080, 888, 735, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.27 (m, 2H, Ph), 7.21-7.17 (m, 3H, Ph), 5.84 (ddt, J = 17.0, 10.0, 7.0 Hz, 1H, =CH), 5.12-5.06 (m, 2H, $=CH_2$), 5.01 (br s, 1H, $=CH_AH_BCMe$), 4.90 (br s, 1H, $=CH_AH_BCMe$), 3.96 (d, J = 12.0 Hz, 1H, OCH_AH_B), 3.87 (d, J = 12.0 Hz, 1H, OCH_AH_B), 3.44-3.38 (m, 1H, CHO), 2.78 (ddd, J = 14.0, 10.0, 6.0 Hz, 1H, CH_AH_BCH), 2.64 (dt, J = 14.0, 10.0, 6.0 Hz, 1H, CH_AH_BCH), 2.40-2.28 (m, 2H, CH_2), 1.87-1.82 (m, 2H, CH_2), 1.80 (s, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 142.7 (*ipso*-Ph), 142.4 (=*C*Me), 134.8 (Ph), 128.4 (Ph), 128.3 (Ph), 125.7 ($=CH_2$), 117.0 (=CH), 112.0 ($=CH_2$), 76.7 (CHO), 72.9 (OCH_2), 38.2 (CH_2), 35.6 (CH_2), 31.7 (CH_2), 19.8 (Me); MS (ESI) *m/z* 253 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{16}H_{22}O$ $(M + Na)^+$ 253.1559, found 253.1563 (1.1 ppm error).



2-*i*-Butyl-5-methyl-3,6-dihydro-2H-pyran 135

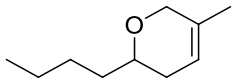
Using general procedure C, Grubbs' 2nd generation catalyst **5** (23 mg, 0.03 mmol, 0.01 eq.) and diene **129** (500 mg, 2.74 mmol, 1.0 eq.) in CH_2Cl_2 (25 mL)

gave the crude product. Purification by flash column chromatography with 99:1 petrol-Et_2O as eluent gave cyclic ether **135** (347 mg, 82%) as a brown oil, R_F (99:1 petrol-Et_2O) 0.3; IR (film) 2956, 2919, 2832, 2808, 1467, 1449, 1379, 1367, 1131, 1100, 1060, 979, 904, 800 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.48-5.47 (m, 1H, =CH), 4.07-3.95 (m, 2H, CH_2O), 3.52-3.40 (m, 1H, CHO), 1.95-1.92 (m, 2H, =CHCH_2), 1.83-1.76 (m, 1H, CHMe$_2$), 1.59 (s, 3H, =CMe), 1.53-1.46 (m, 1H, CH_AH$_B$CHO), 1.28-1.21 (m, 1H, CH$_A$$H_B$CHO), 0.91 (d, J = 7.0 Hz, 6H, CHMe_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 133.0 (=CMe), 118.6 (=CH), 71.8 (CHO), 69.2 (OCH_2), 45.0 (CH_2), 31.4 (CH_2), 24.4 (CH), 23.1 (Me), 22.5 (Me), 18.6 (Me); MS was not obtained successfully by either ESI or APCI.



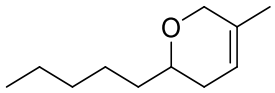
2-*t*-Butyl-5-methyl-3,6-dihydro-2H-pyran 136

Using general procedure C, Grubbs' 2nd generation catalyst **5** (2 mg, 0.003 mmol, 0.01 eq.) and diene **130** (50 mg, 0.27 mmol, 1.0 eq.) in CH_2Cl_2 (1 mL) gave the crude product. Purification by flash column chromatography with 99:1 petrol-Et_2O as eluent gave cyclic ether **136** (34 mg, 80%) as a brown oil, R_F (99:1 petrol-Et_2O) 0.3; IR (film) 2956, 2921, 2871, 2819, 1481, 1465, 1448, 1363, 1108, 1083, 1049, 984, 903, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.52-5.49 (m, 1H, =CH), 4.04-4.03 (m, 2H, CH_2O), 3.07 (dd, J = 8.5, 8.0 Hz, 1H, CHO), 2.19-2.02 (m, 1H, =CHCH_AH$_B$), 1.90-1.85 (m, 1H, =CHCH$_A$$H_B$), 1.60 (s, 3H, =CMe), 0.92 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 133.0 (=CMe), 119.1 (=CH), 81.6 (CHO), 70.2 (OCH_2), 33.7 (CMe$_3$), 25.8 (CMe_3), 25.4 (CH_2), 18.5 (Me); MS was not obtained successfully by either ESI or APCI.



2-Butyl-5-methyl-3,6-dihydro-2H-pyran 137

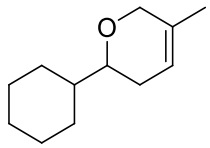
Using general procedure C, Grubbs' 2nd generation catalyst **5** (55 mg, 0.06 mmol, 0.01 eq.) and diene **131** (1.18 g, 6.47 mmol, 1.0 eq.) in CH_2Cl_2 (50 mL) gave the crude product. Purification by flash column chromatography with 99:1 petrol-Et_2O as eluent gave cyclic ether **137** (970 mg, 97%) as a colourless oil, R_F (99:1 petrol-Et_2O) 0.3; IR (film) 2957, 2928, 2859, 1449, 1379, 1358, 1125, 1098, 1068, 978, 909, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.48-5.47 (m, 1H, =CH), 4.08-3.97 (m, 2H, CH_2O), 3.44-3.38 (m, 1H, CHO), 1.97-1.94 (m, 2H, =CHC*H*$_2$), 1.60 (s, 3H, =CMe), 1.56-1.30 (m, 6H, CH), 0.91 (t, J = 6.0 Hz, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 132.9 (=*C*Me), 118.6 (=CH), 73.6 (CHO), 69.2 (OCH_2), 35.5 (CH_2), 31.0 (CH_2), 27.7 (CH_2), 22.7 (CH_2), 18.5 (Me), 14.0 (Me); MS (ESI) *m/z* 155 [$(M + H)^+$, 10], 317 (100); HRMS (ESI) *m/z* calcd for $C_{10}H_{18}O$ $(M + H)^+$ 155.1424, found 155.1430 (+3.4 ppm error).



5-Methyl-2-pentyl-3,6-dihydro-2H-pyran 138

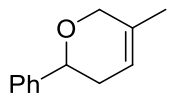
Using general procedure C, Grubbs' 2nd generation catalyst **5** (43 mg, 0.05 mmol, 0.01 eq.) and diene **132** (1.1 g, 5.09 mmol, 1.0 eq.) in CH_2Cl_2 (50 mL) gave the crude product. Purification by flash column chromatography with 99:1 petrol-Et_2O as eluent gave cyclic ether **138** (820 mg, 96%) as a colourless oil, R_F (99:1 petrol-Et_2O) 0.3; IR (film) 2927, 2858, 1449, 1379, 1357, 1125, 1100, 1069, 979, 901, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.48-5.47 (m, 1H, =CH), 4.08-3.97 (m, 2H, CH_2O), 3.44-3.38 (m, 1H, CHO), 1.97-1.91 (m, 2H, =CHC*H*$_2$), 1.59 (s, 3H, =CMe), 1.57-1.30 (m, 8H, CH), 0.89 (t, J = 6.0 Hz, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 132.9 (=*C*Me), 118.5 (=CH), 73.6 (CHO), 69.2 (OCH_2), 35.8 (CH_2), 31.9 (CH_2), 31.0 (CH_2), 25.2 (CH_2), 22.6 (CH_2), 18.6 (Me),

14.1 (Me); MS (APCI) *m/z* 169 [(M + H)$^+$, 20], 151 (100), 95 (70); HRMS (APCI) *m/z* calcd for $C_{11}H_{20}O$ (M + H)$^+$ 169.1579, found 169.1587 (4.5 ppm error).



2-Cyclohexyl-5-methyl-3,6-dihydro-2H-pyran 139

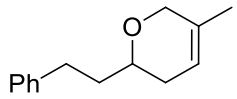
Using general procedure C, Grubbs' 2nd generation catalyst **5** (2 mg, 0.003 mmol, 0.01 eq.) and diene **133** (50 mg, 0.25 mmol, 1.0 eq.) in CH_2Cl_2 (1 mL) gave the crude product. Purification by flash column chromatography with 99:1 petrol-Et_2O as eluent gave cyclic ether **139** (39 mg, 89%) as a colourless oil, R_F (99:1 petrol-Et_2O) 0.5; IR (film) 2922, 2851, 1449, 1378, 1353, 1140, 1105, 1082, 1068, 1027, 986, 906, 888, 823, 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47-5.45 (m, 1H, =CH), 4.03-3.94 (m, 2H, CH_2O), 3.14-3.09 (m, 1H, CHO), 2.04-1.86 (m, 3H, CH), 1.74-1.63 (m, 4H, CH), 1.57 (s, 3H, =CMe), 1.41-1.32 (m, 1H, CH), 1.28-1.01 (m, 3H, CH), 1.04-0.90 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 132.9 (=*C*Me), 118.7 (=CH), 77.9 (CHO), 69.5 (OCH_2), 42.6 (CH), 29.2 (CH_2), 28.4 (CH_2), 28.0 (CH_2), 26.6 (CH_2), 26.1 (CH_2), 26.0 (CH_2), 18.5 (Me); MS (APCI) *m/z* 181 [(M + H)$^+$, 20], 163 (100), 179 (50); HRMS was not obtained successfully by either ESI or APCI.



5-Methyl-2-phenyl-3,6-dihydro-2H-pyran 13

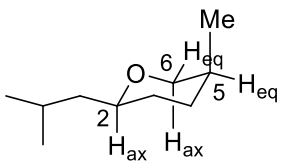
Using general procedure C, Grubbs' 2nd generation catalyst **5** (49 mg, 0.06 mmol, 0.01 eq.) and diene **12** (0.6 g, 0.58 mmol, 1.0 eq.) in CH_2Cl_2 (50 mL) gave the crude product. Purification by flash column chromatography with 99:1 petrol-Et_2O as eluent gave cyclic ether **13** (502 mg, 98%) as a colourless oil, R_F

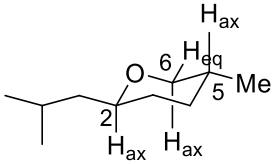
(99:1 petrol-Et_2O) 0.3; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.28 (m, 5H, Ph), 5.62-5.61 (m, 1H, =CH), 4.51 (dd, J = 10.0, 4.0 Hz, 1H, CHO), 4.29-4.16 (m, 2H, OCH_2), 2.38-2.21 (m, 2H, =CHCH_2), 1.68 (s, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 142.5 (*ipso*-Ph), 133.1 (=*C*Me), 128.3 (Ph), 127.4 (Ph), 125.8 (Ph), 118.8 (=CH), 76.7 (CHO), 75.7 (OCH_2), 32.8 (CH_2), 18.5 (Me); MS (ESI) *m/z* 173 [$(M)^+$, 80], 171 (100); HRMS (ESI) *m/z* calcd for $C_{12}H_{13}O$ M^+ 173.0961, found 173.0948 (1.2 ppm error). Spectroscopic data consistent with those reported in the literature.[137]



5-Methyl-2-phenethyl-3,6-dihydro-2H-pyran 140

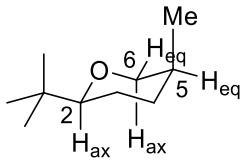
Using general procedure C, Grubbs' 2nd generation catalyst **5** (30 mg, 0.08 mmol, 0.01 eq.) and diene **134** (1.0 g, 7.67 mmol, 1.0 eq.) in CH_2Cl_2 (20 mL) gave the crude product. Purification by flash column chromatography with 99:1 petrol-Et_2O as eluent gave cyclic ether **140** (1.38 g, 89%) as a colourless oil, R_F (99:1 petrol-Et_2O) 0.3; IR (film) 2980, 2879, 2815, 2789, 1429, 1093, 1050, 895, 722, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.27 (m, 2H, Ph), 7.22-7.17 (m, 3H, Ph), 5.48-5.47 (m, 1H, =CH), 4.10-4.00 (m, 2H, OCH_2), 3.42 (ddt, J = 13.0, 9.0, 4.0 Hz, 1H, CHO), 2.85-2.78 (m, 1H, CHOC$H_A$$H_B$), 2.70 (ddd, J = 14.0, 9.0, 7.0 Hz, 1H, CHO$H_A$$H_B$), 2.06-1.73 (m, 4H, CH_2), 1.73 (s, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 142.2 (*ipso*-Ph), 133.0 (=*C*Me), 128.5 (Ph), 128.3 (Ph), 125.7 (Ph), 118.4 (=CH), 72.6 (CHO), 69.2 (OCH_2), 37.4 (CH_2), 31.8 (CH_2), 31.0 (CH_2), 18.6 (Me); MS (ESI) *m/z* 225 [$(M + Na)^+$, 60], 91(100); HRMS (ESI) *m/z* calcd for $C_{14}H_{18}O$ $(M + Na)^+$ 225.1251, found 225.1250 (−1.0 ppm error).

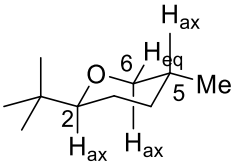




2-*i*-5-Methyltetrahydro-2H-pyran *cis*-141 and *trans*-142

Using general procedure D, Pd/C (69 mg of 5% wt on carbon, 0.06 mmol, 0.1 eq.) and alkene **135** (100 mg, 0.65 mmol, 1.0 eq.) in MeOH (2.5 mL) gave the crude product (24 mg, 23%) as a colourless oil, which contained an 83:17 mixture (by ^{1}H NMR spectroscopy) of cyclic ethers *cis*-**141** and *trans*-**142**, R_F (9:1 petrol-Et_2O) 0.3; IR (film) 2910, 2886, 2800, 1445, 1346, 1186, 1120, 1105, 1069, 1024, 972, 894, 725 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (ddd, J = 11.0, 4.0, 2.0 Hz, 0.17H, $C_6H_{eq}O^{trans}$), 3.63 (dt, J = 11.0, 2.0 Hz, 0.83H, $C_6H_{eq}O^{cis}$), 3.58 (dd, J = 11.0, 3.0 Hz, 0.83H, $C_6H_{ax}O^{cis}$), 3.38-3.32 (m, 0.83H, $C_2H_{ax}{}^{cis}$), 3.27-3.18 (m, 0.17H, $C_2H_{ax}{}^{trans}$), 2.98 (t, J = 11.0 Hz, 0.17H, $C_6H_{ax}{}^{trans}$), 1.80-1.69 (m, 3H, CH), 1.52-1.37 (m, 4H, CH), 1.18-1.12 (m, 1H, CH), 1.07 (d, J = 7.0 Hz, 2.49H, CHMe^{cis}), 0.90 (d, J = 7.0 Hz, 6H, CHMe_2), 0.78 (d, J = 7.0 Hz, 0.51H, CHMe^{trans}); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ for *cis*-**141** 75.7 (CHO), 72.5 (OCH_2), 44.9 (CH_2), 29.0 (CH_2), 28.4 (CH), 27.4 (CH_2), 24.2 (CH), 23.3 (Me), 22.3 (Me), 16.7 (Me); δ for *trans*-**142** 75.5, 74.8, 45.5, 32.5, 32.3, 31.4, 31.0, 25.9, 24.3, 17.3; MS was not obtained successfully by either ESI or APCI.

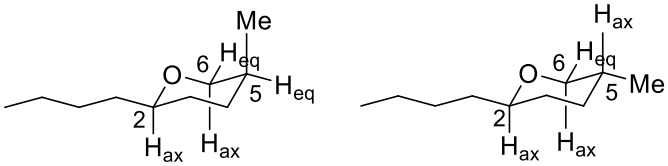




2-*t*-Butyl-5-methyltetrahydro-2H-pyran *cis*-143 and *trans*-144

Using general procedure D, Pd/C (69 mg of 5% wt on carbon, 0.06 mmol, 0.1 eq.) and alkene **136** (100 mg, 0.65 mmol, 1.0 eq.) in MeOH (2.5 mL) gave the crude product (76 mg, 77%), which contained an 89:11 mixture (by ^{1}H NMR spectroscopy) of cyclic ethers *cis*-**143** and *trans*-**144**. IR (film) 2908, 2883, 2811, 1442, 1341, 1189, 1120, 1105, 1059, 1028, 971, 894, 724 cm^{-1}; ^{1}H NMR (400

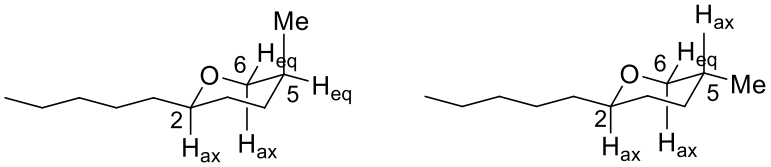
MHz, $CDCl_3$) δ 3.88 (ddd, J = 11.0, 4.0, 2.0 Hz, 0.11H, $C_6H_{eq}O^{trans}$), 3.71 (br dd, J = 11.0, 2.0 Hz, 0.89H, $C_6H_{eq}O^{cis}$), 3.56 (dd, J = 11.0, 2.0 Hz, 0.89H, $C_6H_{ax}O^{cis}$), 2.96 (t, J = 11.0 Hz, 0.11H, $C_6H_{ax}{}^{trans}$), 2.85 (dd, J = 11.0, 2.0 Hz, 0.89H, $C_2H_{ax}{}^{cis}$), 2.80 (dd, J = 11.0, 2.0 Hz, 0.11H, $C_2H_{ax}{}^{trans}$), 1.75-1.48 (m, 5H, CH), 1.08 (d, J = 7.0 Hz, 2.67H, CHMe^{cis}), 0.90 (s, 8.01H, $CMe_3{}^{cis}$), 0.89 (s, 0.99H, $CMe_3{}^{trans}$), 0.76 (d, J = 7.0 Hz, 0.33H, CHMe^{trans}); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ for *cis*-**143** 86.3 (CHO), 73.5 (OCH_2), 34.1 (CMe_3), 29.7 (CH_2), 28.1 (CH), 26.0 (CMe_3), 20.4 (CH_2), 16.5 (Me); δ for *trans*-**144** 85.7 (CHO), 75.3 (OCH_2), 32.9, 31.1, 29.7, 26.2, 22.7, 17.2; MS was not obtained successfully by either ESI or APCI.



2-Butyl-5-methyltetrahydro-2H-pyran *cis*-145 and *trans*-146

Using general procedure D, Pd/C (69 mg of 5% wt on carbon, 0.06 mmol, 0.1 eq.) and alkene **137** (100 mg, 0.65 mmol, 1.0 eq.) in MeOH (2.5 mL) gave the crude product, which contained an 88:12 mixture (by ^{1}H NMR spectroscopy) of cyclic ethers *cis*-**145** and *trans*-**146**. Purification by flash column chromatography with 95:5 petrol-Et_2O as eluent gave an 88:12 mixture (by ^{1}H NMR spectroscopy) of cyclic ethers *cis*-**145** and *trans*-**146** (23 mg, 23%) as a colourless oil, R_F (95:5 petrol-Et_2O) 0.4; IR (film) 2887, 2813, 1441, 1363, 1119, 1078, 1060, 1020, 972, 906, 723 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (ddd, J = 11.0, 4.0, 2.0 Hz, 0.12H, $C_6H_{eq}O^{trans}$), 3.63 (dt, J = 11.0, 2.0 Hz, 0.88H, $C_6H_{eq}O^{cis}$), 3.58 (dd, J = 11.0, 3.0 Hz, 0.88H, $C_6H_{ax}O^{cis}$), 3.30-3.24 (m, 0.88H, $C_2H_{ax}{}^{cis}$), 3.19-3.12 (m, 0.12H, $C_2H_{ax}{}^{trans}$), 2.98 (t, J = 11.0 Hz, 0.12H, $C_6H_{ax}{}^{trans}$), 1.83-1.28 (m, 11H, CH), 1.06 (d, J = 7.0 Hz, 2.64H, CHMe^{cis}), 0.92 (t, J = 7.0 Hz, 3H, $Me^{cis+trans}$), 0.78 (d, J = 7.0 Hz, 0.36H, CHMe^{trans}); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ for

cis-**145** 77.7 (CHO), 72.5 (OCH_2), 35.5 (CH_2), 28.9 (CH_2), 28.4 (CH), 27.8 (CH_2), 26.9 (CH_2), 22.8 (CH_2), 16.7 (Me), 14.1 (Me); δ for *trans*-**146** (one CH, one CH_2 and one Me signals are not resolved) 77.5 (CHO), 74.8 (OCH_2), 36.1 (CH_2), 32.5 (CH_2), 31.8 (CH_2), 31.0 (CH_2), 17.3 (Me); MS was not obtained successfully by either ESI or APCI.



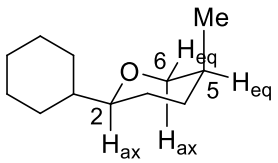
5-Methyl-2-pentyltetrahydro-2H-pyran *cis*-147 and *trans*-148

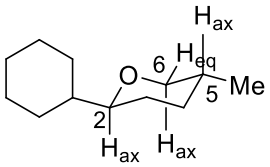
Using general procedure D, Pd/C (63 mg of 5% wt on carbon, 0.06 mmol, 0.1 eq.) and alkene **138** (100 mg, 0.59 mmol, 1.0 eq.) in MeOH (2.5 mL) gave the crude product, which contained an 88:12 mixture (by ^{1}H NMR spectroscopy) of cyclic ethers *cis*-**147** and *trans*-**148**. Purification by flash column chromatography with 95:5 petrol-Et_2O as eluent gave an 83:17 mixture (by ^{1}H NMR spectroscopy) of cyclic ethers *cis*-**147** and *trans*-**148** (87 mg, 86%) as a colourless oil, R_F (95:5 petrol-Et_2O) 0.4; IR (film) 2886, 2812, 1441, 1363, 1119, 1054, 972, 895, 853, 723 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (ddd, J = 11.0, 4.0, 2.0 Hz, 0.17H, $C_6H_{eq}O^{trans}$), 3.63 (dt, J = 11.0, 2.0 Hz, 0.83H, $C_6H_{eq}O^{cis}$), 3.58 (dd, J = 11.0, 3.0 Hz, 0.83H, $C_6H_{ax}O^{cis}$), 3.30-3.24 (m, 0.83H, $C_2H_{ax}O^{trans}$), 3.20-3.12 (m, 0.17H, $C_2H_{ax}{}^{cis}$), 2.98 (t, J = 11.0 Hz, 0.17H, $C_6H_{ax}{}^{trans}$), 1.84-1.63 (m, 2H, CH), 1.55-1.26 (m, 11H, CH), 1.07 (d, J = 7.0 Hz, 2.49H, CHMe^{cis}), 0.89 (t, J = 7.0 Hz, 3H, $Me^{cis+trans}$), 0.78 (d, J = 7.0 Hz, 0.52H, CHMe^{trans}); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ for *cis*-**147** 77.7 (CHO), 72.5 (OCH_2), 35.8 (CH_2), 32.0 (CH_2), 28.9 (CH_2), 28.4 (CH), 26.9 (CH_2), 25.3 (CH_2), 22.7 (CH_2), 16.7 (Me), 14.1 (Me); δ for *trans*-**148** (two CH_2 and one Me signals are not resolved) 77.5 (CHO), 74.8 (OCH_2), 36.4 (CH_2), 32.5 (CH_2), 31.8 (CH_2), 31.0 (CH), 22.6 (CH_2), 17.3 (Me);

MS (ESI) *m/z* 171 [$(M + H)^+$, 30], 169 (100); HRMS (ESI) *m/z* calcd for $C_{11}H_{22}O$ $(M + H)^+$ 171.1743, found 171.1743 (0.7 ppm error).

PtO_2 (13.5 mg, 0.06 mmol, 0.1 eq.) was added to a stirred solution of the ether **138** (100 mg, 0.59 mmol, 1.0 eq.) in MeOH (2 mL) at rt under N_2. The flask was evacuated and back-filled with N_2 three times and finally evacuated and back-filled with H_2. Then, the mixture was stirred at rt for 1 h. Et_2O (10 mL) was added and the solids were removed by filtration through a pad of Celite® and the filter-cake was washed with Et_2O (3 × 10 mL). The combined organic washings were evaporated under reduced pressure to give the crude product, which contained a 55:45 mixture (by ^1H NMR spectroscopy) of cyclic ether *cis*-**147** and *trans*-**148**.

$RhCl(PPh_3)_3$ (55 mg, 0.06 mmol, 0.1 eq.) was added to a stirred solution of the ether **138** (100 mg, 0.59 mmol, 1.0 eq.) in MeOH (2 mL) at rt under N_2. The flask was evacuated and back-filled with N_2 three times and finally evacuated and back-filled with H_2. Then, the mixture was stirred at rt for 16 h. Et_2O (10 mL) was added and the solids were removed by filtration through a pad of Celite® and the filter-cake was washed with Et_2O (3 × 10 mL). The combined organic washings were evaporated under reduced pressure to give the crude product (60% conversion), which contained a 70:30 mixture (by ^1H NMR spectroscopy) of cyclic ether *trans*-**148** and *cis*-**147**.

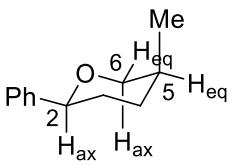


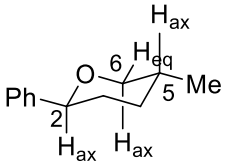


2-Cyclohexyl-5-methyltetrahydro-2H-pyran *cis*-149 and *trans*-150

Using general procedure D, Pd/C (59 mg of 5% wt on carbon, 0.06 mmol, 0.1 eq.) and alkene **139** (100 mg, 0.56 mmol, 1.0 eq.) in MeOH (2.5 mL) gave the crude

product, which contained an 87:13 mixture (by ^{1}H NMR spectroscopy) of cyclic ethers *cis*-**149** and *trans*-**150**. Purification by flash column chromatography with 95:5 petrol-Et_2O as eluent gave an 87:13 mixture (by ^{1}H NMR spectroscopy) of cyclic ethers *cis*-**149** and *trans*-**150** (58 mg, 57%) as a colourless oil, R_F (95:5 petrol-Et_2O) 0.3; IR (film) 2879, 2808, 1427, 1197, 1057, 1019, 975, 872, 723 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (ddd, J = 11.0, 4.0, 2.0 Hz, 0.13H, $C_6H_{eq}O^{trans}$), 3.64 (dt, J = 11.0, 2.0 Hz, 0.87H, $C_6H_{eq}O^{cis}$), 3.56 (dd, J = 11.0, 3.0 Hz, 0.87H, $C_6H_{ax}O^{cis}$), 3.02-2.97 (m, 0.87H, $C_2H_{ax}{}^{cis}$), 2.94-2.89 (m, 0.26H, $C_2H_{ax}{}^{trans}$, $C_6H_{ax}{}^{trans}$), 1.94-1.13 (m, 14H, CH), 1.06 (d, J = 7.0 Hz, 2.61H, Me^{cis}), 1.01-0.83 (m, 2H, CH), 0.78 (d, J = 7.0 Hz, 0.39H, Me^{trans}); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ for *cis*-**149** 82.3 (CHO), 72.8 (OCH_2), 42.4 (CH), 29.1 (CH_2), 29.0 (CH_2), 28.7 (CH_2), 28.4 (CH), 26.2 (CH_2), 26.3 (CH_2), 26.2 (CH_2), 23.4 (CH_2), 16.6 (Me); δ for *trans*-**150** (two CH_2 signals are not resolved) 82.0 (CHO), 75.0 (OCH_2), 43.1 (CH), 32.6 (CH_2), 31.2 (CH), 29.2 (CH_2), 28.6 (CH_2), 28.5 (CH_2), 26.2 (CH_2), 17.2 (Me); MS (APCI) *m/z* 183 [$(M + H)^+$, 100], 165 (70); HRMS (APCI) *m/z* calcd for $C_{12}H_{22}O$ $(M + H)^+$ 183.1743, found 831.1743 (1.9 ppm error).



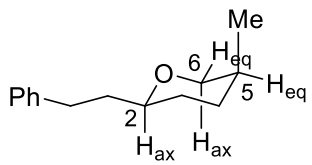


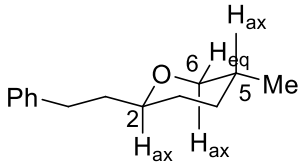
5-Methyl-2-phenyltetrahydro-2H-pyran *cis*-79 and *trans*-78

Using general procedure D, Pd/C (122 mg of 10% wt on carbon, 0.11 mmol, 0.1 eq.) and alkene **13** (200 mg, 1.15 mmol, 1.0 eq.) in MeOH (5 mL) gave the crude product, which contained a 60:40 mixture (by ^{1}H NMR spectroscopy) of cyclic ethers *cis*-**79** and *trans*-**78**. Purification by flash column chromatography with 99:1 petrol-Et_2O as eluent gave a 55:45 mixture (by ^{1}H NMR spectroscopy) of cyclic ethers *cis*-**79** and *trans*-**78** (116 mg, 57%) as a colourless oil, R_F (99:1

petrol-Et_2O) 0.2; IR (film) 2930, 2871, 2850, 1452, 1091, 1072, 1057, 1021, 992, 910, 734, 699, 648 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.25 (m, 5H, Ph), 4.38-4.35 (m, 0.6H, $CHPh^{cis}$), 4.27 (dd, J = 11.0, 2.0 Hz, 0.4H, $CHPh^{trans}$), 4.04 (ddd, J = 11.0, 4.0, 2.0 Hz, 0.4H, $CH_{eq}O^{trans}$), 3.83-3.76 (m, 1.2H, CH_2O^{cis}), 3.20 (t, J = 11.0 Hz, 0.4H, $C_6H_{ax}O^{trans}$), 1.98-1.56 (m, 4.6H, CH), 1.36-1.26 (m, 0.4H, CH), 1.17 (d, J = 7.0 Hz, 1.8H, Me), 0.86 (d, J = 7.0 Hz, 1.2H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.1 (*ipso*-Ph), 143.0 (*ipso*-Ph), 128.2 (Ph), 127.2 (Ph), 127.1 (Ph), 125.8 (Ph), 79.8 (CHO), 79.7 (CHO), 75.2 (OCH_2), 73.0 (OCH_2), 34.0 (CH_2), 32.8 (CH_2), 30.7 (CH), 29.4 (CH_2), 28.7 (CH_2), 28.0 (CH), 17.2 (Me), 16.2 (Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.1 (*ipso*-Ph), 143.0 (*ipso*-Ph), 128.2 (Ph), 127.2 (Ph), 127.1 (Ph), 125.8 (Ph), 79.8 (CHO), 79.7 (CHO), 75.2 (OCH_2), 73.0 (OCH_2), 34.0 (CH_2), 32.8 (CH_2), 30.7 (CH), 29.4 (CH_2), 28.7 (CH_2), 28.0 (CH), 17.2 (Me), 16.2 (Me). Spectroscopic data not consistent with those reported in the literature.[49] We believe that the stereochemical assignment made by Duñach and co-workers is incorrect.

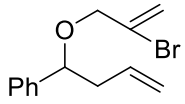
$RhCl(PPh_3)_3$ (55 mg, 0.06 mmol, 0.1 eq.) was added to a stirred solution of the ether **13** (100 mg, 0.57 mmol, 1.0 eq.) in MeOH (2 mL) at rt under N_2. The flask was evacuated and back-filled with N_2 three times and finally evacuated and back-filled with H_2. Then, the mixture was stirred at rt for 16 h. Et_2O (10 mL) was added and the solids were removed by filtration through a pad of Celite® and the filter-cake was washed with Et_2O (3 × 10 mL). The combined organic washings were evaporated under reduced pressure to give the crude product (20% conversion), which contained a 75:25 mixture (by ^1H NMR spectroscopy) of cyclic ether *trans*-**78** and *cis*-**79**.





5-Methyl-2-phenethyltetrahydro-2H-pyran *cis*-151 and *trans*-152

Using general procedure D, Pd/C (100 mg of 10% wt on carbon, 0.09 mmol, 0.1 eq.) and alkene **140** (200 mg, 0.99 mmol, 1.0 eq.) in MeOH (5 mL) gave the crude product, which contained a 65:35 mixture (by ^{1}H NMR spectroscopy) of cyclic ethers *cis*-**151** and *trans*-**152**. Purification by flash column chromatography with 99:1 petrol-Et_2O as eluent gave a 65:35 mixture (by ^{1}H NMR spectroscopy) of cyclic ethers *cis*-**151** and *trans*-**152** (164 mg, 80%) as a colourless oil, R_F (99:1 petrol-Et_2O) 0.3; IR (film) 2980, 2884, 2806, 1472, 1433, 1363, 1121, 1074, 1055, 1017, 895, 723, 688 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.17 (m, 5H, Ph), 3.90 (ddd, J = 12.0, 4.0, 2.0 Hz, 0.35H, $C_6H_{eq}O^{trans}$), 3.67 (dt, J = 11.0, 2.0 Hz, 0.65H, $C_6H_{eq}O^{cis}$), 3.62 (dd, J = 11.0, 3.0 Hz, 0.65H, $C_6H_{ax}O^{cis}$), 3.33-3.27 (m, 0.65H, $C_2H_{ax}{}^{cis}$), 3.23-3.15 (m, 0.35H, $C_2H_{ax}{}^{trans}$), 2.99 (t, J = 12.0 Hz, 0.35H, $C_6H_{ax}{}^{trans}$), 2.82-2.75 (m, 1H, CHOCH_AH$_B$), 2.70-2.63 (m, 1H, CHOCH$_A$$H_B$), 1.95-1.23 (m, 7H, CH), 1.08 (d, J = 7.0 Hz, 1.95H, CHMe^{cis}), 0.79 (d, J = 7.0 Hz, 1.05H, CHMe^{trans}); ^{13}C NMR (100.6 MHz, $CDCl_3$) (one CH_2 signal not resolved) δ 142.4 (*ipso*-Ph), 128.5 (Ph), 128.3 (Ph), 125.6 (Ph), 77.2 (CHO), 76.5 (CHO), 74.8 (OCH_2), 72.4 (OCH_2), 38.0 (CH_2), 37.4 (CH_2), 32.4 (CH_2), 31.9 (CH_2), 31.8 (CH_2), 31.0 (CH), 28.9 (CH_2), 28.4 (CH), 27.0 (CH_2), 17.2 (Me), 16.7 (Me); MS (ESI) *m/z* 205 [(M + H)$^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{14}H_{21}O$ (M + H)$^+$ 205.1590, found 205.1587 (–1.8 ppm error).



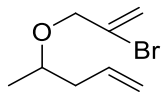
(1-[(2-Bromoprop-2-en-1-yl)oxy]but-3-en-1-yl)benzene 181

A solution of alcohol **127** (500 mg, 3.37 mmol, 1.0 eq.) in THF (10 mL) was added dropwise to a stirred suspension of NaH (162 mg of 60% wt dispersion in

mineral oil, 4.05 mmol, pre-washed with Et_2O (3 × 2 mL), 1.2 eq.) in THF (25 mL) at rt under Ar. The resulting mixture was stirred for 15 min. 2,3-Dibromoprop-1-ene (0.49 mL, 4.05 mmol, 1.2 eq.) was added and the resulting mixture was stirred and heated at reflux for 72 h. After being allowed to cool to rt, the solution was poured into saturated $NH_4Cl_{(aq)}$ (60 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography with 95:5 petrol-Et_2O as eluent gave ether **181** (294 mg, 33%) as a colourless oil, R_F (95:5 petrol-Et_2O) 0.6; IR (NaCl) 3076, 2977, 2906, 2856, 1640 (C=C), 1453, 1161, 1088, 1026, 997, 913, 760, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.29 (m, 5H, Ph), 5.91 (dd, J = 3.0, 1.5 Hz, 1H, BrC=CH_AH$_B$) 5.82 (ddt, J = 17.0, 10.0, 7.0 Hz, 1H, =CH), 5.61-5.60 (m, 1H, BrC=CH$_A$$H_B$), 5.10-5.03 (m, 2H, CH=CH_2), 5.39 (dd, J = 8.0, 6.0 Hz, 1H, CHO), 4.04 (dt, J = 14.0, 1.5 Hz, 1H, OCH_AH$_B$), 3.86 (dt, J = 14.0, 1.5 Hz, 1H, OCH$_A$$H_B$), 2.67-2.60 (m, 1H, C$H_AH_B$CH), 2.48-2.42 (m, 1H, CH$_A$$H_B$CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 141.1 (*ipso*-Ph), 134.5 (Ph), 129.5 (=CBr), 128.5 (Ph), 127.9 (=CH), 126.8 (Ph), 117.5 (=CH_2), 117.2 (=CH_2), 81.2 (CHO), 72.4 (OCH_2), 42.5 (CH_2); MS (ESI) *m/z* 289 [(^{79}M + Na)$^+$, 45], 126 (100), 91 (70), 159 (65), 301 (45); HRMS (ESI) *m/z* calcd for $C_{13}H_{15}{}^{79}BrO$ (M + Na) $^+$ 289.0198, found 289.0196 (0.8 ppm error).

A solution of alcohol **127** (500 mg, 3.37 mmol, 1.0 eq.) in CH_2Cl_2 (10 mL) was added dropwise to a stirred suspension of cetyltrimethylammonium bromide (184 mg, 0.51 mmol, 0.15 eq.) in 50% $NaOH_{(aq)}$ (10 mL) at rt. The resulting mixture was stirred for 15 min. 2,3-Dibromoprop-1-ene (0.41 mL, 3.37 mmol, 1.0 eq.) was added and the resulting mixture was stirred at rt for 1 h. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced

pressure to give the crude product. Purification by flash column chromatography with 95:5 petrol-Et_2O as eluent gave ether **181** (173 mg, 19%) as a colourless oil.

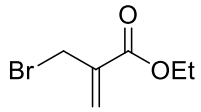


2-((2-Bromoprop-2-en-1-yl)oxy)pentane 177

A solution of alcohol **178** (500 mg, 5.81 mmol, 1.0 eq.) in THF (10 mL) was added dropwise to a stirred suspension of NaH (279 mg of 60% wt dispersion in mineral oil, 6.97 mmol, pre-washed with Et_2O (3 × 5 mL), 1.2 eq.) in THF (25 mL) at rt under Ar. The resulting mixture was stirred for 15 min. 2,3-Dibromoprop-1-ene (0.85 mL, 6.97 mmol, 1.2 eq.) was added and the resulting mixture was stirred and heated at reflux for 72 h. After being allowed to cool to rt, the solution was poured into saturated $NH_4Cl_{(aq)}$ (60 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. No evidence of the desired product was observed in the ^1H NMR spectrum of the crude product and starting material pent-4-en-2-ol was still present.

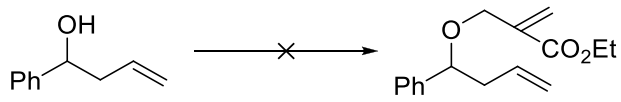
A solution of alcohol **178** (500 mg, 5.81 mmol, 1.0 eq.) in CH_2Cl_2 (10 mL) was added dropwise to a stirred suspension of cetyltrimethylammonium bromide (318 mg, 0.87 mmol, 0.15 eq.) in 50% $NaOH_{(aq)}$ (10 mL) at rt. The resulting mixture was stirred for 15 min. 2,3-Dibromoprop-1-ene (0.71 mL, 5.81 mmol, 1.0 eq.) was added and the resulting mixture was stirred at rt for 16 h. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography with 9:1 petrol-CH_2Cl_2 as eluent gave ether **177** (89 mg, 7%) as a colourless oil, R_F (95:5 petrol-Et_2O) 0.4; IR (NaCl) 2925, 1639 (C=C), 1457, 1092, 895 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 (br s, 1H, C=CH_AH$_B$), 5.84 (ddd, J = 17.0, 10.0, 7.0 Hz, 1H, =CH), 5.61-5.59 (br s, 1H, C=CH$_A$$H_B$), 5.12-5.06 (m, 2H, =$CH_2$), 4.16-4.07 (m, 2H, CH_2O), 3.58 (sext, J = 6.0 Hz, 1H, CHO), 2.39-2.19 (m, 2H, CH_2=CH), 1.18 (d, J = 6.0 Hz, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 134.6 (=CH), 130.1 (=CBr), 117.1 (=CH_2), 116.9 (=CH_2), 75.1 (CHO), 72.5 (OCH_2), 40.9 (CH_2), 19.4 (Me).



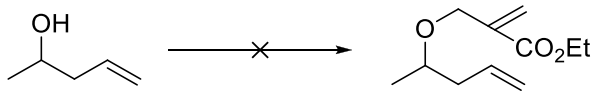
Ethyl (α-bromomethyl)acrylate 184

A solution of K_2CO_3 (3.0 g, 21.71 mmol, 1.2 eq.) in water (3.5 mL) was added to a stirred solution of triethylphosphonoacetate (3.59 mL, 18.09 mmol, 1.0 eq.) and 37% formaldehyde$_{(aq)}$ (2.3 g, 72.35 mmol, 4.0 eq.) at rt. The resulting solution was stirred at rt for 15 min. Then a 1:1 mixture of Et_2O and brine (40 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were washed with water (40 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude alcohol. Phosphorus tribromide (1.03 mL, 10.86 mmol, 0.6 eq.) was added to a stirred solution of the crude alcohol in Et_2O (25 mL) at 0 ºC. The resulting solution was stirred at rt for 16 h. Then, water (25 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic layers were washed with water (40 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by Kügelrohr distillation gave acrylate **184** (590 mg, 30%) as a colourless oil, bp 88-90 ºC/2.0 mmHg;[138] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 (d, J = 1.0 Hz, 1H, =CH_AH$_B$), 5.93 (d, J = 1.0 Hz, 1H, =CH$_A$$H_B$), 4.26 (q, J = 7.0 Hz, 2H, OCH_2Me), 4.18 (s, 2H, BrCH_2), 1.32 (t, J = 7.0 Hz, 3H, Me). Spectroscopic data consistent with those reported in the literature.[138]



Attempted synthesis of ethyl 2-(((1-phenylbut-3-en-1-yl)oxy)methyl)prop-2-enoate 185

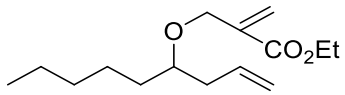
A solution of alcohol **127** (200 mg, 1.35 mmol, 1.0 eq.) in THF (10 mL) was added dropwise to a stirred suspension of NaH (81 mg of 60% wt dispersion in mineral oil, 2.03 mmol, pre-washed with Et_2O (3 × 5 mL), 1.5 eq.) in THF (15 mL) at 0 ºC under Ar. The resulting mixture was stirred for 30 min. Acrylate **184** (390 mg, 2.03 mmol, 1.5 eq.) was added and the resulting mixture was stirred at 0 ºC and allowed to warm to rt and stirred at rt for 16 h. Then, the solution was poured into saturated $NH_4Cl_{(aq)}$ (30 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. No evidence of the desired product was observed in the ^1H NMR spectrum of the crude product.



Attempted synthesis of ethyl 2-((pent-4-en-2-yloxy)methyl)acrylate 180

A solution of alcohol **178** (200 mg, 2.32 mmol, 1.0 eq.) in THF (10 mL) was added dropwise to a stirred suspension of NaH (139 mg of 60% wt dispersion in mineral oil, 3.48 mmol, pre-washed with Et_2O (3 × 5 mL), 1.5 eq.) in THF (15 mL) at 0 ºC under Ar. The resulting mixture was stirred for 30 min. Acrylate **184** (672 mg, 3.48 mmol, 1.5 eq.) was added and the resulting mixture was stirred at 0 ºC and allowed to warm to rt and stirred at rt for 16 h. Then, the solution was poured into saturated $NH_4Cl_{(aq)}$ (30 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the

crude product. No evidence of the desired product was observed in the ^{1}H NMR spectrum of the crude product.

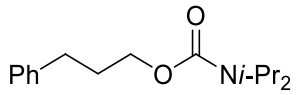


Ethyl 2-((non-1-en-4-yloxy)methyl)acrylate 186

A solution of alcohol **125** (200 mg, 1.41 mmol, 1.0 eq.) in THF (10 mL) was added dropwise to a stirred suspension of NaH (85 mg of 60% wt dispersion in mineral oil, 2.12 mmol, pre-washed with Et_2O (3 × 5 mL), 1.5 eq.) in THF (15 mL) at 0 ºC under Ar. The resulting mixture was stirred for 30 min. Then, acrylate **184** (409 mg, 2.12 mmol, 1.5 eq.) was added and the resulting mixture was stirred at 0 ºC and allowed to warm to rt and stirred at rt for 16 h. Then the solution was poured into saturated $NH_4Cl_{(aq)}$ (30 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 petrol-Et_2O as eluent gave carbamate **186** (114 mg, 24%) as a colourless oil, R_F (4:1 petrol-Et_2O) 0.3; IR (NaCl) 2888, 2816, 1690 (C=O), 1616 (C=C), 1439, 1348, 1329, 1285, 1252, 1157, 1079, 1014, 935, 900 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (dd, J = 3.0, 1.0 Hz, 1H, =CH_AH$_B$CCO$_2$Et), 5.90 (q, J = 2.0 Hz, 1H, =CH$_A$$H_BCCO_2$Et), 5.83 (ddt, J = 17.0, 10.0, 7.0 Hz, 1H, =CH), 5.11-5.04 (m, 2H, =CH$_2$), 4.26-4.15 (m, 4H, OCH_2Me, OCH$_2$), 3.44-3.38 (m, 1H, CHO), 2.32-2.28 (m, 2H, =CHCH_2), 1.58-1.23 (m, 8H, 4 × CH$_2$), 1.31 (t, J = 7.0 Hz, 3H, Me), 0.89 (t, J = 7.0 Hz, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.0 (C=O), 138.0 (*C*=CH$_2$), 135.0 (=CH), 125.4 (=CH$_2$), 116.8 (=CH$_2$), 79.4 (CHO), 67.1 (O*C*H$_2$Me), 60.6 (OCH$_2$), 38.3 (CH$_2$), 33.7 (CH$_2$), 31.9 (CH$_2$), 25.0 (CH$_2$), 22.6 (CH$_2$), 14.2 (Me), 14.0 (Me); MS (ESI) *m/z* 277 [(M + Na)$^+$, 100];

HRMS (ESI) *m/z* calcd for $C_{15}H_{26}O_3$ (M + Na) $^+$ 277.1779, found 277.1774 (−1.7 ppm error).

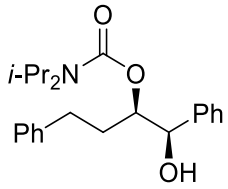
n-BuLi (2.5 M in hexane, 0.68 mL, 1.69 mmol, 1.2 eq.) was added dropwise to a stirred solution of alcohol **125** (200 mg, 1.41 mmol, 1.0 eq.) in THF (15 mL) at −78 ºC under Ar. The resulting solution was stirred at −78 ºC for 15 min before it was transferred to CuI (404 mg, 2.11 mmol, 1.5 eq.). The resulting mixture was stirred for 30 min at −78 ºC. Then, acrylate **184** (407 mg, 2.11 mmol, 1.5 eq.) was added dropwise and the resulting solution was warmed to rt over 16 h. 1 M $HCl_{(aq)}$ (15 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 petrol-Et_2O as eluent gave carbamate **186** (50 mg, 14%) as a colourless oil.

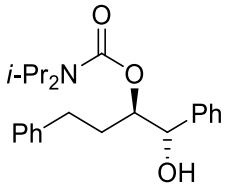


3-Phenylpropyl *N*,*N*-di-*i*-propylcarbamate 193

A solution of 3-phenyl-1-propanol (2.0 mL, 15.40 mmol, 1.2 eq.) in Et_2O (20 mL) was added dropwise over 10 min to a stirred solution of NaH (0.78 g of 60% wt dispersion in mineral oil, 17.90 mmol, pre-washed with Et_2O (3 × 10 mL), 1.3 eq.) and a solution of di-*i*-propylcarbamoyl chloride (2.10 g, 13.30 mmol, 1.0 eq.) in Et_2O (30 mL) at rt under Ar. The resulting mixture was stirred at rt for 16 h. Then, 2 M $HCl_{(aq)}$ (20 mL) was added and the resulting mixture was stirred vigorously for 5 min. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (2:1 Na_2SO_4-$NaHCO_3$) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by flash column chromatography on silica

with 4:1 petrol-Et_2O as eluent gave carbamate **193** (2.90 g, 83%) as a colourless oil, R_F (4:1 petrol-Et_2O) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.28 (m, 2H, Ph), 7.20-7.19 (m, 3H, Ph), 4.11 (t, J = 6.0 Hz, 2H, CH_2O), 3.81 (br s, 2H, CHN), 2.71 (t, J = 8.0 Hz, 2H, C*H*$_2$Ph), 2.01-1.94 (m, 2H, CH), 1.21 (d, J = 7.0 Hz, 12H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.9 (C=O), 141.7 (*ipso*-Ph), 128.5 (Ph), 128.4 (Ph), 126.0 (Ph), 64.1 (OCH_2), 42.0 (NCH), 32.7 (CH_2), 31.0 (Me), 21.2 (CH_2). Spectroscopic data consistent with those reported in the literature.[68]

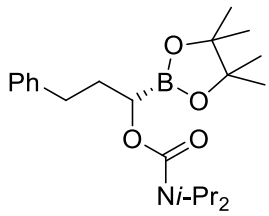




1-Hydroxy-1,4-diphenylbutan-2-yl di-*iso*-propylcarbamate *syn*-204 and *anti*-205

s-BuLi (0.90 mL of a 1.3 M solution in hexane, 0.91 mmol, 1.2 eq.) was added dropwise to a stirred solution of (−)-sparteine (260 mg, 0.91 mmol, 1.2 eq.) in Et_2O (3 mL) at −78 ºC under Ar. After stirring at −78 ºC for 15 min, a solution of *O*-alkyl carbamate **193** (227 mg, 0.76 mmol, 1.0 eq.) in Et_2O (2 mL) was added dropwise. The resulting solution was stirred at −78 ºC for 3 h. Then, benzaldehyde (0.15 mL, 1.52 mmol, 2.0 eq.) was added and the resulting solution was warmed to rt over 16 h. 1 M $HCl_{(aq)}$ (2 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 petrol-Et_2O as eluent gave a 70:30 mixture (by ^{1}H NMR spectroscopy) of diastereomeric alcohols of *syn*-**204** and *anti*-**205** (205 mg, 73%) as a colourless oil, R_F (4:1 petrol-Et_2O) 0.6; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.05 (m, 10H, Ph), 5.12-5.09 (m, 0.3H, OCH), 5.06-5.01 (m, 0.7H, OCH), 4.88 (dd, J = 5.0, 3.0 Hz, 0.3H, C*H*OH), 4.72 (dd, J =

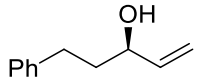
7.0, 5.0 Hz, 0.7H, C*H*OH), 4.71 (d, *J* = 5.0 Hz, 0.7 Hz, OH), 4.10 (d, *J* = 5.0 Hz, 0.3H, OH), 3.97 (br s, 2H, CHN), 2.77-2.53 (m, 2H, CH), 1.94-1.70 (m, 2H, CH), 1.26 (d, *J* = 7.0 Hz, 6H, Me), 1.25 (d, *J* = 7.0 Hz, 6H, Me).



(*S*)-3-Phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl di-*i*-propylcarbamate (*S*)-194

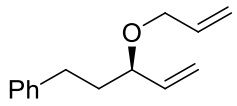
s-BuLi (8.0 mL of 1.3 M solution in hexane, 10.50 mmol, 1.2 eq.) was added dropwise to a stirred solution of (–)-sparteine (2.45 g, 10.50 mmol, 1.2 eq.) in Et_2O (15 mL) at –78 ºC under Ar. After stirring at –78 ºC for 15 min, a solution of *O*-alkyl carbamate **193** (2.30 g, 8.71 mmol, 1.0 eq.) in Et_2O (5 mL) was added dropwise. The resulting solution was stirred at –78 ^oC for 3 h. Then, tri-*i*-propyl borate (3.0 mL, 13.07 mmol, 1.5 eq.) was added dropwise and the resulting solution was warmed to rt over 16 h. 1 M $HCl_{(aq)}$ (15 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. A solution of the crude product, *p*-toluenesulfonic acid (0.05 g, 0.30 mmol, 0.03 eq.), $MgSO_4$ (5.00 g) and pinacol (1.54 g, 13.07 mmol, 1.5 eq.) in CH_2Cl_2 (20 mL) was stirred at rt for 24 h. Then, the solids were removed by filtration and the filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography with 4:1 petrol-Et_2O as eluent gave boronate (*S*)-**194** (2.51 g, 74%) as a viscous yellow oil, $[\alpha]_D$ +42.6 (*c* 1.1 in CH_2Cl_2) (lit.,[19] $[\alpha]_D$ +36.7 (*c* 0.97 in CH_2Cl_2)); R_F (4:1 petrol-Et_2O) 0.3; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.25 (m, 2H, Ph), 7.21-7.17 (m, 3H, Ph), 4.07 (septet, *J* = 7.0 Hz, 1H, CHN), 3.82 (dd, *J* = 11.0, 4.0 Hz, 1H, CHO), 3.75 (septet, *J* = 7.0 Hz, 1H, CHN),

2.89-2.81 (m, 1H, CH), 2.75-2.68 (m, 1H, CH), 2.08-2.00 (m, 1H, CH), 1.94-1.88 (m, 1H, CH), 1.16-1.24 (m, 24H, Me). Spectroscopic data consistent with those reported in the literature.[68]



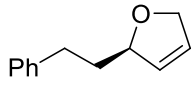
(*R*)-5-Phenylpent-1-en-3-ol (*R*)-208

Vinyl magnesium bromide (1.77 mL of 1 M solution in THF, 1.77 mmol, 2.0 eq.) was added dropwise to a stirred solution of boronate (*S*)-**194** (345 mg, 0.89 mmol, 1.0 eq.) in THF (5 mL) at −78 ºC under Ar. The resulting solution was stirred at −78 ^{o}C for 1 h. Then, the resulting solution was stirred and heated at reflux for 12 h. After being allowed to cool to rt, $NaOH_{(aq)}$ (2.13 mL of a 0.5 M solution, 1.06 mmol, 1.2 eq.) and H_2O_2 (0.11 mL of a 35 wt% solution in water, 1.24 mmol, 1.4 eq.) were added and the mixture was stirred for 30 min. Then, the mixture was poured into brine (5 mL) and extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with saturated $Na_2S_2O_{3(aq)}$ (3 × 10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography with 3:2 petrol-Et_2O as eluent gave alcohol (*R*)-**208** (74 mg, 52%, 91:9 er by CSP-HPLC) as a viscous yellow oil, $[\alpha]_D$ +1.9 (*c* 0.5 in CH_2Cl_2) (lit.,[139] of $[\alpha]_D$ +4.2 (*c* 1.00 in CH_2Cl_2) for (*R*)-**208** of 90:10 er); R_F (3:2 petrol-Et_2O) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.27 (m, 2H, Ph), 7.22-7.19 (m, 3H, Ph), 5.92 (ddd, *J* = 17.0, 10.0, 6.0 Hz, 1H, =CH), 5.25 (dt, *J* = 17.0, 2.0 Hz, 1H, =CH), 5.14 (dt, *J* = 10.0, 2.0 Hz, 1H, =CH), 4.13 (q, *J* = 6.0 Hz, 1H, C*H*OH), 2.84-2.61 (m, 2H, CH_2), 1.97-1.78 (m, 2H, CH_2Ph), 1.64 (br s, 1H, OH); ^{13}C NMR (100.6 MHz, $CDCl_3$) (one aromatic resonance not resolved) δ 142.0 (*ipso*-Ph), 141.1 (=CH), 128.6 (Ph), 126.0 (Ph), 115.1 (=CH_2), 72.6 (CHO), 38.6 (CH_2), 31.7 (CH_2); HPLC: Daicel Chiracel OD, 95:5 *i*-PrOH-hexane, 0.5 mL min^{-1}, (*S*)-**208** 21.3 min, (*R*)-**208** 31.8 min. Spectroscopic data consistent with those reported in the literature.[140]



(*R*)-(3-(Allyloxy)pent-4-enyl)benzene (*R*)-209

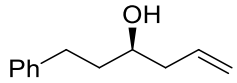
A solution of alcohol (*R*)-**208** (66 mg, 0.41 mmol, 1.0 eq., 91:9 er) in THF (2 mL) was added dropwise to a stirred suspension of NaH (36 mg of 60% wt dispersion in mineral oil, 0.81 mmol, pre-washed with Et_2O (3 × 5 mL), 2.0 eq.) in THF (5 mL) at rt under Ar. The resulting mixture was stirred and heated at reflux for 30 min and then allowed to cool to rt. Allyl bromide (0.07 mL, 0.81 mmol, 2.0 eq.) was added and the resulting mixture was stirred and heated at reflux for 2.5 h. After being allowed to cool to rt, the solution was poured into saturated $NH_4Cl_{(aq)}$ (5 mL) and extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography with 99:1 petrol-Et_2O as eluent gave ether (*R*)-**209** (49 mg, 59%, 91:9 er assumed) as a colourless oil, R_F (99:1 petrol-Et_2O) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.25 (m, 2H, Ph), 7.21-7.16 (m, 3H, Ph), 5.92-5.90 (m, 1H, =CH), 5.73 (ddd, J = 17.0, 8.0, 5.0 Hz, 1H, =CH), 5.27 (dq, J = 17.0, 2.0 Hz, 1H, =CH), 5.22-5.14 (m, 3H, =CH), 4.05 (ddt, J = 13.0, 5.0, 1.0 Hz, 1H, CHO), 3.80 (ddt, J = 13.0, 6.0, 2.0 Hz, 1H, CHO), 3.68 (q, J = 7.0 Hz, 1H, CHO), 2.77-2.63 (m, 2H, CH_2Ph), 1.94-1.91 (m, 1H, CH), 1.83-1.75 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 142.2 (*ipso*-Ph), 138.9 (=CH), 135.2 (=CH), 128.6 (Ph), 128.4 (Ph), 125.8 (Ph), 117.2 (=CH_2), 116.7 (=CH_2), 80.0 (CHO), 69.5 (OCH_2), 37.2 (CH_2), 31.6 (CH_2). Spectroscopic data consistent with those reported in the literature.[16]



(*R*)-2-Phenethyl-2,5-dihydrofuran (*R*)-210

Grubbs' 1st Generation catalyst **4** (3.9 mg, 0.004 mmol, 0.02 eq.) was added in one portion to a stirred solution of diene (*R*)-**209** (42 mg, 0.21 mmol, 1.0 eq.) in

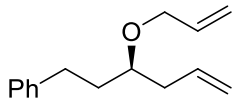
CH_2Cl_2 (1 mL) at rt. The resulting mixture was stirred at rt for 1 h. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography with 99:1 petrol-Et_2O as eluent gave cyclic ether (*R*)-**210** (48 mg, 57%) as a colourless oil, R_F (99:1 petrol-Et_2O) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.26 (m, 2H, Ph), 7.21-7.16 (m, 3H, Ph), 5.90 (dq, J = 8.0, 2.0 Hz, 1H, =CH), 5.78 (dq, J = 8.0, 2.0 Hz, 1H, =CH), 4.90-4.83 (m, 1H, CHO), 4.88-4.61 (m, 2H, OCH_2), 4.60-4.58 (m, 2H, CH_2Ph), 1.98-1.75 (m, 2H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) (one aromatic resonance not resolved) δ 142.3 (*ipso*-Ph), 129.6 (=CH), 128.5 (Ph), 126.8 (=CH), 125.8 (Ph), 85.5 (CHO), 75.2 (OCH_2), 37.8 (CH_2), 31.6 (CH_2). Spectroscopic data consistent with those reported in the literature.[17]



(*R*)-1-Phenylbut-3-en-1-ol (*R*)-128

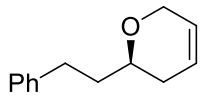
Allyl magnesium bromide (2.27 mL of 2 M solution in THF, 4.54 mmol, 2.0 eq.) was added dropwise to a stirred solution of boronate (*S*)-**194** (883 mg, 2.27 mmol, 1.0 eq.) in THF (25 mL) at –78 ºC under Ar. The resulting solution was stirred at –78 ºC for 1 h. Then, the solution was stirred and heated at reflux for 12 h. After being allowed to cool to rt, $NaOH_{(aq)}$ (5.44 mL of a 0.5 M solution, 2.72 mmol, 1.2 eq.) and H_2O_2 (0.28 mL of a 35 wt% solution in water, 3.18 mmol, 1.4 eq.) were added and the mixture was stirred for 30 min. Then, the mixture was poured into brine (5 mL) and extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with saturated $Na_2S_2O_{3(aq)}$ (3 × 10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography with 3:2 petrol-Et_2O as eluent gave alcohol (*R*)-**128** (215 mg, 54%, 99:1 er by CSP-HPLC) as a viscous yellow oil, $[\alpha]_D$ +2.4 (*c* 0.5 in CH_2Cl_2) (lit.,[141] $[\alpha]_D$ +9.30 (*c* 4.46 in CH_2Cl_2) for (*R*)-**128** of 90:10 er);

HPLC: Daicel Chiracel OD, 95:5 *i*-PrOH-hexane, 0.5 mL min^{-1}, (*S*)-**128** 17.5 min, (*R*)-**128** 25.3 min.



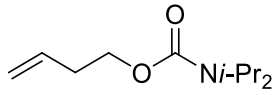
(*R*)-(3-(Allyloxy)hex-5-enyl)benzene (*R*)-211

A solution of alcohol (*R*)-**128** (91 mg, 0.52 mmol, 1.0 eq., 99:1 er) in THF (2 mL) was added dropwise to a stirred suspension of NaH (45 mg of 60% wt dispersion in mineral oil, 1.14 mmol, pre-washed with Et_2O (3 × 5 mL), 2 eq.) in THF (5 mL) at rt under Ar. The resulting mixture was stirred and heated at reflux for 30 min and then allowed to cool to rt. Allyl bromide (0.10 mL, 1.14 mmol, 2.0 eq.) was added and the resulting mixture was stirred and heated at reflux for 3.5 h. After being allowed to cool to rt, the solution was poured into saturated $NH_4Cl_{(aq)}$ (5 mL) and extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography with 99:1 petrol-Et_2O as eluent gave ether (*R*)-**211** (64 mg, 57%, 99:1 er assumed) as a colourless oil, R_F (99:1 petrol-Et_2O) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.24 (m, 2H, Ph), 7.19-7.15 (m, 3H, Ph), 6.01-5.89 (ddt, *J* = 17.0, 10.0, 6.0 Hz, 1H, =CH), 5.94 (ddt, *J* = 16.0, 10.0, 6.0 Hz, 1H, =CH), 5.30 (dq, *J* = 17.0, 2.0 Hz, 1H, CH), 5.16 (dq, *J* = 10.0, 2.0 Hz, 1H, CH), 5.10-5.02 (m, 2H, =CH), 4.06 (ddt, *J* = 13.0, 6.0, 1.0 Hz, 1H, CHO), 3.96 (ddt, *J* = 13.0, 6.0, 1.0 Hz, 1H, CHO), 3.40 (pentet, *J* = 6.0 Hz, 1H, CHO), 2.78 (ddd, *J* = 14.0, 9.0, 7.0 Hz, 1H, CH), 2.63 (ddd, *J* = 14.0, 9.0, 7.0 Hz, 1H, CH), 2.37-2.24 (m, 2H, CH_2), 1.86-1.74 (m, 2H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 142.4 (*ipso*-Ph), 135.4 (=CH), 134.8 (=CH), 128.5 (Ph), 128.4 (Ph), 125.8 (Ph), 117.2 (=CH_2), 116.8 (=CH_2), 77.8 (CHO), 70.1 (OCH_2), 38.4 (CH_2), 35.7 (CH_2), 31.7 (CH_2). Spectroscopic data consistent with those reported in the literature.[16]



(*R*)-2-Phenethyl-3,6-dihydro-2H-pyran (*R*)-212

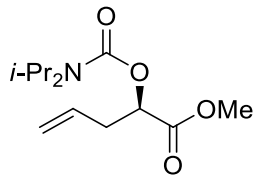
Grubbs' 1st Generation catalyst **4** (3.6 mg, 0.004 mmol, 0.02 eq.) was added in one portion to a stirred solution of diene (*R*)-**211** (42 mg, 0.22 mmol, 1.0 eq.) in CH_2Cl_2 (1 mL) at rt. The resulting mixture was stirred at rt for 2 h. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography with 99:1 petrol-Et_2O as eluent gave cyclic ether (*R*)-**212** (25 mg, 60%) as a colourless oil, R_F (99:1 petrol-Et_2O) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.25 (m, 2H, Ph), 7.21-7.11 (m, 3H, Ph), 5.81-5.75 (m, 1H, =CH), 5.74-5.68 (m, 1H, =CH), 4.25-4.13 (m, 2H, CH_2O), 3.51-3.43 (m, 1H, CHO), 2.84-2.65 (m, 2H, CH_2), 2.10-1.95 (m, 2H, C*H*$_2$Ph), 1.94-1.82 (m, 1H, CH), 1.81-1.70 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 142.3 (*ipso*-Ph), 128.6 (Ph), 128.5 (Ph), 126.5 (=CH), 125.8 (=CH), 124.3 (Ph), 72.7 (CHO), 66.0 (OCH_2), 37.7 (CH_2), 31.8 (CH_2), 31.1 (CH_2). Spectroscopic data consistent with those reported in the literature.[17]



But-3-enyl *N*,*N*-di-*i*-propylcarbamate 213

A solution of but-3-en-1-ol (1.2 mL, 13.88 mmol, 1.2 eq.) in Et_2O (20 mL) was added dropwise over 10 min to a stirred solution of NaH (0.65 g of 60% wt dispersion in mineral oil, 22.84 mmol, pre-washed with Et_2O (3 × 10 mL), 1.4 eq.) and a solution of di-*i*-propylcarbamoyl chloride (1.86 g, 11.56 mmol, 1.0 eq.) in Et_2O (30 mL) at rt under Ar. The resulting mixture was stirred at rt for 16 h. Then, 2 M $HCl_{(aq)}$ (20 mL) was added and the resulting mixture was stirred vigorously for 5 min. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (2:1

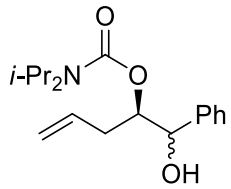
Na_2SO_4-$NaHCO_3$) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by flash column chromatography on silica with 4:1 petrol-Et_2O as eluent gave carbamate **213** (2.49 g, 90%) as a colourless oil, R_F (4:1 petrol-Et_2O) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (ddt, J = 17.0, 10.0, 6.0 Hz, 1H, =CH), 5.11 (dq, J = 17.0, 2.0 Hz, 1H, =CH), 5.06 (dq, J = 10.0, 2.0 Hz, 1H, =CH), 4.13 (t, J = 6.0 Hz, 2H, CH_2O), 3.81 (br s, 2H, CHN), 2.40 (q, J = 6.0 Hz, 2H, =CHC*H*$_2$), 1.18 (d, J = 7.0 Hz, 12H, CH*Me*); HRMS (ESI) *m/z* calcd for $C_{11}H_{21}NO_2$ (M + H) $^+$ 200.1645, found 200.1645 (0.1 ppm error).



(*R*)-Methyl 2-(di-*i*-propylcarbamoyloxy)pent-4-enoate (*R*)-216

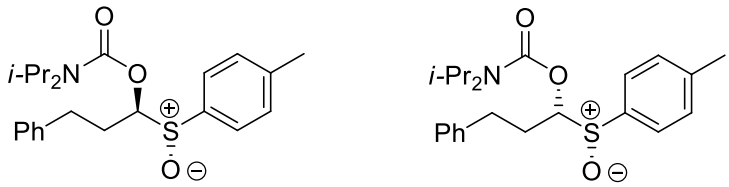
s-BuLi (0.88 mL of a 1.3 M solution in hexane, 1.14 mmol, 1.2 eq.) was added dropwise to a stirred solution of (–)-sparteine (267 mg, 1.14 mmol, 1.2 eq.) in Et_2O (3 mL) at –78 ºC under Ar. After stirring at –78 ºC for 15 min, a solution of *O*-alkyl carbamate **213** (189 mg, 0.95 mmol, 1.0 eq.) in Et_2O (2 mL) was added dropwise. The resulting solution was stirred at –78 ºC for 1 h. Then, $MeCO_2Cl$ (0.17 mL, 2.28 mmol, 2.0 eq.) was added and the resulting solution was warmed to rt over 16 h. 1 M $HCl_{(aq)}$ (2 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 petrol-Et_2O as eluent gave ester (*R*)-**216** (49 mg, 19%) as a colourless oil, R_F(4:1 petrol-Et_2O) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83-5.77 (m, 1H, =CH), 5.16 (br s, 1H, CHO), 5.12-5.09 (m,

2H,=CH_2), 4.11 (br s, 1H, CHN), 3.81 (br s, 1H, CHN), 3.73 (s, 3H, OMe), 2.62-2.58 (m, 2H, =CHC*H*$_2$), 1.27-1.20 (m, 12H, CH*Me*).



1-Hydroxy-1-phenylpent-4-en-2-yl di-*i*-propylcarbamate 217

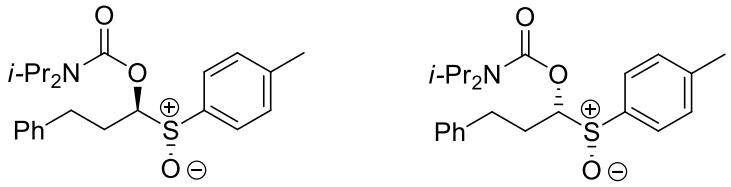
s-BuLi (0.93 mL of a 1.3 M solution in hexane, 1.21 mmol, 1.2 eq.) was added dropwise to a stirred solution of (−)-sparteine (320 mg, 1.21 mmol, 1.2 eq.) in Et_2O (3 mL) at −78 ºC under Ar. After stirring at −78 ^oC for 15 min, a solution of *O*-alkyl carbamate **213** (209 mg, 1.04 mmol, 1.0 eq.) in Et_2O (2 mL) was added dropwise. The resulting solution was stirred at −78 ºC for 3 h. Then, benzaldehyde (0.20 mL, 2.08 mmol, 2.0 eq.) was added and the resulting solution was warmed to rt over 16 h. 1 M $HCl_{(aq)}$ (2 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 petrol-Et_2O as eluent gave a 65:35 mixture (by ^1H NMR spectroscopy) of diastereomeric alcohols **217** (76 mg, 24%) as a colourless oil, R_F(4:1 petrol-Et_2O) 0.3; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.29 (m, 5H, Ph), 5.84-5.72 (m, 1H, =CH), 5.14-5.09 (m, 1H, CHO), 5.08-5.00 (m, 2H,=CH_2), 4.90 (d, J = 3.0 Hz, 0.35H, C*H*OH), 4.72 (d, J = 3.0 Hz, 0.65H, C*H*OH), 3.95 (br s, 2H, CHN), 2.43-2.18 (m, 2H, CH_2), 1.23-1.20 (m, 12H, Me).



1-(*p*-Tolylsulfinyl)-3-phenylpropyl *N*,*N*-di-*i*-propylcarbamate *anti-rac*-226 and *syn-rac*-227

s-BuLi (1.88 mL of a 1.3 M solution in hexane, 2.45 mmol, 1.2 eq.) was added dropwise to a stirred solution of carbamate **193** (538 mg, 2.04 mmol, 1.0 eq.) and TMEDA (0.37 mL, 2.45 mmol, 1.2 eq.) in Et_2O (10 mL) at –78 ºC under Ar. The resulting solution was stirred at –78 ºC for 1 h. Then, methyl *p*-toluenesulfinate (451 mg, 2.65 mmol, 1.3 eq.) was added dropwise and the solution was allowed to warm to rt over 16 h. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 3:1 petrol-EtOAc + 1% Et_3N as eluent gave sulfoxide *anti-rac*-**226** (262 mg, 32%) as a viscous colourless oil, R_F (3:1 petrol-EtOAc) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 8.0 Hz, 2H, *m*-C_6H_4Me), 7.28 (d, J = 8.0 Hz, 2H, *o*-C_6H_4Me), 7.21 (t, J = 7.0 Hz, 2H, *m*-Ph), 7.16 (d, J = 7.0 Hz, 1H, *p*-Ph), 7.02 (d, J = 7.0 Hz, 2H, *o*-Ph), 5.45 (dd, J = 10.0, 3.0 Hz, 1H, OCH), 3.94 (br s, 2H, NCH), 2.74 (ddd, J = 14.0, 10.0, 5.0 Hz, 1H, PhCH_AH$_B$), 2.56 (ddd, J = 14.0, 10.0, 7.0 Hz, 1H, PhCH$_A$$H_B$), 2.40 (s, 3H, Me), 2.36-2.25 (m, 1H, OCHCH_AH$_B$), 2.06-1.98 (m, 1H, OCHCH$_A$$H_B$), 1.26 (br s, 12H, NCH$Me_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 153.5 (C=O), 141.2 (*ipso*-$C_6H_4S(O)$), 140.3 (*ipso*-Ph), 137.4 (*ipso*-C_6H_4Me), 129.7 (Ar), 128.3 (Ar), 128.1 (Ar), 126.0 (Ar), 124.4 (Ar), 91.7 (OCH), 46.7 (br, NCH), 46.0 (br, NCH), 31.1 (CH_2), 26.0 (CH_2), 21.3 (Me), 20.2 (br, Me) and sulfoxide *syn-rac*-**227** (188 mg, 23%) as a colourless oil, R_F (3:1 petrol-EtOAc)

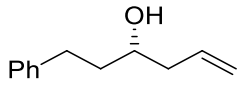
0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 8.0 Hz, 2H, Ar), 7.28-7.24 (m, 4H, Ar), 7.21-7.14 (m, 3H, Ar), 5.72 (dd, J = 9.5, 4.0 Hz, 1H, OCH), 3.99 (br s, 1H, NCH), 3.57 (br s, 1H, NCH), 2.76 (m, 2H, $PhCH_2$), 2.41-2.33 (m, 1H, $OCHCH_AH_B$), 2.37 (s, 3H, Me), 2.17-2.08 (m, 1H, $OCHCH_AH_B$), 1.21-0.99 (m, 12H, $CHMe_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 152.3 (C=O), 141.5 (*ipso*-Ar), 140.3 (*ipso*-Ar), 137.4 (*ipso*-Ar), 129.5 (Ar), 128.5 (Ar), 128.4 (Ar), 126.3 (Ar), 125.3 (Ar), 86.8 (OCH), 46.3 (br, NCH), 45.9 (br, NCH), 31.7 (CH_2), 30.3 (CH_2), 21.3 (Me), 20.2 (Me). Full characterisation and stereochemical assignment proof for *anti*-*rac*-**226** and *syn*-*rac*-**227** has been carried out in the group.[71]



(1*S*)-1-(*p*-Tolylsulfinyl)-3-phenylpropyl *N*,*N*-di-*i*-propylcarbamate *anti*-(*S*,*S*s)-222 and (1*R*)-1-(*p*-Tolylsulfinyl)-3-phenylpropyl *N*,*N*-di-*i*-propylcarbamate *syn*-(*R*,*S*s)-223

s-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.30 mmol, 1.3 eq.) was added dropwise to a stirred solution of carbamate **193** (264 mg, 1.00 mmol, 1.0 eq.), diamine **230** (253 mg, 1.20 mmol, 1.2 eq.) and diamine **203** (39 mg, 0.20 mmol, 0.2 eq.) in Et_2O (7 mL) at −78 ºC under Ar. The resulting solution was stirred at −78 ºC for 5 h and then added dropwise *via* cannula transfer to a solution of Andersen's sulfinate (*S*s)-**224** (383 mg, 1.30 mmol, 1.3 eq.). The resulting solution was stirred at −78 ºC for 1 h and then MeOH (2 mL) was added and the resulting solution was allowed to warm to rt over 2 h. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 3:1

petrol-EtOAc + 1% Et_3N as eluent gave sulfoxide *anti*-(*S*,*S*s)-**222** (44 mg, 13%, 85:15 er by CSP-HPLC) as a white solid, HPLC: Chiracel OD (97.2:2.5 Hexane-*i*PrOH, 1.0 mL min^{-1}) *anti*-(*R*,*R*s)-**222** 13.1 min, *anti*-(*S*,*S*s)-**222** 14.2 min and sulfoxide *syn*-(*R*,*S*s)-**223** (77 mg, 19%, 99:1 er by CSP-HPLC) as a colourless oil, HPLC: Chiracel OD (97.2:2.5 Hexane-*i*PrOH, 1.0 mL min^{-1}) *syn*-(*S*,*R*s)-**223** 20.1 min, *syn*-(*R*,*S*s)-**223** 23.1 min.



(*S*)-1-Phenylbut-3-en-1-ol (*S*)-128

i-PrMgCl (0.17 mL of a 2.0 M solution in THF, 0.34 mmoL, 1.5 eq.) was added dropwise to a stirred solution of sulfoxide *anti-rac*-**226** (90 mg, 0.22 mmoL, 1.0 eq.) in THF (8 mL) at rt under Ar. The resulting solution was stirred at rt for 1 min. Then, allylboronic acid pinacol ester (0.06 mL, 0.34 mmol, 1.5 eq.) was added dropwise and the resulting solution was stirred at rt for 30 min and then heated to reflux for 16 h. The reaction was cooled to rt and 3 M $NaOH_{(aq)}$ (0.5 mL) and 30% $H_2O_{2(aq)}$ (0.25 mL) were added sequentially. The resulting solution was stirred at rt for 2 h and then 3 M $NaOH_{(aq)}$ (5mL) was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography with 3:2 petrol-Et_2O as eluent gave alcohol *rac*-**128** (11 mg, 28%) as a viscous yellow oil.

i-PrMgCl (0.19 mL of a 2.0 M solution in THF, 0.37 mmoL, 1.5 eq.) was added dropwise to a stirred solution of sulfoxide *anti-rac*-**226** (100 mg, 0.25 mmoL, 1.0 eq.) in THF (8 mL) at rt under Ar. The resulting solution was stirred at rt for 1 min. Then, allylboronic acid pinacol ester (0.07 mL, 0.37 mmol, 1.5 eq.) was added dropwise and the resulting solution was stirred at rt for 2 h and then heated

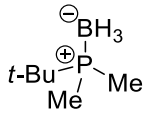
to reflux for 16 h. The reaction was cooled to rt and 3 M $NaOH_{(aq)}$ (0.5 mL) and 30% $H_2O_{2(aq)}$ (0.25 mL) were added sequentially. The resulting solution was stirred at rt for 2 h and then 3 M $NaOH_{(aq)}$ (5mL) was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography with 3:2 petrol-Et_2O as eluent gave alcohol *rac*-**128** (17 mg, 39%) as a viscous yellow oil.

i-PrMgCl (0.18 mL of a 2.0 M solution in THF, 0.37 mmoL, 1.5 eq.) was added dropwise to a stirred solution of sulfoxide *anti-rac*-**226** (98 mg, 0.24 mmoL, 1.0 eq.) in THF (8 mL) at rt under Ar. The resulting solution was stirred at rt for 1 min. Then, allylboronic acid pinacol ester (0.07 mL, 0.37 mmol, 1.5 eq.) was added dropwise and the resulting solution was stirred at rt for 4 h and then heated to reflux for 16 h. The reaction was cooled to rt and 3 M $NaOH_{(aq)}$ (0.5 mL) and 30% $H_2O_{2(aq)}$ (0.25 mL) were added sequentially. The resulting solution was stirred at rt for 2 h and then 3 M $NaOH_{(aq)}$ (5mL) was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography with 3:2 petrol-Et_2O as eluent gave alcohol *rac*-**128** (12 mg, 56%) as a viscous yellow oil.

i-PrMgCl (0.19 mL of a 2.0 M solution in THF, 0.37 mmoL, 1.5 eq.) was added dropwise to a stirred solution of sulfoxide *syn*-(*R*,*S*s)-**223** (100 mg, 0.25 mmoL, 1.0 eq.) in THF (8 mL) at rt under Ar. The resulting solution was stirred at rt for 1 min. Then, allylboronic acid pinacol ester (0.07 mL, 0.37 mmol, 1.5 eq.) was added dropwise and the resulting solution was stirred at rt for 4 h and then heated

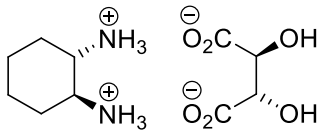
to reflux for 16 h. The reaction was cooled to rt and 3 M $NaOH_{(aq)}$ (0.5 mL) and 30% $H_2O_{2(aq)}$ (0.25 mL) were added sequentially. The resulting solution was stirred at rt for 2 h and then 3 M $NaOH_{(aq)}$ (5mL) was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography with 3:2 petrol-Et_2O as eluent gave alcohol (*S*)-**128** (8 mg, 19%, 93:7 er) as a viscous yellow oil, HPLC: Daicel Chiracel OD, 95:5 *i*-PrOH-hexane, 0.5 mL min^{-1}, (*S*)-**128** 17.6 min, (*R*)-**128** 25.4 min.

4.4 Experimental for Chapter 3



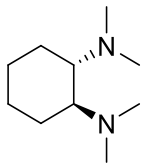
***t*-Butyldimethyl phosphine borane 283**

t-BuMgCl (33.2 mL of a 2.0 M solution in Et_2O, 66.6 mL, 1.1 eq.) was added dropwise over 30 min to a stirred solution of PCl_3 (8.3 g, 60.6 mmol, 1.0 eq.) in THF (85 mL) at –78 ºC under Ar. The resulting heterogeneous mixture was stirred at –78 ºC for 1 h and allowed to warm to rt and stirred for 1 h. The reaction mixture was cooled to 0 ºC and MeMgBr (44.3 mL of a 3.0 M solution in Et_2O, 133.2 mmol, 2.2 eq.) was added dropwise over 20 min. The resulting mixture was allowed to warm to rt over 1 h. Then, the resulting heterogeneous mixture was cooled to 0 ºC and $BH_3 \cdot Me_2S$ (36.3 mL of a 2.0 M solution in Et_2O, 72.6 mmol, 1.5 eq.) was added dropwise and the mixture was allowed to warm to rt and stirred for 16 h. Then, the mixture was poured onto ice/H_2O and conc. $HCl_{(aq)}$ (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 45 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by recrystallisation from hot hexane (40 mL) gave phosphine borane **283** (5.78 g, 72%) as a white solid, mp 161-162 ºC (lit.,[98] 164-165 ºC); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (d, J = 10.0 Hz, 6H, PMe), 1.15 (d, J = 13.5 Hz, 9H, $PCMe_3$), 0.43 (qd, J = 94.0, 15.0 Hz, PBH_3); ^{13}C NMR (100.6 MHz) δ 26.6 (CMe_3), 24.7 (CMe_3), 7.2 (Me); ^{31}P{^{1}H} NMR (109 MHz, $CDCl_3$) δ 21.0. Spectroscopic data consistent with those reported in the literature.[98]



(1*S*,2*S*)-Cyclohexane-1,2-diamine 2,3-dihydroxysuccinate salt (*S*,*S*,*S*,*S*)-306

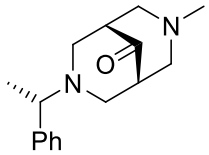
Trans (±)-1,2 Cyclohexane diamine (15.00 mL, 124.8 mmol, 1.0 eq.) was added dropwise to a stirred solution of D-tartaric acid (9.37 g, 62.4 mmol, 0.5 eq.) in water (45 mL) under air, such that the internal temperature did not exceed 70 °C (during this time a white precipitate forms, but this disappears by the point of complete addition). Then, AcOH (3.8 mL) was added dropwise such that the internal temperature did not exceed 90 °C. The resulting solution was allowed to cool to 5 °C over 16 h (refrigerator). The solids were removed by filtration and the filter-cake was washed with cold water (≤ 5 °C, 20 mL) and MeOH (5 x 10 mL) (Washings kept separate). The resulting white solid was dried by suction to give the cyclohexane diamine D-tartaric acid salt (*S*,*S*,*S*,*S*)-**306** (12.45 g, 38%) as a white solid, ^{1}H NMR (400 MHz, D_2O) δ 4.19 (s, 2H, 2 × C*H*OH), 3.23-3.21 (m, 2H, 2 × CH), 2.04-2.00 (m, 2H, CH_2), 1.70-1.69 (m, 2H, CH_2), 1.43-1.35 (m, 2H, CH_2), 1.25-1.20 (m, 2H, CH_2). Spectroscopic data consistent with those reported in the literature.[142]



(1*S*,2*S*)-*N*,*N*,*N*',*N*'-Tetramethylcyclohexane-1,2-diamine (*S*,*S*)-304

Formic acid (7.14 mL, 189.2 mmol, 1.0 eq.) was added to a stirred solution of salt (*S*,*S*,*S*,*S*)-**306** (5.0 g, 18.92 mmol, 10.0 eq) in 37% (w/w) aqueous formaldehyde (14.17 mL, 189.2 mmol, 10.0 eq.). The resulting solution was stirred and heated at 100 °C for 18 h. After being allowed to cool to rt, the solvent was evaporated under reduced pressure. 5 M $NaOH_{(aq)}$ (125 mL) was added and the resulting solution was extracted with $CHCl_3$ (3 x 50 mL). The

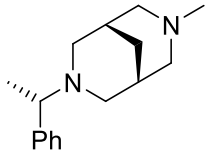
combined organic extracts were washed with saturated brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by Kügelrohr distillation gave (*S*,*S*)-TMCDA (*S*,*S*)-**306** (3.08 g, 96%, 99:1 er by chiral shift ^{1}H NMR spectroscopy) as a colourless oil, b.p 130–138 ^{o}C/5.0 mmHg (lit.,[143] 50 ^{o}C/0.1 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38-2.36 (m, 2H, NCH), 2.26 (s, 12H, NMe), 1.84-1.81 (m, 2H, CH), 1.74-1.73 (m, 2H, CH), 1.10-1.08 (m, 4H, CH). Spectroscopic data consistent with those reported in the literature.[144] The enantiomeric ratio was determined by ^{1}H NMR spectroscopy in the presence of (*S*)-2,2,2-trifluoro-1-(9 anthryl)-ethanol: TMCDA (1 mg, 0.053 mmol) was dissolved in $CDCl_3$ (0.6 mL) and (*S*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol (2.8 mg, 0.22 mmol) was added. Key signal: ^{1}H NMR (400 MHz, CDCl3) δ 2.21 (s, 12H, NMe, major), 2.18 (s, 12H, NMe, minor). Integration of the major and minor NMe signals in the ^{1}H NMR spectrum indicated that TMCDA (*S*,*S*)-**304** was present in 99:1 er.



3-Methyl-7-((*S*)-1-phenylethyl)-3,7-diazabicyclo[3.3.1]nonan-9-one (*S*)-310

(*S*)-Phenylethylamine (2.15 mL, 16.89 mmol, 1.0 eq.) was added dropwise to a stirred solution of 1-methyl-4-piperidone (1.91 g, 16.89 mmol, 1.0 eq., freshly distilled), paraformaldehyde (1.53 g, 50.64 mmol, 3.0 eq.) and AcOH (1.15 mL, 16.89 mmol, 1.0 eq.) in EtOH (45 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 18 h. The solution was cooled to rt and the solvent was evaporated under reduced pressure. 50% $KOH_{(aq)}$ solution (50 mL) and Et_2O (50 mL) were added to the residue and the layers were separated. The aqueous layers was extracted with Et_2O (3 x 50 mL) and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude

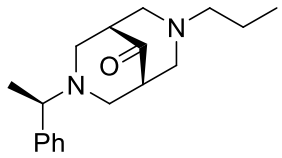
product. Purification by Kügelrohr distillation gave bispidone (*S*)-**310** (2.16 g, 50%) as a clear viscous yellow oil, bp 240-244 ºC/4.0 mmHg; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.23 (m, 5H, Ph), 3.59 (q, *J* = 7.0 Hz, 1H, PhCHN), 3.10-3.07 (m, 1H, NCH), 3.07-2.90 (m, 5H, 5 × NCH) 2.72-2.64 (m, 2H, 2 × (CH)C=O), 2.59-2.53 (m, 2H, 2 × NCH), 2.30 (s, 3H, NMe), 1.37 (d, *J* = 7.0 Hz, 3H, CH*Me*).



3-Methyl-7-((*S*)-1-phenylethyl)-3,7-diazabicyclo[3.3.1]nonane (*S*)-307

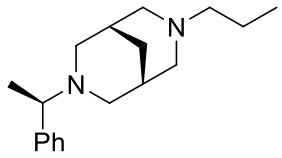
Hydrazine monohydrate (4.26 mL, 85.15 mmol, 5.5 eq.) was added dropwise to a stirred mixture of bispidone (*S*)-**310** (4.0 g, 15.48 mmol, 1.0 eq.) and KOH (10.16 g, 181.12 mmol, 11.7 eq.) in diethylene glycol (120 mL) at rt under Ar. The mixture was stirred and heated at reflux for 20 h. After cooling to 60 ºC (if the diethylene glycol solution is cooled to rt before addition of H_2O then the mixture becomes very viscous and too difficult to work with), the mixture was transferred to a separating funnel. H_2O (200 mL) and Et_2O (80 mL) were added and the layers were separated. The aqueous layer was extracted with Et_2O (6 x 90 mL). The combined organic layers were washed with 20% $NaOH_{(aq)}$ (6 x 50 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by Kügelrohr distillation gave *N*-Me bispidine (*S*)-**307** (2.06 g, 53%) as a clear yellow oil, bp 180-190 ºC/2.5 mmHg (lit.,[6] 120-130 ºC/0.25 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.0 Hz, 2H, *o*-Ph), 7.31 (t, *J* = 7.0 Hz, 2H, *m*-Ph), 7.23 (t, *J* = 7.0 Hz, 1H, *p*-Ph), 3.40 (q, *J* = 7.0 Hz, 1H, PhCHN), 2.78-2.75 (m, 1H, NCH), 2.65-2.59 (m, 1H, NCH), 2.58-2.48 (m, 4H, 4 × NCH), 2.30-2.25 (m, 2H, 2 × NCH), 2.24 (s, 3H, NMe), 1.97-1.90 (m, 2H, CH), 1.63-1.59 (m, 1H, CH), 1.36-1.28 (m, 1H, CH), 1.32 (d, *J* = 7.0 Hz, 3H, CH*Me*);

^{13}C NMR (100.6 MHz) (one Ph resonance not resolved) δ 128.0 (Ph), 127.5 (Ph), 126.4 (Ph), 64.3 (NCH), 59.0 (NCH_2), 58.9 (NCH_2), 55.6 (NCH_2), 54.5 (NCH_2), 46.2 (NMe), 29.1 (CH or Me), 28.9 (CH or Me), 28.7 (CH_2), 19.0 (CH or Me). Spectroscopic data consistent with those reported in the literature.[107]



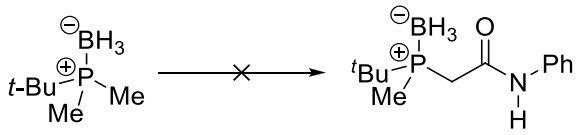
3-((*R*)-1-Phenylethyl)-7-propyl-3,7-diazabicyclo[3.3.1]nonan-9-one (*R*)-312

(*R*)-Phenylethylamine (4.30 g, 35.41 mmol, 1.0 eq.) was added dropwise to a stirred solution of 1-propyl-4-piperidone (5.00 g, 35.41 mmol, 1.0 eq. freshly distilled), paraformaldehyde (3.22 g, 106.23 mmol, 3.0 eq.) and AcOH (2.13 mL, 35.41 mmol, 1.0 eq.) in EtOH (70 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 18 h. The solution was cooled to rt and the solvent was evaporated under reduced pressure. 50% $KOH_{(aq)}$ solution (70 mL) was added and the mixture was extracted with Et_2O (3 x 100 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by Kügelrohr distillation gave bispidone (*R*)-**312** (5.07 g, 50%) as a clear viscous yellow oil, b.p. 254-256 ^{o}C/6.0 mmHg; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.29 (m, 4H, Ph), 7.25-7.21 (m, 1H, Ph), 3.54 (q, J = 7.0 Hz, 1H, PhCHN), 3.10-2.95 (m, 4H, 4 × NCH), 2.86-2.70 (m, 4H, 4 × NCH), 2.57-2.50 (m, 2H, CH), 2.32 (t, J = 7.0 Hz, 2H, NCH_2), 1.50-1.42 (m, 2H, CH), 1.35 (d, J = 7.0 Hz, 3H, CH*Me*), 0.88 (t, J = 7.5 Hz, 3H, CH_2*Me*).



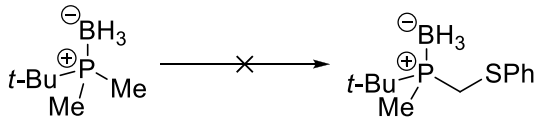
3-((*R*)-1-Phenylethyl)-7-propyl-3,7-diazabicyclo[3.3.1]nonane (*R*)-308

Hydrazine monohydrate (5.6 mL, 0.116 mmol) was added dropwise to a stirred mixture of bispidone (*R*)-**312** (5.69 g, 21.0 mmol) and KOH (19.69 g, 351 mmol) in diethylene glycol (150 mL) at rt under Ar. The mixture was stirred and heated at reflux for 20 h. After cooling to 60 ºC (if the diethylene glycol solution is cooled to rt before addition of H_2O then the mixture becomes very viscous and too difficult to work with), the mixture was transferred to a separating funnel. H_2O (150 mL) and Et_2O (80 mL) were added and the layers were separated. The aqueous layer was extracted with Et_2O (6 x 60 mL). The combined organic layers were washed with 20% $NaOH_{(aq)}$ (6 x 50 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by Kügelrohr distillation gave *N*-Pr bispidine (*R*)-**308** (3.84 g, 71%) as a viscous pale yellow oil, bp 198-204 ºC/4.5 mmHg; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.45 (m, 2H, Ph), 7.30 (t, J = 7.0 Hz, 2H, Ph), 7.23-7.19 (m, 1H, Ph), 3.35 (q, J = 6.5 Hz, 1H, PhCHN), 2.83-2.80 (m, 1H, NCH), 2.69-2.62 (m, 3H, 3 × NCH), 2.43-2.36 (m, 2H, 2 × NCH), 2.33-2.27 (m, 2H, 2 × NCH), 2.26-2.20 (m, 2H, 2 × NCH), 1.93-1.83 (m, 2H, CH), 1.59-1.38 (m, 3H, CH), 1.43-1.34 (m, 1H, CH), 1.30 (d, J = 6.5 Hz, 3H, CH*Me*), 0.96 (t, J = 7 Hz, 3H, CH_2*Me*); MS (ESI) *m/z* 273 [M^+, 100]; HRMS (ESI) *m/z* calcd for $C_{18}H_{29}N_2$ M^+ 273.2325, found 273.2325 (0.4 ppm error).



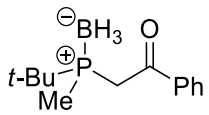
Attempted synthesis of *rac*-314

s-BuLi (0.64 mL of a 1.3 M in hexane, 0.83 mmol, 1.1 eq.) was added dropwise to a stirred solution of phosphine borane **283** (100 mg, 0.76 mmol, 1.0 eq.) in THF (10 mL) at 0 ºC under Ar. The resulting solution was stirred at 0 ºC for 30 min. Then, PhNCO (0.09 mL, 0.83 mmol, 1.1 eq.) was added dropwise and the mixture was allowed to warm to rt over 1 h. 1 M $HCl_{(aq)}$ (10 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. No evidence of the desired product was observed in the ^1H NMR spectrum of the crude product.



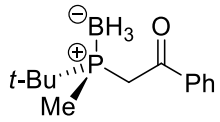
Attempted synthesis of *rac*-315

s-BuLi (0.74 mL of a 1.3 M in hexane, 0.97 mmol, 1.1 eq.) was added dropwise to a stirred solution of phosphine borane **283** (116 mg, 0.88 mmol, 1.0 eq.) in THF (10 mL) at 0 ºC under Ar. The resulting solution was stirred at 0 ºC for 30 min. Then, a solution of PhSSPh (211 mg, 0.97 mmol, 1.1 eq.) in THF (2 mL) was added dropwise and the mixture was allowed to warm to rt over 1 h. 1 M $HCl_{(aq)}$ (10 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. No evidence of the desired product was observed in the ^1H NMR spectrum of the crude product.



***rac*-2-[Boranylidene(*t*-butyl)methylphosphanyl]-1-phenylethan-1-one *rac*-316**

s-BuLi (0.71 mL of a 1.3 M in hexane, 0.92 mmol, 1.1 eq.) was added dropwise to a stirred solution of phosphine borane **283** (110 mg, 0.83 mmol, 1.0 eq.) in THF (10 mL) at 0 ºC under Ar. The resulting solution was stirred at 0 ºC for 30 min. Then, Weinreb amide **313** (151 mg, 0.92 mmol, 1.1 eq.) was added dropwise and the mixture was allowed to warm to rt over 1 h. 1 M $HCl_{(aq)}$ (10 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash colum chromatography with 8:2 petrol-Et_2O as eluent gave ketone *rac*-**316** (132 mg, 67%) as a colourless oil.



(*S*)-2-[Boranylidene(*t*-butyl)methylphosphanyl]-1-phenylethan-1-one (*S*)-316

(Table 3.11, entry 1)

s-BuLi (0.71 mL of a 1.3 M in hexane, 0.92 mmol, 1.1 eq.) was added dropwise to a stirred solution of (−)-sparteine (213 mg, 0.91 mmol, 1.2 eq.) in Et_2O (8 mL) at -78 ºC. After stirring for 15 min, a solution of phosphine borane **283** (100 mg, 0.76 mmol, 1.0 eq.) in Et_2O (2 mL) was added dropwise. The resulting solution was stirred at -78 ºC for 3 h. Then, Weinreb amide **313** (134 mg, 0.83 mmol, 1.1 eq.) was added dropwise and the mixture was allowed to warm to rt overnight. 1 M $HCl_{(aq)}$ (10 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give

the crude product. Purification by flash column chromatography with 8:2 petrol-Et_2O as eluent gave ketone (*S*)-**316** (100 mg, 56%, 91:9 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +49.7 (*c* 1 in CH_3Cl); R_F (8:2 petrol-Et_2O) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98-7.96 (m, 2H, Ph), 7.61-7.56 (m, 1H, Ph), 7.49-7.27 (m, 2H, Ph), 3.64 (dd, *J* = 13.0, 8.0 Hz, 1H, PCH_AH_B), 3.05 (t, *J* = 13.0 Hz, 1H, PCH_AH_B), 1.35 (d, *J* = 10.0 Hz, 3H, PMe), 1.22 (d, *J* = 14.0 Hz, 9H, $PCMe_3$), 0.43 (qd, *J* = 94.0, 15.0 Hz, PBH_3); ^{13}C NMR (100.6 MHz) δ 194.9 (C=O), 137.0 (*ipso*-Ph), 133.7 (Ph), 128.9 (Ph), 128.6 (Ph), 31.3 (CH_2), 28.4 (CMe_3), 24.9 (CMe_3), 5.6 (Me); MS (ESI) *m/z* 1235 [M^+, 100]; HRMS (ESI) *m/z* calcd for $C_{13}H_{21}BOP$ M^+ 235.1415, found 235.1420 (−3.4 ppm error); HPLC: Daicel Chiracel OD, 90:10 hexane-*i*-PrOH, 1 mL min^{-1}, (*S*)-**316** 7.72 min, (*R*)-**316** 8.51 min.

(Table 3.11, entry 2)

s-BuLi (0.49 mL of a 1.3 M in hexane, 0.63 mmol, 1.1 eq.) was added dropwise to a stirred solution of diamine **203** (177 mg, 0.91 mmol, 1.2 eq.) in Et_2O (8 mL) at -78 ºC. After stirring for 15 min, a solution of phosphine borane **283** (77 mg, 0.58 mmol, 1.0 eq.) in Et_2O (2 mL) was added dropwise. The resulting solution was stirred at -78 ºC for 3 h. Then, Weinreb amide **313** (105 mg, 0.63 mmol, 1.1 eq.) was added dropwise and the mixture was allowed to warm to rt and stirred at rt for 16 h. 1 M $HCl_{(aq)}$ (10 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography with 8:2 petrol-Et_2O as eluent gave ketone (*R*)-**316** (88 mg, 65%, 91:9 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ −45.8 (*c* 1 in CH_3Cl); HPLC: Daicel Chiracel OD, 90:10 hexane-*i*-PrOH, 1 mL min^{-1}, (*S*)-**316** 7.71 min, (*R*)-**316** 8.48 min.

(Table 3.11, entry 3)

s-BuLi (0.64 mL of a 1.3 M in hexane, 0.83 mmol, 1.1 eq.) was added dropwise to a stirred solution of diamine (*S*,*S*)-**304** (154 mg, 0.91 mmol, 1.2 eq.) in Et_2O (8 mL) at -78 ºC. After stirring for 15 min, a solution of phosphine borane **283** (100 mg, 0.78 mmol, 1.0 eq.) in Et_2O (2 mL) was added dropwise. The resulting solution was stirred at -78 ºC for 3 h. Then, Weinreb amide **313** (134 mg, 0.83 mmol, 1.1 eq.) was added dropwise and the mixture was allowed to warm to rt and stirred at rt for 16 h. 1 M $HCl_{(aq)}$ (10 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography with 8:2 petrol-Et_2O as eluent gave ketone (*R*)-**316** (87 mg, 50%, 78:22 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ -31.8 (*c* 1 in CH_2Cl_2); HPLC: Daicel Chiracel OD, 90:10 hexane-*i*-PrOH, 1 mL min^{-1}, (*S*)-**316** 7.65 min, (*R*)-**316** 8.38 min.

(Table 3.11, entry 4)

s-BuLi (0.62 mL of a 1.3 M in hexane, 0.80 mmol, 1.1 eq.) was added dropwise to a stirred solution of diamine (*S*)-**307** (237 mg, 0.87 mmol, 1.2 eq.) in Et_2O (8 mL) at -78 ºC. After stirring for 15 min, a solution of phosphine borane **283** (96 mg, 0.73 mmol, 1.0 eq.) in Et_2O (2 mL) was added dropwise. The resulting solution was stirred at -78 ºC for 3 h. Then, Weinreb amide **313** (132 mg, 0.80 mmol, 1.1 eq.) was added dropwise and the mixture was allowed to warm to rt and stirred at rt for 16 h. 1 M $HCl_{(aq)}$ (10 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography with 8:2 petrol-Et_2O as eluent gave ketone (*R*)-**316**

(71 mg, 41%, 61:39 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ -6.6 (*c* 1 in CH_3Cl); HPLC: Daicel Chiracel OD, 90:10 hexane-*i*-PrOH, 1 mL min $^{-1}$, (*S*)-**316** 7.55 min, (*R*)-**316** 8.32 min.

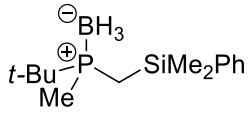
(Table 3.11, entry5)

s-BuLi (0.68 mL of a 1.3 M in hexane, 0.88 mmol, 1.1 eq.) was added dropwise to a stirred solution of diamine (*R*)-**308** (263 mg, 0.96 mmol, 1.2 eq.) in Et_2O (8 mL) at -78 ºC. After stirring for 15 min, a solution of phosphine borane **283** (106 mg, 0.80 mmol, 1.0 eq.) in Et_2O (2 mL) was added dropwise. The resulting solution was stirred at -78 ºC for 3 h. Then, Weinreb amide **313** (146 mg, 0.88 mmol, 1.1 eq.) was added dropwise and the mixture was allowed to warm to rt and stirred at rt for 16 h. 1 M $HCl_{(aq)}$ (10 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography with 8:2 petrol-Et_2O as eluent gave ketone (*S*)-**316** (52 mg, 33%, 55:45 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +5.7 (*c* 1 in CH_2Cl_2); HPLC: Daicel Chiracel OD, 90:10 hexane-*i*-PrOH, 1 mL min $^{-1}$, (*S*)-**316** 7.54 min, (*R*)-**316** 8.32 min.

(Table 3.11, entry 6)

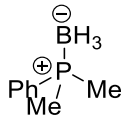
s-BuLi (0.74 mL of a 1.3 M in hexane, 0.97 mmol, 1.1 eq.) was added dropwise to a stirred solution of diamine (*S,S*)-**317** (366 mg, 1.05 mmol, 1.2 eq.) in Et_2O (8 mL) at -78 ºC. After stirring for 15 min, a solution of phosphine borane **283** (116 mg, 0.88 mmol, 1.0 eq.) in Et_2O (2 mL) was added dropwise. The resulting solution was stirred at -78 ºC for 3 h. Then, Weinreb amide **313** (160 mg, 0.97 mmol, 1.1 eq.) was added dropwise and the mixture was allowed to warm to rt and stirred at rt for 16 h. 1 M $HCl_{(aq)}$ (10 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The

combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography with 8:2 petrol-Et_2O as eluent gave ketone (*S*)-**316** (140 mg, 67%, 45:55 er by CSP-HPLC) as a colourless oil, HPLC: Daicel Chiracel OD, 90:10 hexane-*i*-PrOH, 1 mL min $^{-1}$, (*S*)-**316** 7.48 min, (*R*)-**316** 8.26 min.



***rac*-*t*-Butylmethylphosphinothioyl(methyl)dimethylphenylsilane *rac*-293**

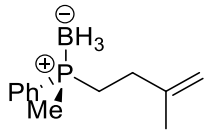
s-BuLi (0.70 mL of a 1.3 M in hexane, 0.91 mmol, 1.1 eq.) was added dropwise to a stirred solution of phosphine borane **283** (109 mg, 0.83 mmol, 1.0 eq.) in THF (10 mL) at 0 ºC under Ar. The resulting solution was stirred at 0 ºC for 30 min. Then, $PhMe_2SiCl$ (155 mg, 0.92 mmol, 1.1 eq.) was added dropwise and the mixture was allowed to warm to rt over 1 h. 1 M $HCl_{(aq)}$ (10 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography with 98:2 petrol-Et_2O as eluent gave silyl phosphine borane *rac*-**293** (162 mg, 60%) as a colourless oil.



***P*,*P*-Dimethylphenylphosphine borane 261**

MeMgBr (41.2 mL of a 3.0 M solution in Et_2O, 123.63 mmol, 2.2 eq.) was added dropwise to a stirred solution of $PhPCl_2$ (5.3 mL, 56.20 mmol, 1.0 eq.) in THF (100 mL) at 0 ºC under Ar. The resulting solution was stirred at rt for 16 h. Then, $BH_3 \cdot Me_2S$ (33.7 mL of a 2.0 M solution in THF, 67.43 mmol, 1.2 eq.) was added dropwise, and the resulting solution was stirred at rt for 2 h. The solution was

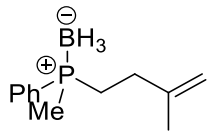
poured onto a mixture of ice and conc. $HCl_{(aq)}$ (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (60 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography with 9:1 petrol-EtOAc as eluent gave phosphine borane **261** (5.3 g, 88%) as a colourless oil, R_F (9:1 petrol-EtOAc) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76-7.71 (m, 2H, Ph), 7.50-7.48 (m, 3H, Ph), 1.58 (d, J = 10.5 Hz, 6H, Me), 1.17-0.44 (m, 3H, BH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 131.2 (d, J = 2.0 Hz, Ph), 130.9 (d, J = 55.0 Hz, *ipso*-Ph), 130.7 (d, J = 9.5 Hz, Ph), 128.8 (d, J = 10.0 Hz, Ph), 12.9 (d, J = 39.0 Hz, PMe); ^{31}P NMR (109 MHz, $CDCl_3$) δ 3.40 (q, J = 40.0 Hz). Spectroscopic data consistent with those reported in the literature.[93]



(*S*)-Methyl-(3-methylbut-3-en-1-yl)phenylphosphine borane (*S*)- 345

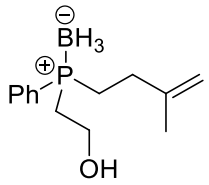
Using procedure E, *s*-BuLi (1.63 mL of a 1.3 M solution in hexane, 2.12 mmol, 1.1 eq.) and (–)-sparteine (543 mg, 2.32 mmol, 1.2 eq.) in Et_2O (8 mL), phosphine borane **261** (300 mg, 1.93 mmol, 1.0 eq.) in Et_2O (2 mL) and methallyl bromide (0.33 mL, 2.32 mmol, 1.2 eq.) gave the crude product. Purification by flash column chromatography with 95:5 petrol-Et_2O as eluent gave allylated phosphine borane (*S*)-**345** (291 mg, 73%, 89:11 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ –1.0 (*c* 1.0 in $CHCl_3$); R_F (8:2 petrol-Et_2O) 0.4; IR (film) 3030, 2925, 2892, 2868, 2338, 2300, 1625 (C=C), 1414, 1396, 1117, 1099, 1049, 940, 884, 733, 684, 576 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76-7.71 (m, 2H, Ph), 7.55-7.47 (m, 3H, Ph), 4.73 (br s, 1H, =CH), 4.69 (br s, 1H, =CH), 2.25-1.94 (m, 4H, CH), 1.70 (s, 3H, =CMe), 1.58 (d, J = 10.5 Hz, 3H, PMe), 1.09-0.38 (m,

3H, BH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.4 (d, J = 14.0 Hz, C=CH_2), 131.3 (d, J = 9.0 Hz, Ph), 131.2 (d, J = 2.0 Hz, Ph), 129.5 (d, J = 53.0 Hz, *ipso*-Ph), 128.7 (d, J = 10.0 Hz, Ph), 110.2 (=CH_2), 30.6 (CH_2), 25.5 (d, J = 36.0 Hz, PCH_2), 22.3 (Me), 10.8 (d, J = 39.0 Hz, PMe); $^{31}P\{^1H\}$ NMR (109 MHz, $CDCl_3$) δ 10.0 (q, J = 26.0 Hz); MS (ESI) m/z 229 [$(M + Na)^+$, 100]; HRMS (ESI) m/z calcd $C_{12}H_{20}BP$ $(M + Na)^+$ 229.1285, found 229.1290 (1.6 ppm error); HPLC: Daicel Chiracel AD-H, 99.5:0.5 hexane-*i*-PrOH, 0.5 mL min^{-1}, (*R*)-**345** 20.6 min, (*S*)-**345** 27.2 min.



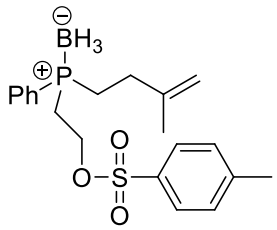
Methyl-(3-methylbut-3-en-1-yl)phenylphosphine borane *rac*-345

s-BuLi (3.82 mL of a 1.3 M solution in hexane, 4.97 mmol, 1.2 eq.) was added dropwise to a stirred solution of phosphine borane **261** (630 mg, 4.14 mmol, 1.0 eq.) in THF (10 mL) at −78 ºC under Ar. The resulting solution was stirred at −78 ºC for 1 h. Then, methallyl bromide (0.63 mL, 4.97 mmol, 1.2 eq.) was added dropwise and the mixture was allowed to warm to rt over 1 h. 1 M $HCl_{(aq)}$ (10 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography with 8:2 petrol-Et_2O as eluent gave allylated phosphine borane *rac*-**345** (760 mg, 90%) as a colourless oil.



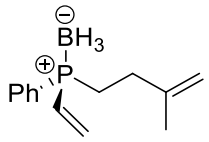
2-Boranyl-(3-methylbut-3-en-1-yl)(phenylphosphaniumyl)ethan-1-ol *rac*-346

s-BuLi (0.76 mL of a 1.3 M in solution hexane, 0.99 mmol, 1.2 eq.) was added dropwise to a stirred solution of allylated phosphine borane *rac*-**345** (170 mg, 0.83 mmol, 1.0 eq.) in THF (5 mL) at –78 ºC under Ar. The resulting solution was stirred at –78 ºC for 1 h. Then, a solution of paraformaldehyde (37 mg, 1.24 mmol, 1.5 eq.) in THF (5 mL) was added dropwise and the mixture was allowed to warm to rt over 16 h. 1 M $HCl_{(aq)}$ (10 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography with 6:4 petrol-Et_2O as eluent gave hydroxy phosphine borane *rac*-**346** (93 mg, 48%) as a colourless oil, R_F (6:4 petrol-Et_2O) 0.1; IR ($CDCl_3$) 3198, 2860, 2334, 2306, 1412, 1096, 1050, 1020, 969, 879, 655 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77-7.73 (m, 2H, Ph), 7.57-7.48 (m, 3H, Ph), 4.74 (br s, 1H, =CH), 4.69 (br s, 1H, =CH), 3.96-3.78 (m, 2H, C*H*$_2$OH), 2.29-2.20 (m, 3H, CH), 2.10-1.85 (m, 3H, CH), 1.70 (s, 3H, =CMe), 1.15-0.45 (m, 3H, BH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.5 (d, J = 13.5 Hz, *C*=CH$_2$), 131.8 (d, J = 9.0 Hz, Ph), 131.5 (d, J = 2.0 Hz, Ph), 129.8 (d, J = 10.0 Hz, Ph), 127.5 (d, J = 53.0 Hz, *ipso*-Ph), 110.3 (=CH_2), 57.4 (OCH_2), 30.3 (CH_2), 29.0 (d, J = 35.0 Hz, PCH_2), 24.3 (d, J = 36.0 Hz, PCH_2), 22.2 (Me); $^{31}P\{^1H\}$ NMR (109 MHz, $CDCl_3$) δ 12.6 (q, J = 26.0 Hz); MS (ESI) m/z 259 [$(M + Na)^+$, 60], 90 (100); HRMS (ESI) m/z calcd $C_{13}H_{22}BP$ $(M + Na)^+$ 259.1399, found 259.1396 (–1.1 ppm error).



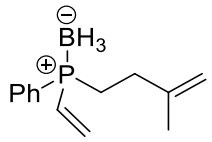
2-Boranyl-(3-methylbut-3-en-1-yl)(phenylphosphaniumyl)ethyl 4-methylbenzene-1- sulfinate *rac*-347

A solution of *p*-toluenesulfonyl chloride (109 mg, 0.57 mmol, 1.5 eq.) in CH_2Cl_2 (2 mL) was added dropwise to a stirred solution of phosphine borane *rac*-**346** (90 mg, 0.38 mmol, 1.0 eq.) and pyridine (15 mg, 0.19 mmol, 0.5 eq.) in CH_2Cl_2 (2 mL) at rt under Ar. The resulting mixture was stirred at rt for 16 h. 2 M $HCl_{(aq)}$ (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography with 8:2 petrol-Et_2O as eluent gave tosylate *rac*-**347** (50 mg, 34%) as a white solid, mp 90-91 ºC; R_F (8:2 petrol-Et_2O) 0.3; IR (film) 3031, 2923, 2872, 2349, 1415, 1340, 1158, 1080, 1050, 947, 735, 652 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72-7.66 (m, 4H, Ar), 7.58-7.47 (m, 3H, Ar), 7.33 (d, J = 8.0 Hz, 2H, Ar), 4.73 (br s, 1H, =CH), 4.67 (br s, 1H, =CH), 4.33-4.24 (m, 1H, OCH_AH_B), 4.12-4.03 (m, 1H, OCH_AH_B), 2.46 (s, 3H, MeC_6H_4), 2.39-1.92 (m, 6H, CH), 1.68 (s, 3H, =CMe), 1.02-0.24 (m, 3H, BH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 145.1 (*ipso*-Ar), 144.1 (d, J = 14.0 Hz, C=CH_2), 132.4 (*ipso*-Ar), 131.9 (Ar), 131.8 (d, J = 9.0 Hz, Ar), 129.9 (Ar), 129.0 (d, J = 10.0 Hz, Ar), 127.8 (Ar), 126.4 (d, J = 52.0 Hz, *ipso*-Ph), 110.5 (=CH_2), 65.0 (d, J = 5.0 Hz, OCH_2), 30.2 (CH_2), 26.0 (d, J = 34.0 Hz, PCH_2), 24.2 (d, J = 36.0 Hz, PCH_2), 22.2 (Me), 21.6 (Me); $^{31}P\{^1H\}$ NMR (109 MHz, $CDCl_3$) δ 13.9-13.4 (m); MS (ESI) m/z 389 M^+ (100); HRMS (ESI) m/z calcd $C_{20}H_{27}BO_3PS$ M^+ 389.1516, found 389.1510 (–2.5 ppm error).



(*R*)-Ethenyl-(3-methylbut-3-en-1-yl)phenylphosphine borane (*R*)-348

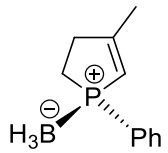
Using general procedure F, *s*-BuLi (0.81 mL of a 1.3 M solution in hexane, 1.05 mmol, 1.2 eq.), allylated phosphine borane (*S*)-**345** (180 mg, 0.87 mmol, 1.0 eq.) in THF (5 mL) and paraformaldehyde (40 mg, 1.05 mmol, 1.2 eq.) in THF (5 mL), followed by *p*-toluenesulfonyl chloride (230 mg, 1.21 mmol) in CH_2Cl_2 (5 mL) and pyridine (0.10 mL, 1.21 mmol) in CH_2Cl_2 (5 mL) and then KO*t*-Bu (212 mg, 1.89 mmol) in Et_2O (5 mL) gave the crude product. Purification by flash column chromatography with 95:5 petrol-Et_2O as eluent gave vinyl phosphine borane (*R*)-**348** (108 mg, 58%) as a colourless oil, $[\alpha]_D$ –29.7 (*c* 0.5 in $CHCl_3$); R_F (95:5 petrol-Et_2O) 0.3; IR (film) 3031, 2925, 2890, 2870, 2346, 2305, 1415, 1094, 1048, 967, 878, 733, 684 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74-7.69 (m, 2H, Ph), 7.51-7.48 (m, 3H, Ph), 6.40 (dt, *J* = 18.0, 13.0 Hz, 1H, PCH=), 6.27-6.14 (m, 2H, PCH=CH_2), 4.75 (br s, 1H, =CH), 4.70 (br s, 1H, =CH), 2.21-2.04 (m, 4H, CH), 1.72 (s, 3H, Me), 1.13-0.43 (m, 3H, BH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.6 (d, *J* = 14.0 Hz, *C*=CH_2), 134.6 (d, *J* = 5.0 Hz, PCH=*C*H_2), 131.6 (d, *J* = 9.0 Hz, Ph), 131.3 (d, *J* = 2.0 Hz, Ph), 128.8 (d, *J* = 10.0 Hz, Ph), 128.4 (d, *J* = 57.0 Hz, *ipso*-Ph), 127.9 (d, *J* = 52.0 Hz, PCH=), 110.3 (=CH_2), 30.5 (CH_2), 24.2 (d, *J* = 38.0 Hz, PCH_2), 22.5 (Me); $^{31}P\{^1H\}$ NMR (109 MHz, $CDCl_3$) δ 13.3 (q, *J* = 30.5 Hz); MS (ESI) *m*/*z* 241 [$(M + Na)^+$, 100]; HRMS (ESI) *m*/*z* calcd $C_{13}H_{20}BP$ $(M + Na)^+$ 241.1283, found 241.1290 (2.7 ppm error).



Ethenyl-(3-methylbut-3-en-1-yl)phenylphosphine borane *rac*-348

KO*t*-Bu (209 mg, 1.86 mmol, 2.2 eq.) was added in one portion to a stirred solution of tosylate *rac*-**345** (330 mg, 0.85 mmol, 1.0 eq.) in Et_2O (8 mL) at rt under Ar. The resulting mixture was stirred at rt for 2 h. Then, the solid was removed by filtration through Celite®. The solid was washed with Et_2O (3 × 5 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography with 95:5 petrol-Et_2O as eluent gave vinyl phosphine borane *rac*-**348** (180 mg, 98%) as a colourless oil.

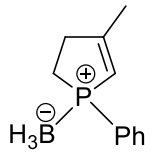
Using general procedure B, *s*-BuLi (2.62 mL of a 1.3 M solution in hexane, 3.41 mmol, 1.2 eq.), allylated phosphine borane *rac*-**345** (586 mg, 2.84 mmol, 1.0 eq.) in THF (10 mL) and paraformaldehyde (128 mg, 3.41 mmol, 1.2 eq.) in THF (10 mL), followed by *p*-toluenesulfonyl chloride (545 mg, 2.86 mmol) in CH_2Cl_2 (5 mL) and pyridine (0.23 mL, 2.86 mmol) in CH_2Cl_2 (5 mL) and then KO*t*-Bu (506 mg, 4.51 mmol) in Et_2O (10 mL) gave the crude product. Purification by flash column chromatography with 95:5 petrol-Et_2O as eluent gave vinyl phosphine borane *rac*-**348** (530 mg, 86%) as a colourless oil.



(*R*)-4-Methyl-1-phenyl-2,3-dihydro-1H-phosphol-1-ane borane (*R*)-349

Using general procedure G, Grubbs-Hoveyda 2nd generation catalyst **350** (14 mg, 0.02 mmol, 0.1 eq.) and vinyl phosphine borane (*R*)-**348** (50 mg, 0.23 mmol, 1.0 eq.) in CH_2Cl_2 (2 mL) gave the crude product. Purification by flash column

chromatography with 99:1 petrol-Et_2O as eluent gave cyclic phosphine borane (*R*)-**349** (20 mg, 46%) as a colourless oil, $[\alpha]_D$ +75.7 (*c* 0.3 in $CHCl_3$); R_F (99:1 petrol-Et_2O) 0.3; IR (film) 2926, 2870, 2340, 2210, 1588, 1415, 1093, 1044, 896, 722, 683 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71-7.67 (m, 2H, Ph), 7.49-7.42 (m, 3H, Ph), 5.70 (ddd, *J* = 32.0, 3.0, 1.5 Hz, 1H, PCH=), 2.83-2.76 (m, 2H, CH), 2.40-2.32 (m, 1H, CH), 2.20-2.10 (m, 1H, CH), 2.09 (s, 3H, Me), 1.24-0.53 (m, 3H, BH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.6 (d, *J* = 10.0 Hz, =*C*Me), 131.7 (d, *J* = 10.0 Hz, Ph), 131.4 (d, *J* = 47.0 Hz, *ipso*-Ph), 131.2 (d, *J* = 2.0 Hz, Ph), 128.7 (d, *J* = 10.0 Hz, Ph), 116.3 (d, *J* = 56.5 Hz, =CH), 37.3 (Me), 24.8 (d, *J* = 39.0 Hz, PCH_2), 20.2 (d, *J* = 13.0 Hz, CH_2); $^{31}P\{^1H\}$ NMR (109 MHz, $CDCl_3$) δ 45.6 (q, *J* = 35.0 Hz); MS (ESI) *m*/*z* 213 [$(M + Na)^+$, 100]; HRMS (ESI) *m*/*z* calcd $C_{11}H_{16}BP$ $(M + Na)^+$ 213.0968, found 213.0977 (3.7 ppm error).



4-Methyl-1-phenyl-2,3-dihydro-1H-phosphol-1-ane borane *rac*-349
(Table 3.12, entry 1)

Grubbs 1st generation catalyst **4** (2 mg, 0.002 mmol, 0.02 eq.) was added in one portion to a stirred solution of vinyl phosphine borane *rac*-**348** (25 mg, 0.11 mmol, 1.0 eq.) in CH_2Cl_2 (1 mL) at rt. The resulting mixture was stirred at rt for 16 h. The solvent was evaporated under reduced pressure to give the crude product which contained a 100:0 ratio of *rac*-**348** and *rac*-**349** (by ^1H NMR spectroscopy).

(Table 3.12, entries 2 and 3)

Grubbs 2nd generation catalyst **5** (8 mg, 0.009 mmol, 0.02 eq.) was added in one portion to a stirred solution of vinyl phosphine borane *rac*-**348** (100 mg, 0.46 mmol, 1.0 eq.) in CH_2Cl_2 (2 mL) at rt. The resulting mixture was stirred at rt for

72 h. The solvent was evaporated under reduced pressure to give the crude product which contained a 77:23 ratio of *rac*-**348** and *rac*-**349** (by the ^{1}H NMR spectroscopy). The crude mixture was then dissolved in CH_2Cl_2 (2 mL) and stirred and heated at reflux for 16 h. After being allowed to cool to rt, the solvent was evaporated under reduced pressure to give the crude product which contained an 83:17 ratio of *rac*-**348** and *rac*-**349** (by ^{1}H NMR spectroscopy).

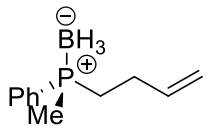
(Table 3.12, entry 4)

Grubbs 2nd generation catalyst **5** (5 mg, 0.008 mmol, 0.02 eq.) was added in one portion to a stirred solution of vinyl phosphine borane *rac*-**348** (85 mg, 0.39 mmol, 1.0 eq.) in toluene (2 mL) at rt. The resulting mixture was stirred and heated at reflux for 16 h. The solvent was evaporated under reduced pressure to give the crude product which contained a 78:22 ratio of *rac*-**348** and *rac*-**349** (by ^{1}H NMR spectroscopy).

(Table 3.13, entries 1-5)

Grubbs-Hoveyda 2nd generation catalyst **350** (3 mg, 0.005 mmol, 0.02 eq.) was added in one portion to a stirred solution of vinyl phosphine borane *rac*-**348** (50 mg, 0.23 mmol, 1.0 eq.) in CH_2Cl_2 (2 mL) at rt. The resulting mixture was stirred at rt for 16 h. The solvent was evaporated under reduced pressure to give the crude product which contained an 87:13 ratio of *rac*-**348** and *rac*-**349** (by ^{1}H NMR spectroscopy). The crude mixture was dissolved in CH_2Cl_2 (2 mL) and Grubbs-Hoveyda 2nd generation catalyst **350** (13 mg, 0.02 mmol, 0.1 eq.) was added the resulting mixture was stirred at rt for 16 h. The solvent was evaporated under reduced pressure to give the crude product which contained a 50:50 ratio of *rac*-**348** and *rac*-**349** (by ^{1}H NMR spectroscopy). The crude mixture was then dissolved in CH_2Cl_2 (2 mL) and stirred at rt for 26 h. The solvent was evaporated under reduced pressure to give the crude product which contained a 40:60 ratio of *rac*-**348** and *rac*-**349** (by ^{1}H NMR spectroscopy). The crude mixture was then

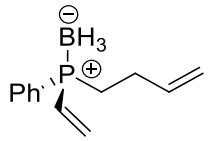
dissolved in CH_2Cl_2 (2 mL) and stirred at rt for 24 h. The solvent was evaporated under reduced pressure to give the crude product which contained a 40:60 ratio of *rac*-**348** and *rac*-**349** (by ^{1}H NMR spectroscopy). The crude mixture was then dissolved in CH_2Cl_2 (2 mL) and stirred and heated at reflux for 16 h. After being allowed to cool to rt, the solvent was evaporated under reduced pressure. Neither *rac*-**348** and *rac*-**349** was observed by ^{1}H NMR spectroscopy of the crude product.



(*S*)-Methyl-(but-3-en-1-yl)phenylphosphine borane (*S*)-351

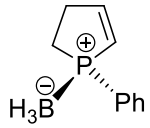
Using procedure E, *s*-BuLi (2.41 mL of a 1.3 M solution in hexane, 3.13 mmol, 1.1 eq.) and (−)-sparteine (802 mg, 3.42 mmol, 1.2 eq.) in Et_2O (8 mL), phosphine borane **261** (433 mg, 2.85 mmol, 1.0 eq.) in Et_2O (2 mL) and allyl bromide (0.30 mL, 3.42 mmol, 1.2 eq.) gave the crude product. Purification by flash column chromatography with 95:5 petrol-Et_2O as eluent gave allylated phosphine borane (*S*)-**351** (312 mg, 57%, 88:12 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +0.1 (*c* 1.0 in $CHCl_3$); R_F (95:5 petrol-Et_2O) 0.3; IR (film) 3031, 2934, 2870, 2335, 1615, 1414, 1395, 1118, 1100, 1046, 982, 903, 733, 683 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75-7.71 (m, 2H, Ph), 7.53-7.46 (m, 3H, Ph), 5.84-5.75 (m, 1H, =CH), 5.03 (dq, J = 17.0, 2.0 Hz, 1H, =CH_AH$_B$), 5.00-4.97 (m, 1H, =CH$_A$$H_B$), 2.34-2.07 (m, 2H, CH), 1.98-1.91 (m, 2H, CH), 1.58 (d, J = 10.0 Hz, 3H, Me), 1.08-0.37 (m, 3H, BH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 137.1 (d, J = 14.0 Hz, =CH), 131.3 (d, J = 9.0 Hz, Ph), 131.2 (d, J = 2.0 Hz, Ph), 129.4 (d, J = 53.0 Hz, *ipso*-Ph), 128.7 (d, J = 10.0 Hz, Ph), 115.3 (=CH_2), 27.0 (CH_2), 26.5 (d, J = 36.0 Hz, PCH_2), 10.6 (d, J = 39.0 Hz, PMe); ^{31}P{^{1}H} NMR (109 MHz, $CDCl_3$) δ 9.6 (q, J = 26.0 Hz); MS (ESI) *m*/*z* 215 [(M + Na)$^+$, 100]; HRMS (ESI)

m/*z* calcd $C_{11}H_{18}BP$ $(M + Na)^+$ 215.1128, found 215.1133 (1.6 ppm error); HPLC: Daicel Chiracel AD-H, 99.5:0.5 hexane-*i*-PrOH, 0.5 mL min^{-1}, (*R*)-**351** 19.4 min, (*S*)-**351** 31.3 min.



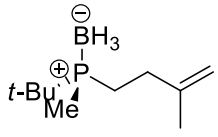
(*R*)-Ethenyl-(but-3-en-1-yl)phenylphosphine borane (*R*)-356

Using general procedure F, *s*-BuLi (0.99 mL of a 1.3 M solution in hexane, 1.29 mmol, 1.2 eq.), allylated phosphine borane (*S*)-**351** (206 mg, 1.07 mmol, 1.0 eq.) in THF (10 mL) and paraformaldehyde (40 mg, 1.29 mmol, 1.2 eq.) in THF (5 mL), followed by *p*-toluenesulfonyl chloride (338 mg, 1.77 mmol) in CH_2Cl_2 (5 mL) and pyridine (0.14 mL, 1.77 mmol) in CH_2Cl_2 (5 mL) and then KO*t*-Bu (373 mg, 3.32 mmol) in Et_2O (10 mL) gave the crude product. Purification by flash column chromatography with 95:5 petrol-Et_2O as eluent gave vinyl phosphine borane (*R*)-**356** (156 mg, 71%) as a colourless oil, $[\alpha]_D$ –52.6 (*c* 0.5 in $CHCl_3$); R_F (95:5 petrol-Et_2O) 0.3; IR (film) 3381, 2916, 2826, 2345, 2310, 1440, 1053, 1007, 876, 624 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73-7.69 (m, 2H, Ph), 7.54-7.46 (m, 3H, Ph), 6.45-6.34 (m, 1H, PCH=), 6.27-6.14 (m, 2H, PCH=CH_2), 5.80 (ddt, *J* = 16.5, 10.0, 6.0 Hz, 1H, =CH), 5.06-4.98 (m, 2H, $=CH_2$), 2.33-2.13 (m, 2H, CH), 2.06-2.00 (m, 2H, CH), 1.14-0.45 (m, 3H, BH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 137.2 (d, *J* = 15.0 Hz, =CH), 134.6 (d, *J* = 5.0 Hz, $=CH_2$), 134.6 (d, *J* = 5.0 Hz, Ph), 131.7 (d, *J* = 9.0 Hz, Ph), 131.3 (d, *J* = 2.0 Hz, Ph), 128.2 (=CH), 128.0 (d, *J* = 52.0 Hz, *ipso*-Ph), 115.3 ($=CH_2$), 26.9 (CH_2), 25.1 (d, *J* = 37.0 Hz, PCH_2); $^{31}P\{^1H\}$ NMR (109 MHz, $CDCl_3$) δ 13.2 (q, *J* = 33.0 Hz); MS (ESI) *m*/*z* 227 [$(M + Na)^+$, 100]; HRMS (ESI) *m*/*z* calcd $C_{12}H_{18}BP$ $(M + Na)^+$ 227.1119, found 227.1134 (4.9 ppm error).



(*R*)-1-Phenyl-2,3-dihydro-1H-phosphol-1-ane borane (*R*)-359

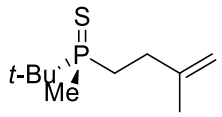
Using general procedure G, Grubbs-Hoveyda 2nd generation catalyst **350** (2 mg, 0.02 mmol, 0.01 eq.) and vinyl phosphine borane (*R*)-**356** (50 mg, 0.24 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography with 99:1 petrol-Et_2O as eluent gave cyclic phosphine borane (*R*)-**359** (32 mg, 71%, 87:13 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +82.3 (*c* 0.3 in $CHCl_3$); R_F (99:1 petrol-Et_2O) 0.3; IR (film) 2347, 1417, 1045, 894, 722 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71-7.66 (m, 2H, Ph), 7.51-7.43 (m, 3H, Ph), 6.90 (ddt, *J* = 33.0, 8.0, 2.5 Hz, 1H, PCH=), 6.15 (ddt, *J* = 32.0, 8.0, 2.0 Hz, 1H, =CH), 2.94-2.88 (m, 2H, CH), 2.35-2.27 (m, 1H, CH), 2.18-2.09 (m, 1H, CH), 1.23-0.56 (m, 3H, BH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 149.8 (d, *J* = 9.5 Hz, =CH), 131.8 (d, *J* = 10.0 Hz, Ph), 131.4 (d, *J* = 2.0 Hz, Ph), 130.3 (d, *J* = 47.0 Hz, *ipso*-Ph), 128.7 (d, *J* = 10.0 Hz, Ph), 122.8 (d, *J* = 51.0 Hz, PCH=), 33.2 (CH_2), 23.6 (d, *J* = 39.0 Hz, CH_2); $^{31}P\{^1H\}$ NMR (109 MHz, $CDCl_3$) δ 43.6 (q, *J* = 30.5 Hz); MS (ESI) *m*/*z* 199 [$(M + Na)^+$, 100]; HRMS (ESI) *m*/*z* calcd $C_{10}H_{14}BP$ $(M + Na)^+$ 199.0827, found 199.0820 (–4.2 ppm error); HPLC: Daicel Chiracel AD-H, 99.5:0.5 hexane-*i*-PrOH, 0.5 mL min^{-1}, (*S*)-**359** 43.3 min, (*R*)-**359** 47.8 min.



(*S*)-*t*-Butylmethyl-(3-methylbut-3-en-1-yl)phosphine borane (*S*)-352

Using procedure E, *s*-BuLi (3.20 mL of a 1.3 M solution in hexane, 4.16 mmol, 1.1 eq.) and (–)-sparteine (1.1 g, 4.54 mmol, 1.2 eq.) in Et_2O (8 mL), phosphine borane **283** (500 mg, 3.78 mmol, 1.0 eq.) in Et_2O (2 mL) and methallyl bromide (0.46 mL, 4.54 mmol, 1.2 eq.) gave the crude product. Purification by flash column chromatography with 95:5 petrol-Et_2O as eluent gave allylated

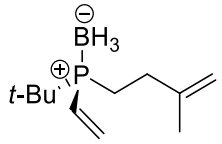
phosphine borane (*S*)-**352** (400 mg, 57%, 96:4 er by CSP-HPLC of phosphine sulfide (*S*)-**354**) as a colourless oil, $[\alpha]_D$ –9.3 (*c* 1.0 in $CHCl_3$); R_F (95:5 petrol-Et_2O) 0.3; IR (film) 2929, 2827, 2334, 1616, 1442, 1398, 1347, 1277, 1048, 1003, 981, 901 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.77 (br s, 1H, =CH), 4.74 (br s, 1H, =CH), 2.42-2.30 (m, 1H, CH), 2.15-2.06 (m, 1H, CH), 1.76 (s, 3H, =CMe), 1.79-1.59 (m, 2H, CH), 1.20 (d, *J* = 11.0 Hz, 3H, PMe), 1.16 (d, *J* = 13.5 Hz, 9H, $PCMe_3$), 0.78-0.07 (m, 3H, BH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 145.0 (d, *J* = 13.0 Hz, *C*=CH_2), 110.2 (=CH_2), 30.9 (CH_2), 27.5 (d, *J* = 36.0 Hz, P*C*Me_3), 25.0 (PC*Me*$_3$), 22.4 (Me), 19.4 (d, *J* = 32.0 Hz, PCH_2), 5.0 (d, *J* = 34.0 Hz, PMe); $^{31}P\{^1H\}$ NMR (109 MHz, $CDCl_3$) δ 26.5 (q, *J* = 37.0 Hz); MS (ESI) *m*/*z* 209 [$(M + Na)^+$, 100]; HRMS (ESI) *m*/*z* calcd $C_{10}H_{24}BP$ $(M + Na)^+$ 209.1597, found 209.1603 (2.1 ppm error).



(*R*)-*t*-Butylmethyl-(3-methylbut-3-en-1-yl)phosphine sulfide 354

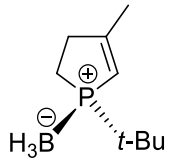
Using general procedure H, phosphine borane (*S*)-**352** (20 mg, 0.11 mmol, 1.0 eq.), DABCO (27 mg, 0.24 mmol, 2.2 eq.) and sulfur (17 mg, 0.54 mmol, 5.0 eq.) gave the crude product. Purification by flash column chromatography with 8:2 petrol-Et_2O as eluent gave phosphine sulfide **354** (19 mg, 87%, 96:4 er by CSP-HPLC) as a white solid, mp 88-89 ºC; $[\alpha]_D$ +2.4 (*c* 1.0 in $CHCl_3$); R_F (99:1 petrol-Et_2O) 0.3; IR (film) 2927, 2862, 2825, 1615, 1441, 1394, 1344, 1273, 981, 902, 866, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.77 (br s, 1H, =CH), 4.74 (br s, 1H, =CH), 2.60-2.49 (m, 1H, CH), 2.24-2.23 (m, 1H, CH), 1.95-1.94 (m, 2H, CH), 1.76 (s, 3H, =CMe), 1.58 (d, *J* = 11.5 Hz, 3H, PMe), 1.24 (d, *J* = 16.0 Hz, 9H, $PCMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.7 (d, *J* = 14.5 Hz, *C*=CH_2), 110.3 (=CH_2), 30.0 (d, *J* = 51.0 Hz, P*C*Me_3), 30.4 (CH_2), 25.4 (d, *J* = 48.0 Hz, PCH_2), 24.5 (PC*Me*$_3$), 22.5 (Me), 14.0 (d, *J* = 50.0 Hz, PMe); $^{31}P\{^1H\}$ NMR

(109 MHz, $CDCl_3$) δ 60.4; MS (ESI) *m*/*z* 205 M^+ (100); HRMS (ESI) *m*/*z* calcd $C_{10}H_{21}PS$ $(M + H)^+$ 205.1171, found 205.1174 (0.9 ppm error); HPLC: Daicel Chiracel AD-H, 99.5:0.5 hexane-*i*-PrOH, 0.5 mL min^{-1}, (*S*)- **354** 18.2 min, (*R*)-**354** 33.3 min.



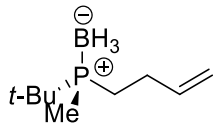
(*R*)-*t*-Butylethenyl-(3-methylbut-3-en-1-yl)phosphine borane (*R*)-357

Using general procedure F, *s*-BuLi (0.74 mL of a 1.3 M solution in hexane, 0.97 mmol, 1.2 eq.), allylated phosphine borane (*S*)-**352** (150 mg, 0.81 mmol, 1.0 eq.) in THF (10 mL) and paraformaldehyde (29 mg, 0.97 mmol, 1.2 eq.) in THF (5 mL), followed by *p*-toluenesulfonyl chloride (111 mg, 0.99 mmol) in CH_2Cl_2 (5 mL) and pyridine (0.06 mL, 0.99 mmol) in CH_2Cl_2 (5 mL) and then KO*t*-Bu (344 mg, 3.07 mmol) in Et_2O (10 mL) gave the crude product. Purification by flash column chromatography with 95:5 petrol-Et_2O as eluent gave vinyl phosphine borane (*R*)-**357** (89 mg, 56%) as a colourless oil, $[\alpha]_D$ +17.8 (*c* 0.3 in $CHCl_3$); R_F (95:5 petrol-Et_2O) 0.4; IR (film) 3032, 2345, 2306, 1616, 1415, 1373, 1094, 1045, 1004, 971, 903, 781, 733, 684 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.33-6.20 (m, 2H, CH=CH_2), 6.12 (ddd, *J* = 17.5, 12.0, 8.5 Hz, 1H, PCH=), 4.75 (br s, 1H, =CH), 4.71 (br s, 1H, =CH), 2.35-2.25 (m, 1H, CH), 2.00-1.91 (m, 1H, CH), 1.80-1.72 (m, 2H, CH), 1.74 (s, 3H, =CMe), 1.15 (d, *J* = 13.5 Hz, 9H, $PCMe_3$), 0.78-0.08 (m, 3H, BH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 145.2 (d, *J* = 13.0 Hz, *C*=CH_2), 137.3 (d, *J* = 5.5 Hz, =CH_2), 125.0 (d, *J* = 46.0 Hz, PCH=), 110.0 (=CH_2), 30.8 (CH_2), 28.1 (d, *J* = 35.0 Hz, P*C*Me_3), 25.3 (PC*Me*$_3$), 22.5 (Me), 18.1 (d, *J* = 34.0 Hz, PCH_2); $^{31}P\{^1H\}$ NMR (109 MHz, $CDCl_3$) δ 30.2 (q, *J* = 33.0 Hz); MS (ESI) *m*/*z* 221 [$(M + Na)^+$, 100]; HRMS (ESI) *m*/*z* calcd $C_{11}H_{24}BP$ $(M + Na)^+$ 221.1594, found 221.1603 (3.0 ppm error).



(*R*)-*t*-Butyl-4-methyl-2,3-dihydro-1H-phosphol-1-ane borane (*R*)-360

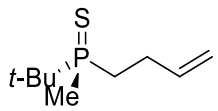
Using general procedure G, Grubbs-Hoveyda 2nd generation catalyst **350** (41 mg, 0.07 mmol, 0.1 eq.) and vinyl phosphine borane (*R*)-**357** (130 mg, 0.66 mmol, 1.0 eq.) in CH_2Cl_2 (2 mL) gave the crude product. Purification by flash column chromatography with 95:5 petrol-Et_2O as eluent gave cyclic phosphine borane (*R*)-**360** (46 mg, 41%) as a white solid, mp 71-72 ºC; $[\alpha]_D$ +22.5 (*c* 0.7 in $CHCl_3$); R_F (95:5 petrol-Et_2O) 0.3; IR ($CDCl_3$) 2913, 2899, 2824, 2339, 2210, 1589, 1439, 1048, 900, 889, 713, 640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.52 (ddd, J = 31.0, 3.0, 1.5 Hz, 1H, PCH=), 2.69-2.62 (m, 2H, CH), 2.07-1.98 (m, 2H, CH), 1.95 (s, 3H, Me), 1.12 (d, J = 13.5 Hz, 9H, $PCMe_3$), 0.91-0.21 (m, 3H, BH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 160.6 (d, J = 8.5 Hz, =*C*Me), 114.2 (d, J = 52.0 Hz, PCH=), 37.7 (CH_2), 29.3 (d, J = 28.5 Hz, P*C*Me_3), 25.1 (PC*Me*$_3$), 20.2 (d, J = 12.0 Hz, Me), 18.0 (d, J = 35.5 Hz, PCH_2); $^{31}P\{^1H\}$ NMR (109 MHz, $CDCl_3$) δ 68.2 (q, J = 38.0 Hz); MS (ESI) *m*/*z* 193 [$(M + Na)^+$, 100); HRMS (ESI) *m*/*z* calcd $C_9H_{20}BP$ $(M + Na)^+$ 193.1285, found 193.1290 (1.2 ppm error).



(*S*)-*t*-Butylmethyl-(but-3-en-1-yl)phosphine borane (*S*)-353

Using procedure E, *s*-BuLi (2.24 mL of a 1.3 M solution in hexane, 2.91 mmol, 1.1 eq.) and (–)-sparteine (745 mg, 3.18 mmol, 1.2 eq.) in Et_2O (8 mL), phosphine borane **283** (350 mg, 2.65 mmol, 1.0 eq.) in Et_2O (2 mL) and allyl bromide (0.28 mL, 3.18 mmol, 1.2 eq.) gave the crude product. Purification by flash column chromatography with 95:5 petrol-Et_2O as eluent gave allylated phosphine borane (*S*)-**353** (247 mg, 58%, 93:7 er by CSP-HPLC of phosphine sulfide (*S*)-**355**) as a colourless oil, $[\alpha]_D$ –10.2 (*c* 1.0 in $CHCl_3$); R_F (95:5

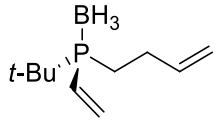
petrol-Et_2O) 0.3; IR (film) 2929, 2826, 2335, 1616, 1442, 1398, 1375, 1347, 1277, 1118, 1048, 1003, 981, 902, 807, 780 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.91-5.80 (m, 1H, =CH), 5.11-5.01 (m, 2H, $=CH_2$), 2.41-2.39 (m, 1H, CH), 2.26-2.14 (m, 1H, CH), 1.78-1.55 (m, 2H, CH), 1.20 (d, J = 10.0 Hz, 3H, Me), 1.16 (d, J = 13.5 Hz, 9H, $PCMe_3$), 0.75-0.03 (m, 3H, BH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 137.8 (d, J = 13.0 Hz, C=CH_2), 115.2 (=CH_2), 27.3 (CH_2), 27.2 (d, J = 34.0 Hz, PCMe$_3$), 25.0 (PCMe_3), 20.4 (d, J = 31.5 Hz, PCH_2), 5.2 (d, J = 34.0 Hz, PMe); $^{31}P\{^1H\}$ NMR (109 MHz, $CDCl_3$) δ 26.5 (q, J = 40.0 Hz); MS (ESI) m/z 195 [$(M + Na)^+$, 100]; HRMS (ESI) m/z calcd $C_9H_{22}BP$ $(M + Na)^+$ 195.1439, found 195.1446 (2.5 ppm error).



(*R*)-*t*-Butylmethyl-(but-3-en-1-yl)phosphine sulfide 355

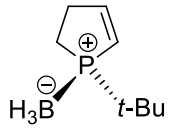
Using general procedure H, phosphine borane (*S*)-**353** (20 mg, 0.12 mmol, 1.0 eq.), DABCO (29 mg, 0.26 mmol, 2.2 eq.) and sulfur (19 mg, 0.58 mmol, 5.0 eq.) gave the crude product. Purification by flash column chromatography with 8:2 petrol-Et_2O as eluent gave phosphine sulfide **355** (19 mg, 80%, 93:7 er by CSP-HPLC) as a white solid, mp 80-82 ºC; $[\alpha]_D$ +0.6 (*c* 0.8 in $CHCl_3$); R_F (99:1 petrol-Et_2O) 0.3; IR (film) 2928, 2862, 2825, 1616, 1442, 1394, 1344, 1273, 981, 902, 867, 801, 738, 686, 628 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.92-5.82 (m, 1H, =CH), 5.11 (dq, J = 17.0, 2.0 Hz, 1H, =CH_AH_B), 5.05-5.01 (m, 1H, =CH_AH_B), 2.69-2.57 (m, 1H, CH), 2.34-2.22 (m, 1H, CH), 1.91-1.83 (m, 2H, CH), 1.59 (d, J = 11.5 Hz, 3H, PMe), 1.24 (d, J = 16.0 Hz, 9H, $PCMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 137.4 (d, J = 15.5 Hz, CH=), 115.5 (=CH_2), 33.0 (d, J = 51.0 Hz, PCMe$_3$), 26.8 (d, J = 3.0 Hz, PCH_2CH_2), 26.5 (d, J = 47.5 Hz, PCH_2), 24.5 (d, J = 1.5 Hz, PCMe_3), 14.0 (d, J = 50.0 Hz, PMe); $^{31}P\{^1H\}$ NMR (109 MHz, $CDCl_3$) δ 60.1; MS (ESI) m/z 213 [$(M + Na)^+$, 100]; HRMS (ESI)

m/*z* calcd $C_9H_{19}PS$ $(M + Na)^+$ 213.0838, found 213.0837 (−1.7 ppm error); HPLC: Daicel Chiracel AD-H, 99.5:0.5 hexane-*i*-PrOH, 0.5 mL min^{-1}, (*S*)-**355** 19.3 min, (*R*)-**355** 30.0 min.



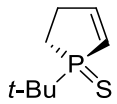
(*R*)-*t*-Butylethenyl-(but-3-en-1-yl)phosphine borane (*R*)-358

Using general procedure F, *s*-BuLi (1.50 mL of a 1.3 M solution in hexane, 1.94 mmol, 1.2 eq.), allylated phosphine borane (*S*)-**353** (256 mg, 1.62 mmol, 1.0 eq.) in THF (10 mL) and paraformaldehyde (58 mg, 1.94 mmol, 1.2 eq.) in THF (5 mL), followed by *p*-toluenesulfonyl chloride (326 mg, 1.71 mmol) in CH_2Cl_2 (5 mL) and pyridine (0.14 mL, 1.71 mmol) in CH_2Cl_2 (5 mL) and then KO*t*-Bu (492 mg, 4.40 mmol) in Et_2O (10 mL) gave the crude product. Purification by flash column chromatography with 95:5 petrol-Et_2O as eluent gave vinyl phosphine borane (*R*)-**358** (175 mg, 60%) as a colourless oil, $[\alpha]_D$ +14.5 (*c* 0.4 in $CHCl_3$); R_F (95:5 petrol-Et_2O) 0.4; IR (film) 2929, 2914, 2344, 2309, 1440, 1373, 1346, 1047, 1006, 974, 901 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.33-6.06 (m, 3H, PCH=, $=CH_2$), 5.85 (ddt, *J* = 17.0, 10.0, 6.0 Hz, 1H, =CH), 5.05 (dq, *J* = 17.0, 1.5 Hz, 1H, $=CH_AH_B$), 5.01-4.97 (m, 1H, $=CH_AH_B$), 2.43-2.32 (m, 1H, CH), 2.11-2.01 (m, 1H, CH), 1.75-1.68 (m, 2H, CH), 1.15 (d, *J* = 13.5 Hz, 9H, $PCMe_3$), 0.83-0.06 (m, 3H, BH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 137.9 (d, *J* = 14.0 Hz, =CH), 137.4 (d, *J* = 6.0 Hz, PCH=CH_2), 125.1 (d, *J* = 46.0 Hz, PCH=), 115.1 ($=CH_2$), 28.0 (d, *J* = 35.0 Hz, P*C*Me_3), 27.2 (CH_2), 25.2 (d, *J* = 2.0 Hz, PC*Me*$_3$), 19.2 (d, *J* = 34.0 Hz, PCH_2); $^{31}P\{^1H\}$ NMR (109 MHz, $CDCl_3$) δ 30.0 (q, *J* = 39.0 Hz); MS (ESI) *m*/*z* 207 [$(M + Na)^+$, 100]; HRMS (ESI) *m*/*z* calcd $C_{10}H_{22}BP$ $(M + Na)^+$ 207.1449, found 207.1446 (−3.6 ppm error).



(*R*)-*t*-Butyl-2,3-dihydro-1H-phosphol-1-ane borane (*R*)-361

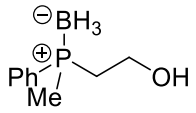
Using general procedure G, Grubbs-Hoveyda 2nd generation catalyst **350** (2 mg, 0.03 mmol, 0.01 eq.) and vinyl phosphine borane (*R*)-**358** (50 mg, 0.27 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography with 99:1 petrol-Et_2O as eluent gave cyclic phosphine borane (*R*)-**361** (36 mg, 85%) as a white solid, mp 68-69 ºC; $[\alpha]_D$ +8.5 (*c* 0.8 in $CHCl_3$); R_F (99:1 petrol-Et_2O) 0.3; IR ($CDCl_3$) 2914, 2339, 2219, 891, 716, 640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.70 (ddt, *J* = 31.0, 8.0, 2.5 Hz, 1H, PCH=), 6.00 (ddt, *J* = 30.0, 8.0, 2.0 Hz, 1H, =CH), 2.88-2.66 (m, 2H, CH), 2.07-1.88 (m, 2H, CH), 1.13 (d, *J* = 14.0 Hz, 9H, $PCMe_3$), 0.92-0.21 (m, 3H, BH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 149.0 (d, *J* = 7.5 Hz, =CH), 120.0 (d, *J* = 46.0 Hz, PCH=), 33.7 (CH_2), 29.2 (d, *J* = 28.5 Hz, P*C*Me_3), 25.2 (PC*Me*$_3$), 17.0 (d, *J* = 35.0 Hz, PCH_2); $^{31}P\{^1H\}$ NMR (109 MHz, $CDCl_3$) δ 66.8 (q, *J* = 36.5 Hz); MS (ESI) *m*/*z* 179 [(M + Na)$^+$, 100]; HRMS (ESI) *m*/*z* calcd $C_8H_{18}BP$ (M + Na)$^+$ 179.1137, found 179.1133 (−2.9 ppm error).



1-*t*-Butyl-2,3-dihydro-1H-phosphine sulfide (*R*)-362

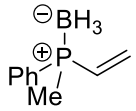
Using general procedure H, phosphine borane (*R*)-**361** (20 mg, 0.13 mmol, 1.0 eq.), DABCO (32 mg, 0.28 mmol, 2.2 eq.) and sulfur (20 mg, 0.64 mmol, 5.0 eq.) gave the crude product. Purification by flash column chromatography with 99:1 Et_2O-petrol as eluent gave phosphine sulfide (*R*)-**362** (6 mg, 27%, 93:7 er by CSP-HPLC) as a white solid, $[\alpha]_D$ +19.5 (*c* 0.5 in $CHCl_3$); R_F (99:1 Et_2O-petrol) 0.1; ^1H NMR (400 MHz, $CDCl_3$) δ 6.75 (ddt, *J* = 41.0, 8.0, 2.5 Hz, 1H, PCH=), 6.15-6.05 (ddt, *J* = 28.0, 8.0, 2.5 Hz, 1H, =CH), 2.99-2.88 (m, 1H, CH),

2.72-2.61 (m, 1H, CH), 2.48-2.40 (m, 1H, CH), 2.09-1.98 (m, 1H, CH), 1.23 (d, J = 17.0 Hz, 9H, $PCMe_3$); $^{31}P\{^1H\}$ NMR (109 MHz, $CDCl_3$) δ 91; MS (ESI) m/z 197 [$(M + Na)^+$, 100]; HRMS (ESI) m/z calcd $C_8H_{15}PS$ $(M + Na)^+$ 197.0522, found 197.0524 (0.7 ppm error); HPLC: Daicel Chiracel AD-H, 99.5:0.5 hexane-*i*-PrOH, 0.5 mL min^{-1}, (*S*)-**362** 19.3 min, (*R*)-**362** 30.0 min.



Methyl-(2-hydroxyethyl)-phenylphosphine borane *rac*-364

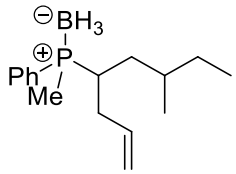
s-BuLi (3.10 mL of a 1.3 M in solution hexane, 4.02 mmol, 1.2 eq.) was added dropwise to a stirred solution of phosphine borane **261** (510 mg, 3.35 mmol, 1.0 eq.) in THF (15 mL) at −78 ºC under Ar. The resulting solution was stirred at −78 ºC for 1 h. Then, a solution of paraformaldehyde (121 mg, 4.02 mmol, 1.2 eq.) in THF (10 mL) was added dropwise and the mixture was allowed to warm to rt over 16 h. 1 M $HCl_{(aq)}$ (25 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (25 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography with 6:4 petrol-Et_2O as eluent gave hydroxy phosphine borane *rac*-**364** (317 mg, 52%) as a colourless oil, R_F (6:4 petrol-Et_2O) 0.1; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77-7.75 (m, 2H, Ph), 7.54-7.47 (m, 3H, Ph), 3.96-3.79 (m, 2H, CH_2OH), 2.21-2.15 (m, 2H, CH_2), 1.63 (d, J = 10.5 Hz, 3H, PMe), 1.15-0.45 (m, 3H, BH_3); $^{31}P\{^1H\}$ NMR (109 MHz, $CDCl_3$) δ 6.85-5.78 (m).



Ethenyl-methylphenylphosphine borane *rac*-365

A solution of *p*-toluenesulfonyl chloride (471mg, 2.47 mmol, 1.5 eq.) in CH_2Cl_2 (15 mL) was added dropwise to a stirred solution of hydroxy phosphine borane

rac-**364** (300 mg, 1.65 mmol, 1.0 eq.) and pyridine (0.20 mL, 2.47 mmol, 1.5 eq.) in CH_2Cl_2 (5 mL) at rt under Ar. The resulting mixture was stirred at rt for 16 h. 2 M $HCl_{(aq)}$ (20 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude tosylate. KO*t*-Bu (389 mg, 3.47 mmol, 2.2 eq.) was added in one portion to a stirred solution of the crude tosylate in Et_2O (15 mL) at rt under Ar. The resulting mixture was stirred at rt for 2 h. Then, the solid was removed by filtration through Celite®. The solid was washed with Et_2O (3 × 15 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography with 95:5 petrol-Et_2O as eluent gave vinyl phosphine borane *rac*-**365** (191 mg, 70%) as a colourless oil, R_F (95:5 petrol-Et_2O) 0.1; IR (film) 3011, 2346, 2304, 1415, 1394, 1373, 1118, 1096, 1048, 1006, 967, 890, 883, 768, 732, 715, 684 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73-7.68 (m, 2H, Ph), 7.52-7.45 (m, 3H, Ph), 6.42-6.31 (m, 1H, PCH=), 6.21-6.07 (m, 2H, $=CH_2$), 1.65 (d, J = 10.5 Hz, 3H, PMe), 1.18-0.45 (m, 3H, BH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 133.1 (d, J = 3.5 Hz, $=CH_2$), 131.3 (d, J = 9.0 Hz, Ph), 131.2 (d, J = 2.0 Hz, Ph), 129.6 (d, J = 52.0 Hz, *ipso*-Ph), 129.5 (d, J = 57.0 Hz, PCH=), 128.8 (d, J = 10.0 Hz, =CH), 11.3 (d, J = 40.5 Hz, Me); $^{31}P\{^1H\}$ NMR (109 MHz, $CDCl_3$) δ 7.61-6.54 (m); MS (ESI) m/z 187 [$(M + Na)^+$, 100], 163 (90); HRMS (ESI) m/z calcd $C_9H_{14}BP$ $(M + Na)^+$ 187.0815, found 187.0820 (2.6 ppm error);



Methyl(6-methyloct-1-en-4-yl)(phenyl)phosphine borane *rac*-368

s-BuLi (0.41 mL of a 1.3 M solution in hexane, 0.53 mmol, 1.2 eq.) was added dropwise to a stirred solution of vinyl phosphine borane *rac*-**365** (72 mg, 0.44 mmol, 1.0 eq.) at –78 ºC under Ar. The resulting solution was stirred at –78 ºC for 1 h. Then, allyl bromide (0.05 mL, 0.53 mmol, 1.2 eq.) was added dropwise and the mixture was allowed to warm to rt over 1 h. Sat. $NH_4Cl_{(aq)}$ (10 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography with 9:1 petrol-Et_2O as eluent gave substituted phosphine borane *rac*-**368** (27 mg, 8%) as a colourless oil, R_F (9:1 petrol-Et_2O) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76-7.70 (m, 2H, Ph), 7.53-7.45 (m, 3H, Ph), 5.82-5.57 (m, 1H, =CH), 5.11-4.91 (m, 2H, =CH_2), 2.55-1.79 (m, 3H, CH), 1.59 (d, J = 10.0 Hz, 0.75 H, PMe), 1.58 (d, J = 10.0 Hz, 0.75 H, PMe), 1.57 (d, J = 9.5 Hz, 0.75 H, PMe), 1.56 (d, J = 10.0 Hz, 0.75 H, PMe), 1.52-0.95 (m, 5H, CH), 0.87-0.61 (m, 6H, Me); MS (ESI) *m*/*z* 197 [(M + Na)$^+$, 100]; HRMS (ESI) *m*/*z* calcd $C_8H_{15}PS$ (M + Na)$^+$ 197.0522, found 197.0524 (0.7 ppm error); MS (ESI) *m*/*z* 285 [(M + Na)$^+$, 100], 261 (95); HRMS (ESI) *m*/*z* calcd $C_{16}H_{28}PS$ (M + Na)$^+$ 285.1912, found 285.1917 (0.5 ppm error).

Chapter 5. Definitions

Abbreviations

δ	chemical shift

[α]	specific rotation
AIBN	azobis-*i*-butylonitrile
aq	aqueous
Ar	aromatic
Atm	atmosphere
9-BBN	9-borabicyclo[3.3.1]nonabe
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
bp	boiling point
br	broad
calcd	calculated
CETBA	cetyltrimethylammonium bromide
cm^{-1}	wavenumber
Cy	cyclohexyl
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DEPT	distortionless enhancement by polarisation transfer
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereoisomeric ratio
E	electrophile
eq.	equivalents

EI	electron impact
er	enantiomeric ratio
ESI	electrospray ionisation
h	hour
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IR	infrared
J	coupling constant
LDA	lithium di-*iso*-propylamide
Lit.	literature
M	molar (mol dm^{-3})
m	multiplet
m	meta
m-CPBA	*m*-chloroperoxybenzoic acid
Me	methyl
Mes	1,3,5-trimethylbenzene
mg	milligram
min	mintue
mL	millilitre
mmol	millimoles
mp	melting point
MS	mass spectrometry
Ms	mesylate

4 Å MS	molecular sieves with a pore size of 4 Ångströms
NMR	nuclear magnetic resonance
o	ortho
p	para
PCC	pyridinium chlorochromate
Ph	phenyl
PMB	*p*-methoxybenzyl
PMDETA	*N*,*N*,*N'*,*N''*,*N''*-pentamethyldiethylenetriamine
ppm	parts per million
PPTS	pyridiumn *p*-toluenesulfonate
q	quartet
quin	quintet
R	alkyl group
rac	racemic
RCM	ring-closing metathesis
R_F	retention time
rt	room temperature
s	singlet
t	triplet
TBAI	tetrabutylammonium iodide
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*t*-butyldiphenylsilyl
THF	tetrahydrofuran
THP	tetrahydropyran

TLC	thin layer chromatography
TMCDA	*N*,*N*,*N'*,*N'*-tetramethylcyclohexane-1,2-diamine
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethane-1,2-diamine
TMS	trimethylsilyl
Ts	tosylate
UV	ultraviolet
Vis	visable

Chapter 6. References

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