Stereoselective Synthesis of Disubstituted Allylic Alcohols by Wittig-Schlosser Type Reaction

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Abstract

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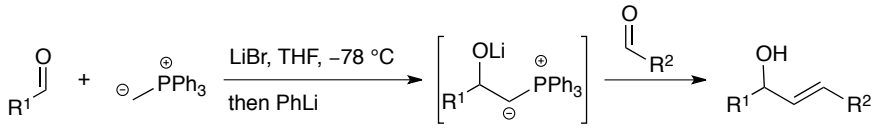
The work presented in this thesis describes the development of reactions of β-lithiooxyphosphonium ylides and aldehydes to form disubstituted allylic alcohols in a regio- and stereoselective fashion.

Firstly, β-lithiooxyphosphonium ylides prepared from methylenetriphenyl-phosphorane and aldehydes, were shown to react with a second aldehyde to access allylic alcohols. The regio- and stereoselectivity in the formation of the double bond was shown to be greatly influenced by the nature of both the first and the second aldehyde used, and by the lack of further substitution on the phosphorane used. This one-pot methodology was used in the synthesis of a simple natural product (*E*)-4-(3,4-dimethoxyphenyl)-but-3-en-2-ol, previously synthesised in four steps.



Secondly, β-lithiooxyphosphonium ylides prepared *in situ* from α-lithiated terminal epoxides and triphenylphosphine, were shown to react with aldehydes, with retention of the selectivity in the formation of the double bond. To the best of our knowledge, this represents the first examples of the generation of β-oxido phosphonium ylides by the trapping of metalated epoxides with a phosphine.

Acknowledgements

I would like to thank my supervisor, Professor David Hodgson, for allowing me the opportunity to work under his supervision on this fascinating project. His academic experience and support throughout have been invaluable to me, and I am indebted to him in the preparation of this thesis.

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My parents, Joan and Anand, and my family have been an unwavering source of guidance and emotional support over the years. I am eternally grateful to my parents for their financial support throughout the past two years. This thesis would certainly not have existed without them; for this, I dedicate this work to my mom and dad.

Abbreviations

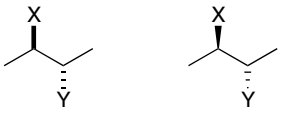
°C	degree(s) Celsius
$E^{\oplus}$	generic electrophile
Ac	acetate
Ar	aryl
aq	aqueous
br	broad
Bu	butyl
Bz	benzoate
COSY	correlation spectroscopy
Cy	cyclohexyl
d	day(s)
DCM	dichloromethane
equiv	equivalent(s)
ESI	electrospray ionisation
Et	ethyl
FI	field ionisation
GC	gas chromatography
h	hour(s)
HRMS	high resolution mass spectrometry
IR	infra-red (spectroscopy)
LRMS	low resolution mass spectrometry
LTMP	lithium 2,2,6,6-tetramethylpiperidide
m	medium
M	molar concentration (mol/dm^3)
m-	*meta*-
m-CPBA	*meta*-chloroperoxybenzoic acid

Me	methyl
MHz	megahertz
min	minute(s)
mL	mililitre(s)
mmol	milimole(s)
n-Bu	*n*-butyl
NOESY	nuclear Overhauser effect spectroscopy
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
o-	*ortho*-
p-	*para*-
Ph	phenyl
Piv	pivalate
PMA	phosphomolybdic acid
ppm	parts per million
Pr	propyl
i-Pr	isopropyl
R	generic alkyl group
R_f	retention factor
rt	room temperature
s	strong
sat	saturated
t-Bu	*tert*-butyl
t-BuOMe	*tert*-butyl methyl ether
temp.	temperature
TMP	2,2,6,6-tetramethylpiperidine
THF	tetrahydrofuran
TLC	thin layer chromatography
TS	transition state

w	weak

Stereochemistry

Throughout this thesis, the following nomenclature is used to represent compound configuration in three-dimensional space.[†]



relative absolute

[†] Maehr, H. *J. Chem. Inf. Comput. Sci*. **2002**, *42*, 894-902.

Contents

Chapter 3: Studies toward the synthesis of chiral disubstituted *E*-allylic alcohols *via* β-lithiooxyphosphonium ylides

Chapter 1: Introduction

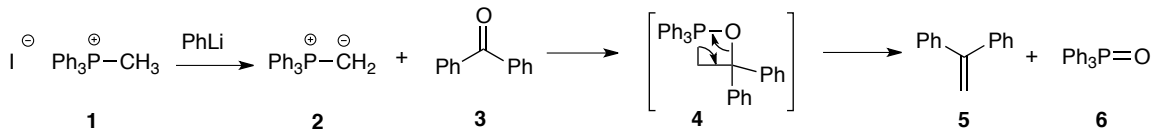
The work presented in this thesis describes the generation and reactivity of aldehyde or epoxide-derived β-lithiooxyphosphonium ylides with aldehydes in the synthesis of 1,2-disubstituted allylic alcohols. This introductory section serves to make the reader aware of the chemistry of β-lithiooxyphosphonium ylides, and to briefly describe the development of reactions of these species with various electrophiles. In order to put the work presented in this thesis into perspective and to explain why this work is important, overviews of the Wittig reaction, the Wittig-Schlosser reaction and SCOOPY (α -Substitution plus Carbonyl Olefination via β-Oxido Phosphonium Ylides) reactions are presented.

1.1 The Wittig reaction

Alkenes, in particular, geometrically defined alkenes, are of central importance in organic chemistry. They are pervasive structural motifs present in many molecules of biological and physical relevance, and from a reactivity-based perspective these stereodefined structures are considered as serving as a foundation for stereoselective synthesis.[1] A host of methods have been developed for their synthesis,[2] but the Wittig reaction remains one of the most important and widely used methods of synthesising alkenes.[2d, 3] This synthetic method has enjoyed extensive prominence and recognition owing to its simplicity, convenience, complete positional selectivity and generally good geometrical control.[4]

The Wittig reaction involves direct olefination of carbonyl compounds with phosphoranes. The reaction between these two species was described by Wittig and Geissler in 1953.[5] During their investigations of the chemistry of pentavalent phosphorus, these

researchers observed the reaction between methylenetriphenylphosphorane (**2**), made by reacting methyltriphenylphosphonium iodide (**1**) with PhLi, and benzophenone (**3**), which produced triphenylphosphine oxide (**6**) and 1,1-diphenylethene (**5**) in good yield (Scheme 1.1).



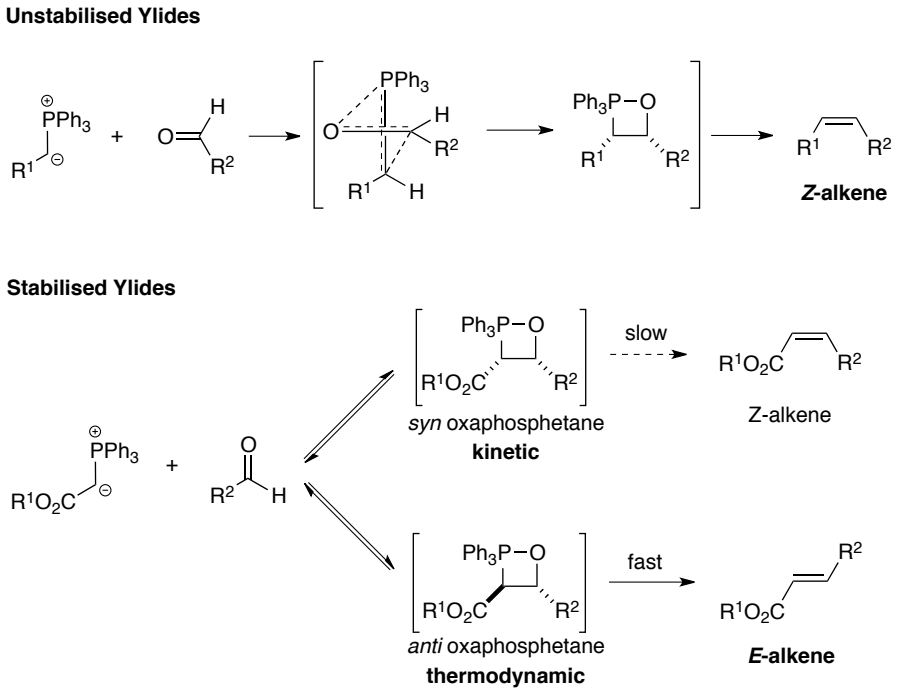
Scheme 1.1: The first Wittig reaction[5]

In the past, it was thought that the elimination of triphenylphosphine oxide (**6**) from the oxaphosphetane intermediate **4** formed was driven by the strength of the O=P bond (~544 kJ/mol). The formation of this bond was thought to adequately compensate for the fact that a C=C bond (~607 kJ/mol) is weaker than a C=O bond (~799 KJ/mol). This elimination, which provided the thermodynamic driving force for the reaction, was viewed as a one-step process, occurring spontaneously from the oxaphosphetane intermediate **4** made *in situ*. It is now known that oxaphosphetane intermediates are formed irreversibly, and their decomposition to alkenes by elimination of Ph_3PO is stereospecific and occurs under kinetic control.

Having recognised the importance of this observation, Wittig and co-workers conducted studies using various triphenylphosphoranes [$Ph_3P^+-C^-HR$] and various aldehydes and ketones to yield the corresponding olefins.[6] They noted that stereoselectivity depended on the nature of the ylide: stabilised ylides, ylides that have conjugating or anion-stabilising substituents adjacent to the negative charge (R = CO_2R' or CN), were observed to be *E*-selective, while unstabilised ylides (R = alkyl) were observed to be *Z*-selective.

Extensive studies have been carried out in order to elucidate the mechanism by which the Wittig olefination occurs.[3, 4, 10] In the past, it was viewed that the addition of an

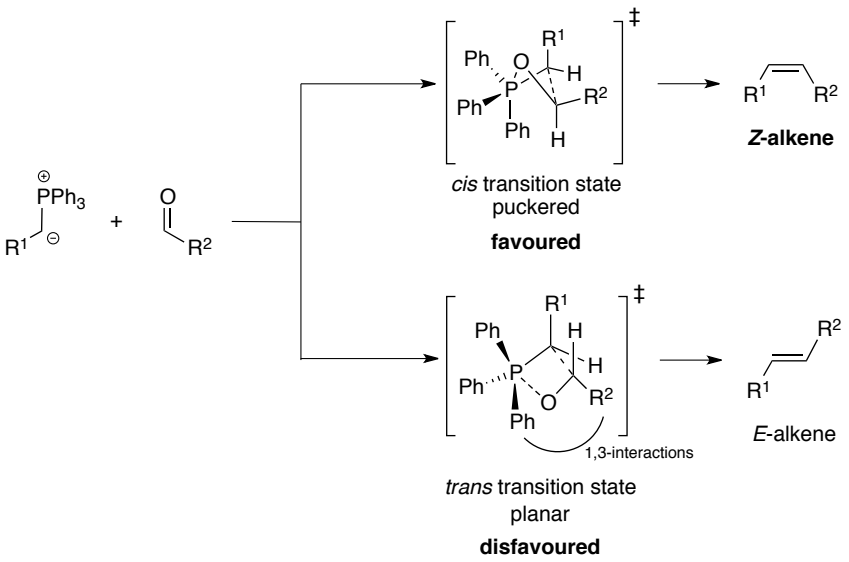
unstabilised ylide to a carbonyl compound was irreversible, with the carbonyl compound and the ylide approaching each other perpendicularly, so as to keep the large substituents apart, under kinetic control. Keeping the large substituents apart produces a transition state which leads to the *syn*-stereochemistry of the oxaphosphetane. The elimination of Ph_3PO occurs stereospecifically to give the *Z*-alkene product in a ratio which is, therefore, reflective of the initial addition step (Scheme 1.2). With stabilised ylides, on the other hand, the addition of ylide to carbonyl compound to form oxaphosphetane was, in the past, viewed as no longer kinetically controlled, but thermodynamically controlled. Due to the added stability offered by the starting ylide, the addition step is therefore reversible and allows the oxaphosphetane diastereomers to interconvert. The elimination of Ph_3PO to give the alkene product therefore no longer reflects the initial kinetic ratio of the oxaphosphetane diastereomers. The thermodynamically more stable *anti*-oxaphosphetane diastereomer, with the two bulky substituents on opposite sides to each other, leads to *E*-alkene formation preferentially (Scheme 1.2).



Scheme 1.2 Past mechanistic view of Wittig olefination

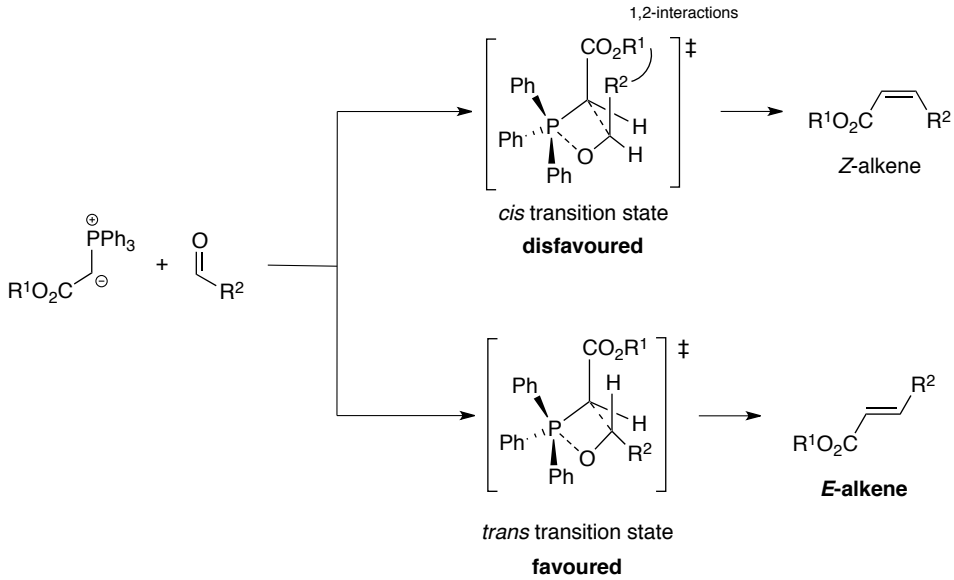
The extensive mechanistic studies done by Vedejs and co-workers,[4a, 7] Maryanoff and co-workers,[8] Aggarwal and co-workers,[9] Gilheany and Byrne,[10] and other researchers[11] have led to the presently accepted mechanism. The latter involves a formal asynchronous [2+2] cycloaddition of the ylide and carbonyl compound to directly generate the oxaphosphetane with the ring oxygen, derived from the aldehyde, in the more stable apical position of the trigonal bipyramidal structure of the oxaphosphetane. Pseudo-rotation, over a low energy barrier, then occurs to put the carbon from the ylide in an apical position, from which stereospecific *syn*-cycloreversion can occur, forming the alkene and Ph_3PO.

The Vedejs model of Wittig olefination for unstabilised ylides explains the stereoselectivity seen in terms of a balance between 1,2- and 1,3-steric interactions of the substituents in the oxaphosphetane intermediate. These researchers proposed that the transition state formed when unstabilised ylides and aldehydes add favourably is puckered and *cis*, which minimises 1,2- and 1,3-steric interactions between the substituents of the oxaphosphetane ring, and ultimately results in the formation of *Z*-alkene (Scheme 1.3). When the transition state formed is *trans*, on the other hand, which is more planar, puckering to relieve the unfavourable 1,3-steric interactions results in increased 1,2-interactions. The desired geometry in this case would be planar and so is disfavoured (Scheme 1.3).



Scheme 1.3 The Vedejs model of Wittig olefination using unstabilised ylides

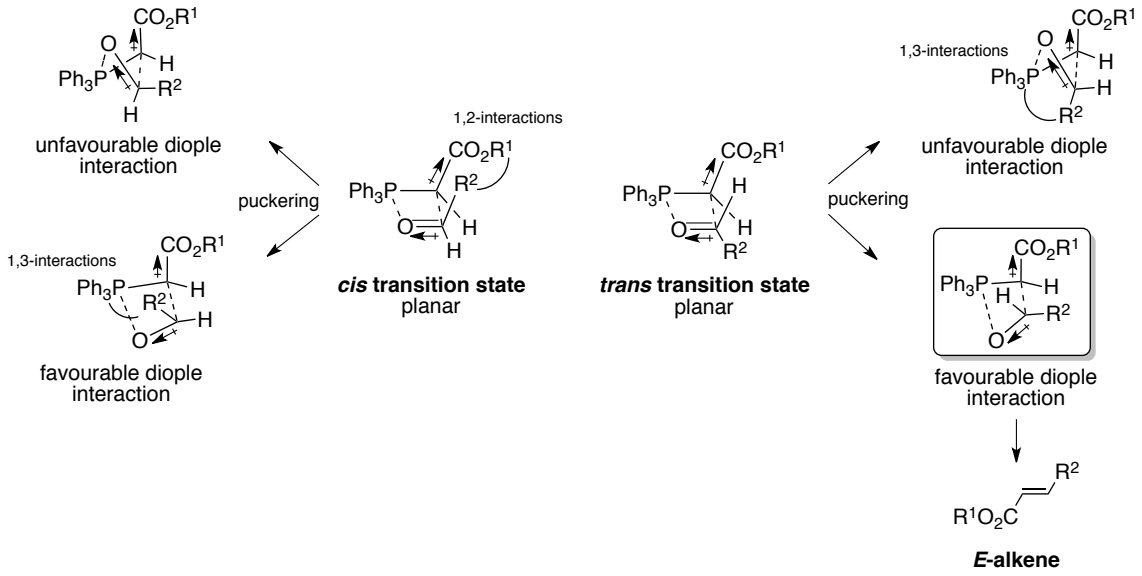
Vedejs proposed that the transition state formed when stabilised ylides and aldehydes add must be oxaphosphetane-like. This transition state is thought to be less flexible and is therefore constrained to a planar geometry in which *cis* stereochemistry leads to unfavourable 1,2-interactions, but the *trans* stereochemistry reduces unfavourable steric interactions and results in *E*-selectivity seen for stabilised ylides (Scheme 1.4).



Scheme 1.4 The Vedejs model of Wittig olefination using stabilised ylides

Further work done by Aggarwal and co-workers[9] support Vedejs' mechanistic model for stabilised ylides, that *trans*-oxaphosphetanes yield *E*-alkenes. However, their studies

indicated, that dipole-dipole interactions in the transition states, and not steric interactions, play the principal role in the high *E*-selectivity when using stabilised ylides (Scheme 1.5). This electrostatic influence adds to the stability of the *trans* transition state, while it destabilises the *cis* transition state (Scheme 1.5).

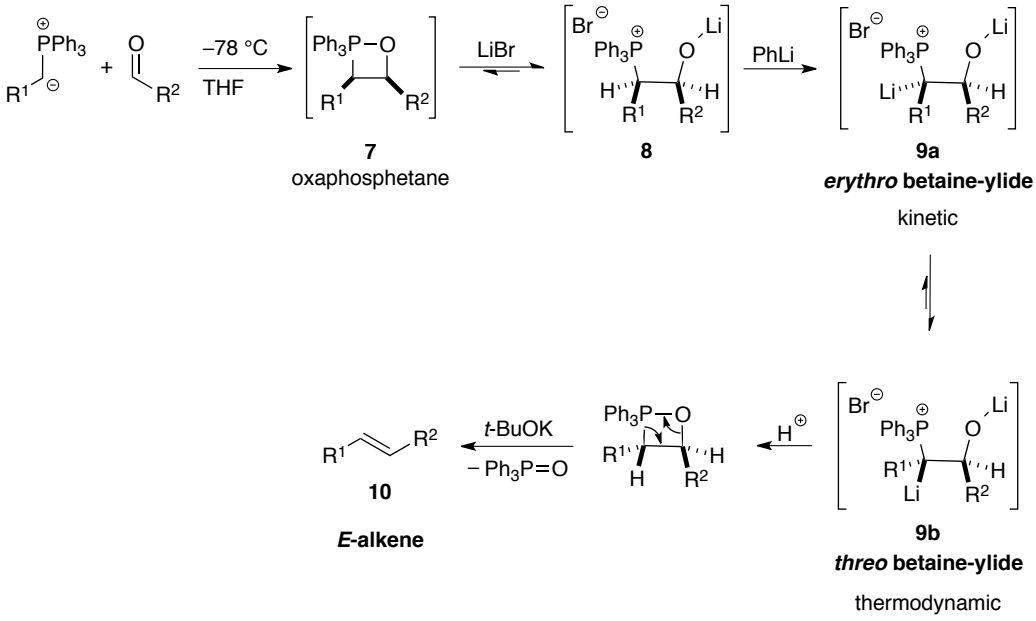


Scheme 1.5 The Aggarwal model of Wittig olefination using stabilised ylides

1.2 The Schlosser modification

The Schlosser modification of the Wittig reaction allows a synthetically important entry to *trans*-1,2-disubstituted alkenes with the use of unstabilised phosphorus ylides. It is believed that in the presence of an excess of soluble lithium halide,[12] the usual Ph_3PO elimination is delayed by a lithium ion-promoted ring-opening of the first-formed oxaphosphetane by cleavage of the P−O bond to form the corresponding betaine salt complex **8**[13] (Scheme 1.6). Schlosser *et al.*[13] posited that diastereomeric betaine ylides **9a** and **9b**, formed as a result of *α*-deprotonation of **8** with the use of an organolithium, rapidly equilibrate to give the thermodynamically favoured *threo*-stereoisomer **9b**. Protonation of this isomer using ethereal HCl (1 equiv) and subsequent treatment with a 1:1 mixture of *t*-

BuOK/*t*-BuOH was then carried out to furnish the *E*-olefin. Adding *t*-BuOK at this stage of the reaction was thought to effect an exchange of O−Li for O−K, resulting in a freer O^- ion, which was considered to then facilitate oxaphosphetane formation, followed by elimination of Ph_3PO. Using various alkyltriphenylphosphonium halide salts and aldehydes (aliphatic, α,β-unsaturated and aromatic), these researchers demonstrated that their methodology ensured *E*-olefin formation in good yield and excellent stereocontrol.[13a]



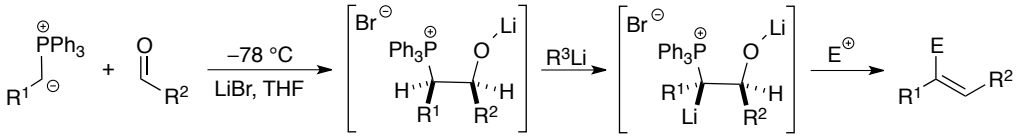
Scheme 1.6: The Wittig-Schlosser reaction[13a]

Schlosser *et al.*[12] later reported that α-lithiation of **8** is the key step in *trans*-selective olefination and only phenyllithium effected this deprotonation appreciably. In comparison, other organolithiums were described as reacting "sluggishly and incompletely." Additionally, Maryanoff *et al.*[14] reported that the presence of soluble lithium ions, principally from LiBr, was believed to aid in stabilising intermediates of type **7** against decomposition to the corresponding simple terminal alkenes. In their studies, Maryanoff *et al.*[14] found that yield of *E*-alkene increased as concentration of soluble lithium ions increased.

In essence, the Schloser modification involves delaying the normal phosphine oxide elimination by a Li^+ ion promoted cleavage of the P−O bond in the first formed oxphosphetane followed by α-lithiation, preferably with PhLi, at low temperature to give a β-lithiooxyphosphonium ylide. This new ylide can then be trapped at the ylidic carbon by a subsequently added electrophile. Quenching with a proton as the electrophile leads to stereoselective protonation and consequently the *E*-alkene.

1.3 The SCOOPY reaction

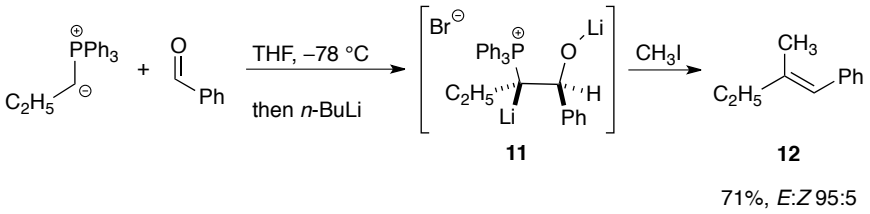
Using electrophiles other than a proton to trap the ylidic carbon of the β-lithiooxyphosphonium intermediate **9** constitutes a powerful approach to trisubstituted alkenes (Scheme 1.7). Such reactions are called SCOOPY (α -Substitution plus Carbonyl Olefination via β-Oxido Phosphonium Ylides) reactions and have been reported with methyl iodide,[15] halogen electrophiles,[15b, 16] halomethyl esters[17] and formaldehyde.[15c]



Scheme 1.7 The SCOOPY reaction

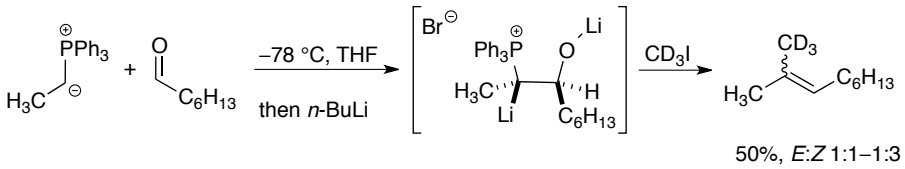
1.3.1 The SCOOPY reaction with alkyl halides

Schlosser and Christmann[15a] were the first to report the reaction of β-lithiooxy-phosphonium ylides with methyl iodide (Scheme 1.8). In their studies, propylidene-triphenylphosphorane, and benzaldehyde were reacted at low temperature to give the corresponding β-lithiooxyphosphonium ylide **11** after deprotonation with *n*-BuLi. The trisubstituted olefin **12,** formed when methyl iodide was added to this ylide, was obtained in good yield and isomeric purity.



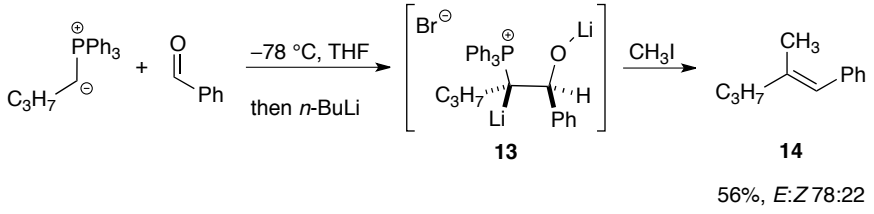
Scheme 1.8 SCOOPY reaction with CH_3I by Schlosser *et al*.[15a]

Corey *et al*.[15b-c, e] also studied the reactions of β-lithiooxyphosphonium ylides and alkyl halides to produce trisubstituted olefins. In contrast to Schlosser's[15a] earlier work, these researchers reported that formation of product using alkyl halides, with the exception of methyl iodide, failed. Using trideuteriomethyl iodide to trap the β-lithiooxyphosphonium ylide formed was reported to react non-stereoselectively (*Z*:*E* 1:1 to 3:1) and afforded only a moderate, 50%, yield of product (Scheme 1.9).



Scheme 1.9 SCOOPY reaction with CD_3I by Corey *et al*.[15b]

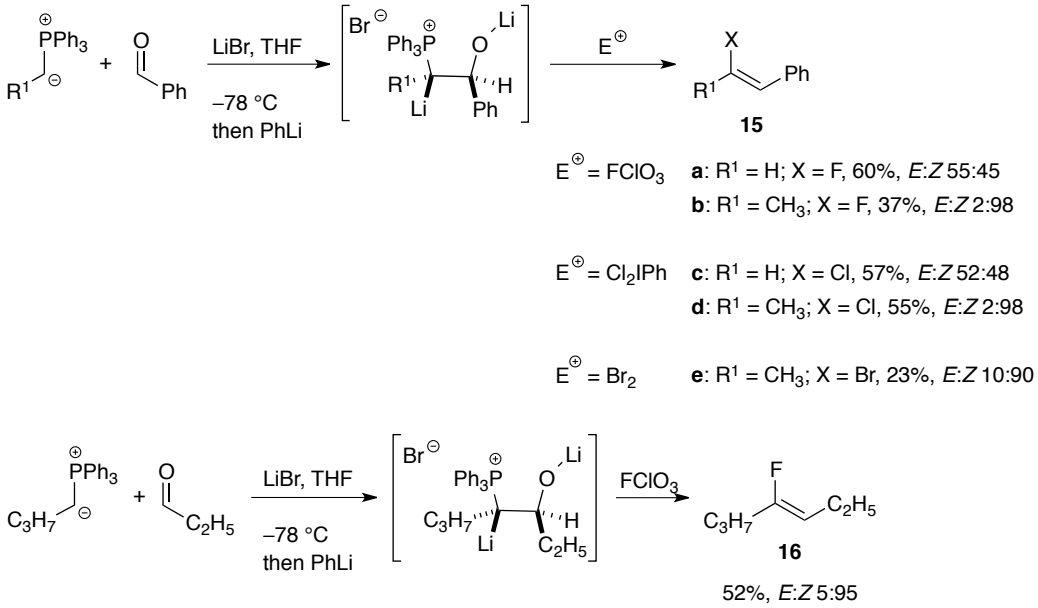
Upon reinvestigating the alkylation of β-lithiooxyphosphonium ylides (made from butylidenetriphenylphosphorane and benzaldehyde), Schlosser and coworkers[15d] reported an *E*:*Z* selectivity and yield which was lower than they had previously reported (71%, *E*:*Z* 95:5)[15a] (Scheme 1.10). These results suggested that *E*:*Z* selectivity depended on the size of the phosphorane used.



Scheme 1.10 Reinvestigated SCOOPY reaction with with CH_3I by Schlosser *et al*.[15d]

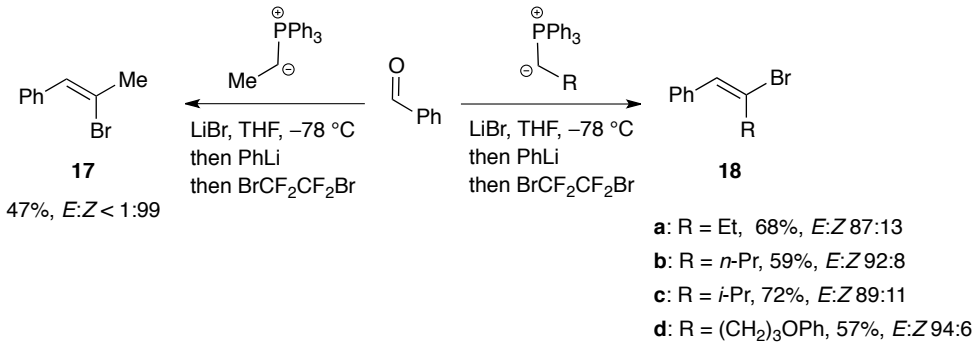
1.3.2 The SCOOPY reaction with halogens

Schlosser and Christmann[15a] were also the first to report the reaction of β-lithiooxyphosphonium ylides with halogen electrophiles. In their studies, these researchers observed excellent *Z*-selectivity (**15c–e**, **16** *E*:*Z* 10:90 to 2:98) using ethylidenetriphenylphosphorane and butylidenetriphenylphosphorane but obtained an approximately equal mixture of *E*- and *Z*-isomers using methylidenetriphenylphosphorane (Scheme 1.11).[15a, b]



Scheme 1.11 Synthesis of alkenyl halides by Schlosser and Christmann[15a]

A number of other researchers have also investigated the reaction of β-lithiooxyphosphonium ylides with halogen electrophiles.[15b, 16] More recent studies on the synthesis of alkenyl bromides showed that the stereochemical outcome of the bromination step was dependent on the size of the alkylidenephosphorane used to make the β-lithiooxy ylide.[16d] It was found that increasing the size of the Wittig reagent beyond the ethylidene-phosphorane used in Schlosser's work[15a] led predominantly to the *E*-isomer (Scheme 1.12). *E*-selectivity of a similar nature was also observed for heteroaromatic aldehydes, an α,β-unsaturated aldehyde and aliphatic aldehydes by these researchers.

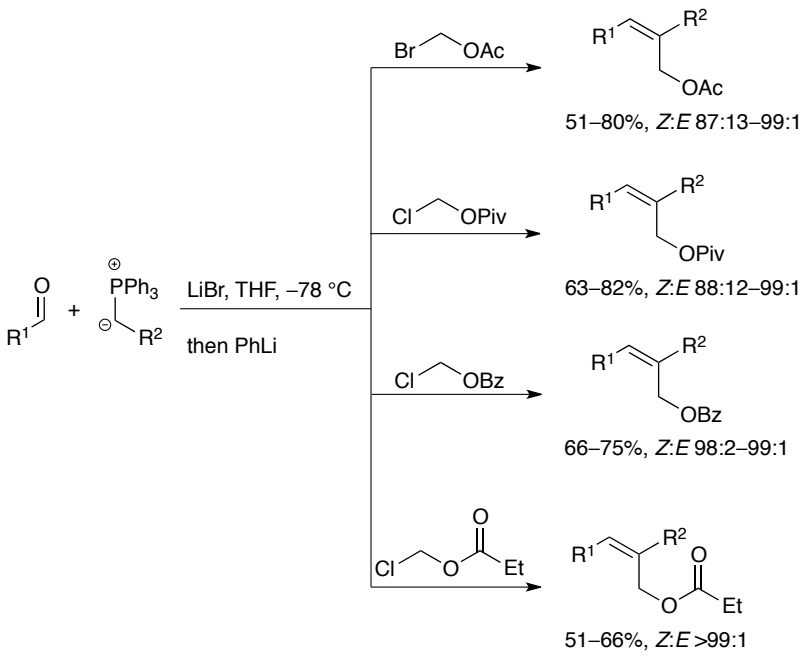


Scheme 1.12 Synthesis of alkenyl bromides by Hodgson and Arif[16d]

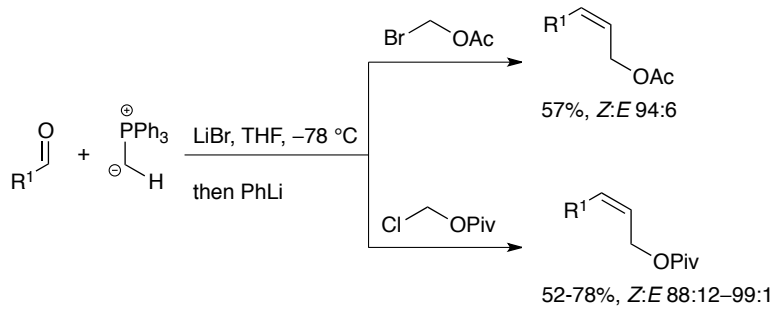
The synthesis of alkenyl iodides[16d] also displayed a similar *E*-selectivity profile as that observed in the brominations. On moving from 1,2-diiodoethane to iodine as electrophile, yields improved; particularly geometrical purities of the iodoalkenes derived from aromatic aldehydes. Shen *et al*.[16b] in their investigations using ethylidenephosphorane and various aldehydes observed a similar *Z*-selectivity as reported by Hodgson and Arif.[16d]

1.3.3 The SCOOPY reaction with α-halomethyl esters

Work was also carried out on the synthesis of trisubstituted[17a] and disubstituted allylic esters.[17b] Good yields and excellent *Z*-stereoselectivity was obtained for trisubstituted allylic acetates, pivalates, benzoates and propionates (Scheme 1.13) as well as for disubstituted allylic acetates and pivalates (Scheme 1.14).



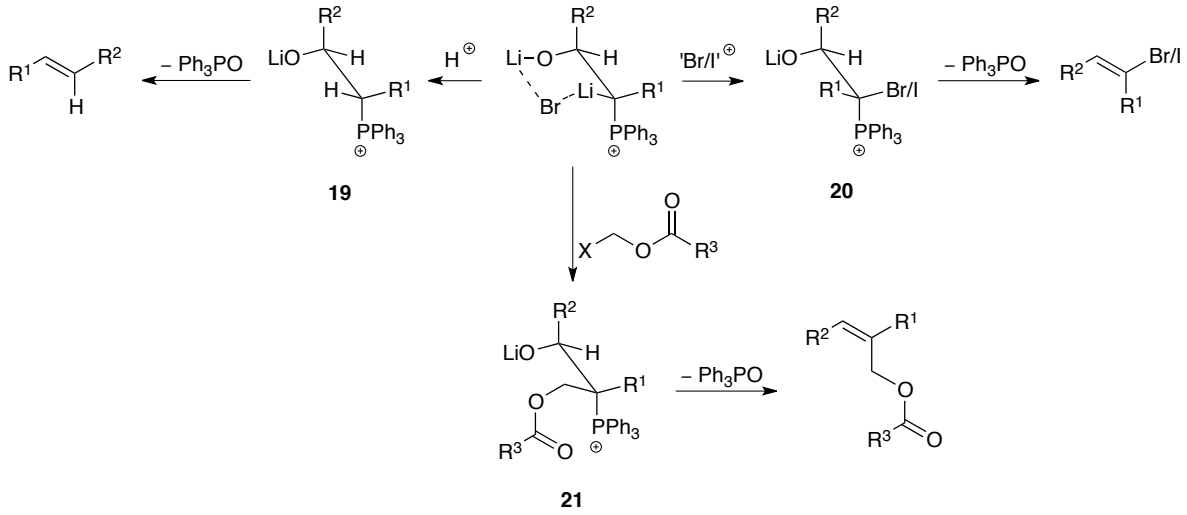
Scheme 1.13: Synthesis of trisubstituted allylic esters[17a]



Scheme 1.14: Synthesis of disubstituted allylic esters[17b]

During their studies, Hodgson and Arif[17] noted some differences in stereoselectivity when trapping β-lithiooxyphosphonium ylides with a proton, halomethyl esters and halogen electrophiles. Trapping with a proton source or halomethyl esters were shown to generate product where R^1 and R^2 were always *trans* regardless of the size of R^1. Trapping with halogen electrophiles, on the other hand, were found to generate product where R^1 and R^2 were always *cis* (unless R^1 = Me). To rationalize this difference, they suggested that the reaction of β-lithiooxyphosphonium ylides with halogens, non-coordinating electrophiles, may have occurred by means of an inversion of configuration *via* betaine **20** while trapping

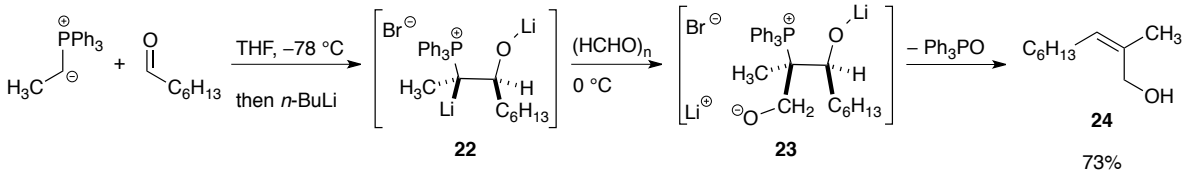
with the other electrophiles may have proceeded by retention in which the electrophiles were coordinated to the oxygen of betaines **19** and **21** (Scheme 1.15).



Scheme 1.15 Possible dependence of alkene stereochemistry on electrophile used[17]

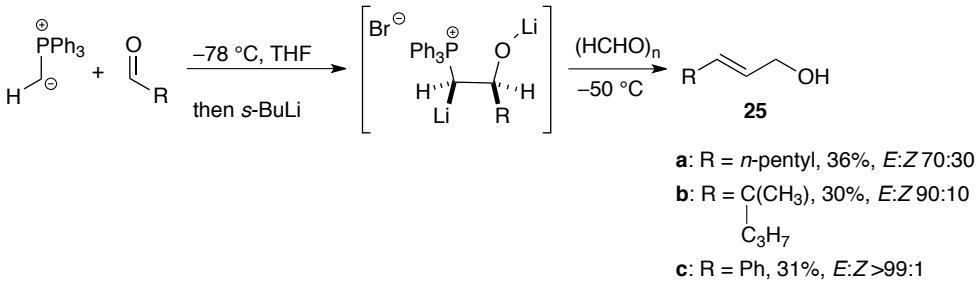
1.3.4 The SCOOPY reaction with formaldehyde

Using an aldehyde as the electrophile to trap the ylidic carbon of the β-lithiooxy-phosphonium ylide results in an allylic alcohol. Allylic alcohols are widely used substrates for a number of synthetic reactions as they are versatile and allow opportunities for further modification.[18] Corey and Yamamoto[15c] were the first to accomplish the synthesis of trisubstituted allylic alcohols (Scheme 1.15). β-lithiooxyphosphonium ylide **22**, made by reacting ethylidenetriphenylphosphorane and *n*-heptanal followed by subsequent α-deprotonation with *n*-BuLi, was then treated with 2 equiv dry paraformaldehyde to generate the β,β'-dioxido phosphonium derivative **23**. Elimination of triphenylphosphine oxide, occurring regioselectively to produce the more stable alkyl substituted alkene, produced *Z*-allylic alcohol **24** in 73% yield (Scheme 1.16).



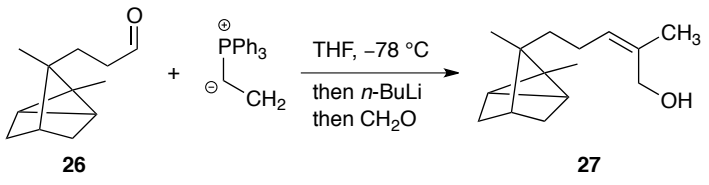
Scheme 1.16: Corey's synthesis of trisubstituted allylic alcohols[17]

Schlosser and Coffinet[19] subsequently reported the SCOOPY reaction of β-lithiooxy-phosphonium ylides, made using methylidenetriphenylphosphorane and ethylidene-triphenylphosphorane and a range of aldehydes and ketones, and formaldehyde (Scheme 1.17). These researchers reported a similarly high *Z*-selectivity (*Z*:*E* >99:1), as observed by Corey and Yamamoto,[15c] using ethylidenetriphenylphosphorane and both aliphatic and aromatic aldehydes. However, they reported varying *E*-selectivity depending on the nature of the starting aldehyde used, when methylidenetriphenylphosphorane was the Wittig reagent used.



Scheme 1.17 Schlosser's synthesis of disubstituted allylic alcohols[19]

Corey and Yamamoto[15c] applied their methodology to the synthesis of α-santalol **27**, an important essential oil that displays anti-cancer properties. These researchers reported producing this natural product "stereospecifically and efficiently" in a single step from aldehyde **26** (Scheme 1.18). However, no yield was reported.

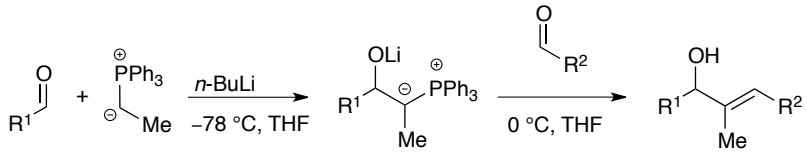


Scheme 1.18 Corey's synthesis of α-santalol[15c]

Their method has subsequently found significant use in natural product syntheses;[20] the yields in most cases, however, are variable and often only moderate.

1.3.5 The reaction of β-lithiooxyphosphonium ylides with other aldehydes

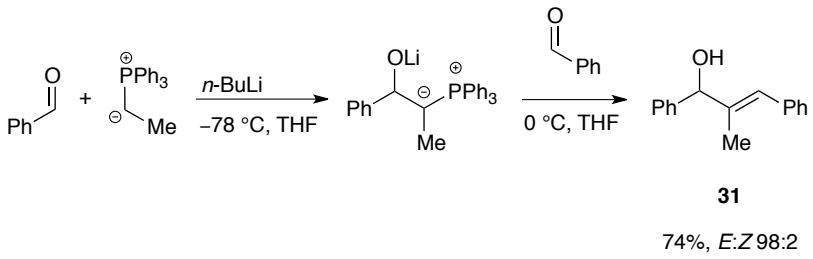
Using aldehydes other than formaldehyde to trap β-lithiooxyphosphonium ylides was only reported by Corey and Yamamoto in the synthesis of trisubstituted allylic alcohols using ethylidenetriphenylphosphorane (Scheme 1.19).[15c] However, there seems to be some contradiction in their experimental outcomes. Reacting ethylenetriphenylphosphorane with acetaldehyde first then with *n*-heptanal after ylide formation produced allylic alcohol **28** as exclusively one isomer. Allylic alcohol **29** was also produced as exclusively one isomer when ethylenetriphenylphosphorane was reacted with *n*-heptanal first followed by acetaldehyde after ylide formation. On the other hand, reacting ethylenetriphenyl-phosphorane with heptanal first followed by heptanal after ylide formation produced alcohol **30** as a 90:10 *E*:*Z* isomeric mixture. It is unclear why slightly reduced selectivity occurred in the formation of alcohol **30**, and no explanation was offered by these researchers.



28: $R^1 = CH_3$, R^2 = *n*-hexyl, 67%, *E*:*Z* 100:0
29: R^1 = *n*-hexyl, $R^2 = CH_3$, 67%, *E*:*Z* 100:0
30: $R^1 = R^2$ = *n*-hexyl, *E*:*Z* 90:10

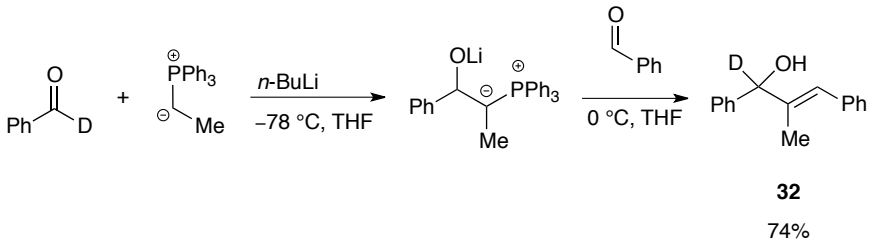
Scheme 1.19 Synthesis of trisubstituted allylic alcohols by Corey and Yamamoto[15c]

These researchers also found that the sequential treatment of ethylidenetriphenyl-phosphorane with 1 equivalent benzaldehyde, 1 equivalent *n*-BuLi and again with 1 equivalent benzaldehyde produced *E*-allylic alcohol **31** along with ~2% of its geometrical isomer (Scheme 1.20).



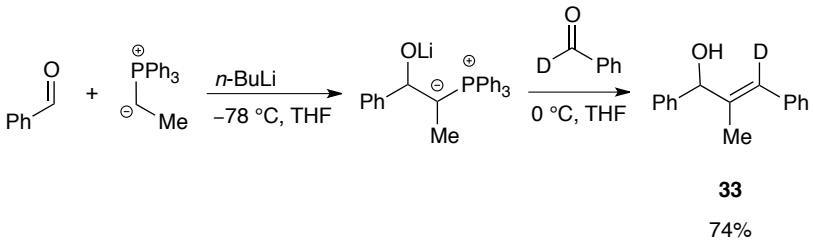
Scheme 1.20

The stereochemical course of the synthesis of **31** was then investigated: ethylidenetriphenylphosphorane was treated with 1 equivalent 1-deuterobenzaldehyde, 1 equivalent *n*-BuLi, then with 1 equivalent benzaldehyde to form **32** in 74% yield (Scheme 1.21).



Scheme 1.21

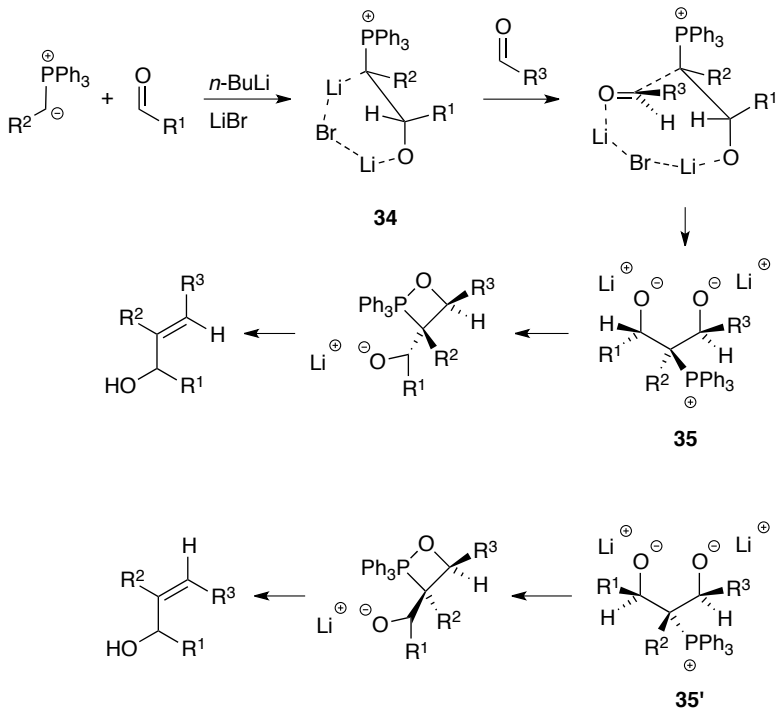
On the other hand, treatment of ethylidenetriphenylphosphorane with 1 equivalent benzaldehyde, 1 equivalent *n*-BuLi, then with 1 equivalent 1-deuterobenzaldehyde formed **33** in similar yield (Scheme 1.22).



Scheme 1.22

These observations demonstrate that Wittig elimination of Ph_3PO form the β,β'-dioxido phosphonium derivative **35** involves a highly selective loss of the oxygen which originates from the second aldehyde used in the reaction sequence. The *E*-stereoselectivity

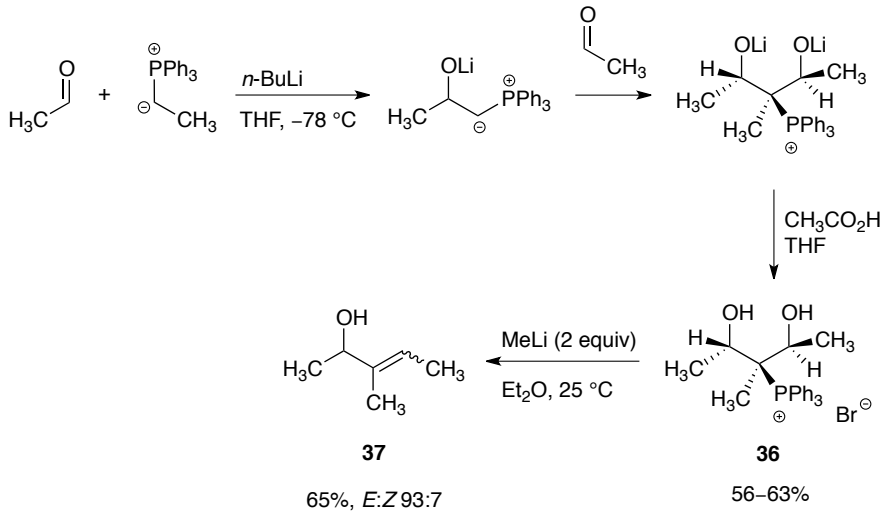
has been discussed in terms of the formation of a *racemic*-dioxido phosphonium adduct **35** (rather than the stereoisomeric *meso* structure **35′**) which has a preference for elimination to furnish the *E*-isomer[3b, 15c, 15e] (Scheme 1.23).



Scheme 1.23 Proposed mechanism of *E*-selectivity[3b, 15c, 15e]

In 1977, Corey and co-workers[15e] carried out an incisive study in which they were able to isolate and analyse dihydroxyphosphonium bromide salt **36** by ^{1}H NMR analysis. This salt was obtained form the reaction of the β-lithiooxy ylide derived from acetaldehyde and ethylidenephosphorane, with acetaldehyde in THF at −78 °C. The β,β'-dioxido adduct formed was then treated with acetic acid in THF to precipitate the colourless bromide salt **36** (Scheme 1.24). By ^{1}H NMR analysis, the hydroxyl, methine and methyl protons were observed to be diastereotopic, indicating the *racemic* form of this species (and not the *meso* form, in which case these protons would be equivalent). A confirmatory test was carried out in which the dihydroxyphosphonium bromide salt **36** formed was treated with MeLi (2

equiv) and stirred at ambient temperature to effect elimination of Ph_3PO. Allylic alcohol **37** was obtained as predominantly the *E*-isomer (Scheme 1.24).

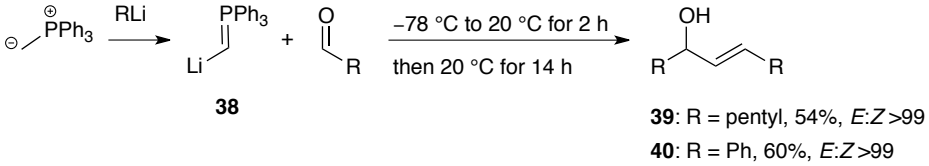


Scheme 1.24

Another interesting study was reported by Corey and Kang,[21a] involving the formation and reaction of lithiated methylenephosphonium ylide (or its reaction equivalent)[21b] with 2 equivalents of an aldehyde (Scheme 1.25). Formation of the lithiated ylide was reported to have been accomplished in several ways:

- treating methylenetriphenylphosphorane with *t*-BuLi (1 equiv) in THF at −78 °C, warming this mixture to −40 °C over 1 h, then stirring at this temperature for a further 1 h to produce a red to red-orange solution of the lithiated ylide;
- treating methyltriphenylphosphonium bromide with *s*-BuLi (2 equiv) in Et_2O at −78 °C, warming this mixture to −40 °C over 1 h, then stirring at 20 °C for 3 h to produce an orange suspension;
- treating methylenetriphenylphosphorane with *t*-BuLi (1 equiv) in Et_2O at −78 °C, warming this mixture to 20 °C over 2 h, then stirring at this temperature for a further 3 h.

These researchers reported the formation of exclusively the *trans* allylic alcohols **39** and **40** in good yield using 2 equivalents hexanal and 2 equivalents benzaldehyde, respectively, *via* this method.

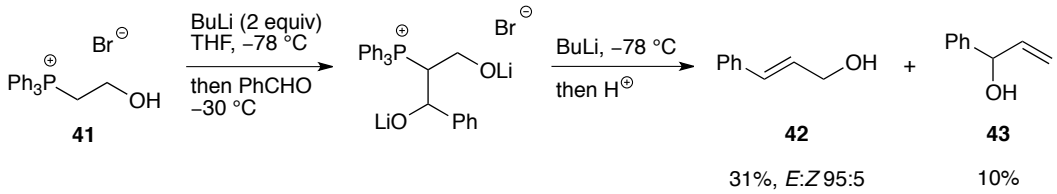


Scheme 1.25 Synthesis of 1,2-disubstituted allylic alcohol using a lithiated phosphorane and an aldehyde by Corey and Kang[21a]

Importantly, no mention was made of the outcome of any experiments carried out using 1 equivalent each of two different aldehydes. It is expected that mixtures of allylic alcohols would be the result in this case, and this method of generating disubstituted allylic alcohols may possibly be useful only in the formation of symmetric allylic alcohols.

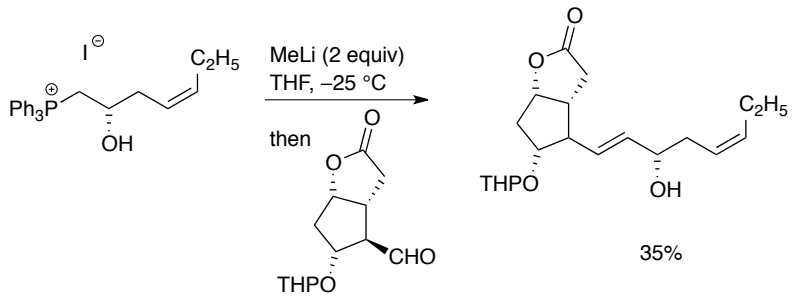
1.3.6 Synthesis of allylic alcohols using β-hydroxy phosphonium salts

To the best of our knowledge, the above chemistry has not been studied with methylenetriphenylphosphorane and two aldehydes (other than with the second aldehyde used in the sequence being formaldehyde, Scheme 1.16, p 14)[19] despite its potential as an attractive route to 1,2-disubstituted *E*-allylic alcohols. However, the presumed intermediate β-lithiooxyphosphonium ylide **34** has been generated on several occasions, from the double deprotonation of a β-hydroxy primary phosphonium salt. Schlosser *et al.*[15d] reported the first synthesis of disubstituted *E*-allylic alcohols by a two-carbon homologation of aldehydes using the β-lithiooxy ylide derived from hydroxyphosphonium bromide salt **41** and benzaldehyde to produce allylic alcohol **42** in low yield and high isomeric purity along with a significant yield of side product **43** (Scheme 1.26).



Scheme 1.26 Synthesis of 1,2-disubstituted allylic alcohol using β-hydroxy primary phosphonium salt by Schlosser *et al.*[15d]

Subsequently, it was shown by Corey *et al*.[22] that the β-lithiooxy ylide derived from a β-hydroxy primary phosphonium salt undergoes the desired synthesis of 1,2-disubstituted allylic alcohols on reaction with aldehydes in their total synthesis of prostaglandins E_3 and $F_{3\alpha}$ (Scheme 1.27).



Scheme 1.27 Synthesis of prostaglandins by Corey *et al*.[22]

This way of synthesising allylic alcohols is little used (since these reactions appear to be very sensitive to experimental conditions, and yields are highly variable) but has, none-the-less, found use in the synthesis of enantiomerically pure (or enriched) allylic alcohols and natural products starting from enantiopure or enriched phosphonium salts (Table 1.1).[22, 23]

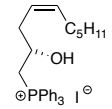
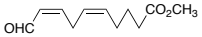
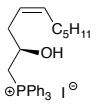
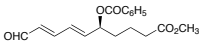
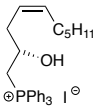
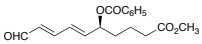
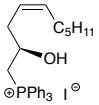
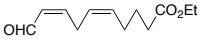
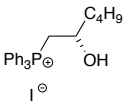
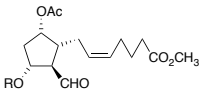
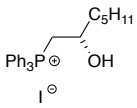
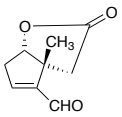
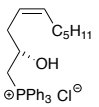
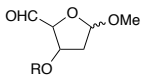
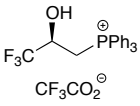
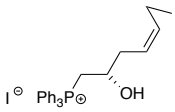
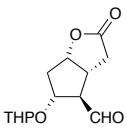
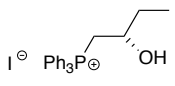
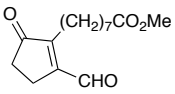
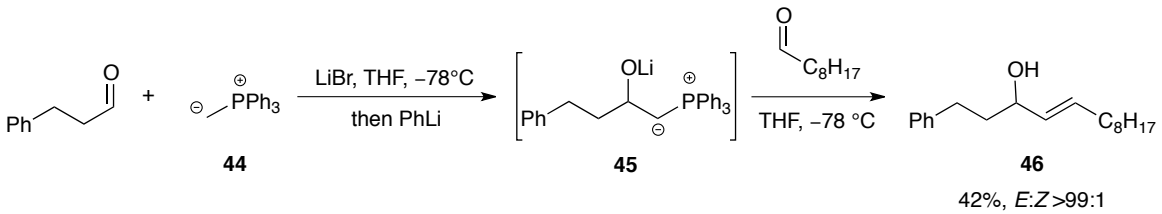
Entry	Phosphonium salt	Aldehyde	Conditions	Yield (%)	*E*:*Z*
1[23a]			MeLi (2 equiv), THF, −78 °C, 5 min then −25 °C, 30 min then aldehyde, −78 °C, 5 min then −30 °C, 5 min, then $O=P(N(CH_3)_2)_3$, warm to −10 °C over 2 h.	No yield reported	100:0
2[23b]			*n*-BuLi (2 equiv), THF, −78 °C, 1 h then $O=P(N(CH_3)_2)_3$,	25	100:0
3[23b]			then aldehyde, warm to −30 °C over 1.5 h, stir for 1 h then warm to 0 °C	25	100:0
4[23c]			MeLi (2 equiv), THF, −78 °C to −30 °C then aldehyde, −78 °C, 30 min then warm to −30 °C then $O=P(N(CH_3)_2)_3$, −30 °C to −10 °C over 2 h.	58% (minor impurities), 76% *ee*	*Z*/*E* isomers
5[23d]			*n*-BuLi (2 equiv), THF, −78 °C to −20 °C then aldehyde, warm to 0 °C then warm to rt	12	100:0
6[23e]			*n*-BuLi (2 equiv), THF, −70 °C to −25 °C then aldehyde, −70 °C, 15 min, warm to 0 °C, 1 h	12	100:0
7[23f]			*s*-BuLi (2 equiv), −30 °C, THF, 30 min then aldehyde, −78 °C to 0 °C over 3.5 h, then 0 °C, 10 h	52	100:0
9[23h]		Various aliphatic and α,β-unsaturated aldehydes	*n*-BuLi (2 equiv), THF, −78 °C then aldehyde	46–89, 74–75% *ee*	56:24 to 100:0
10[23j]			MeLi (2 equiv), THF, −78 °C, 5 min then −40 °C, 30 min then aldehyde, −78 °C, 5 min then −40 °C, 40 min	40	100:0
11[23k]			LiHMDS (1.9 equiv), THF, −78 °C then −25 °C, 15 min then aldehyde, −78 °C 20 min	29	100:0

Table 1.1

1.4 Observations that led to the present work

Previous work carried out in the Hodgson group[16d, 17] has shown that β-lithiooxy-phosphonium ylides undergo reactions with various ester and halogen electrophiles in good yield and stereoselectivity (p 11−12). In spite of the previous discouraging results reported by Schlosser *et al*.,[19] preliminary work done by the DPhil student who carried out the above-mentioned investigations, using more recent experimental conditions in the generation of β-lithiooxyphosphonium ylides and aldehydes (other than formaldehyde) to trap these ylides proved promising. β-Lithiooxy ylide **45**, made using methylene-phosphorane and hydrocinnamaldehyde and using PhLi as the base, was reacted with nonanal to yield allylic alcohol **46** in moderate yield and excellent stereoselectivity (*E*:*Z* >99:1) (Scheme 1.28).



Scheme 1.28

1.5 Project aims

One aim of my work was, therefore, to further investigate this relatively underdeveloped chemistry of using aldehydes as the electrophile source to trap β-lithiooxy-phosphonium ylides to produce allylic alcohols using methylenetriphenylphosphorane as the Wittig reagent. The wide availability of aldehyde substrates suggested that this route into stereodefined alkenes via β-lithiooxyphosphonium ylides would be of significant utility.

A second aim of my work was to investigate an efficient route into chiral 1,2-disubstituted *E*-allylic alcohols by a 'true' asymmetric Wittig reaction *via* β-lithiooxy-

phosphonium ylides. This would be investigated using PPh_3 to ring-open terminal epoxides. β-Lithiooxyphosphonium ylides formed in this way can then be trapped using aldehydes to form allylic alcohols. Using PPh_3 to ring-open chiral terminal epoxides, followed by trapping with aldehydes after ylide formation would result in the formation of the corresponding chiral allylic alcohols.

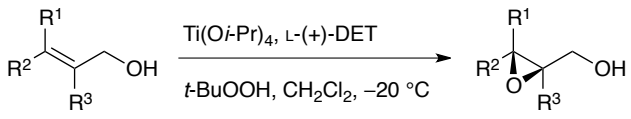
Chapter 2: Synthesis of *E*-allylic alcohols using methylene-triphenylphosphorane

This chapter details my studies on the synthesis of 1,2-disubstituted *E*-allylic alcohols *via* a convergent and stereoselective route using β-lithiooxyphosphonium ylides, generated using aldehydes and methylenetriphenylphosphorane, followed by trapping with a second aldehyde substrate.

2.1 Background

Allylic alcohols and their derivatives are widely used substrates in organic synthesis as they are versatile and allow opportunities for further modification.[18] Usually, regio-, chemo- and stereocontrolled manipulations of the alkene component of allylic alcohols are made possible by the coordinating and directing feature of the hydroxy group.[18a] For this reason, experimentally straightforward and efficient methods of synthesising allylic alcohols from readily available starting materials in a stereocontrolled manner are of significance.

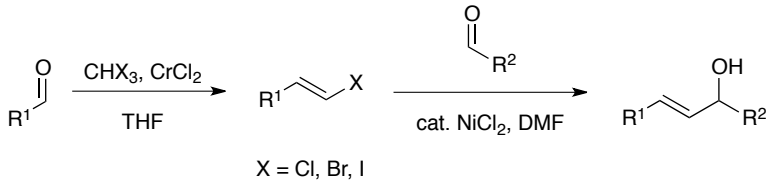
Arguably, one of the most important developments in asymmetric synthesis has been the catalytic asymmetric oxidation of allylic alcohols to 2,3-epoxy alcohols. This work, by Sharpless and co-workers highlights just one of the major importances of allylic alcohols (Scheme 2.1).[6c, 24]



Scheme 2.1 Sharpless asymmetric epoxidation of allylic alcohols[6c, 24]

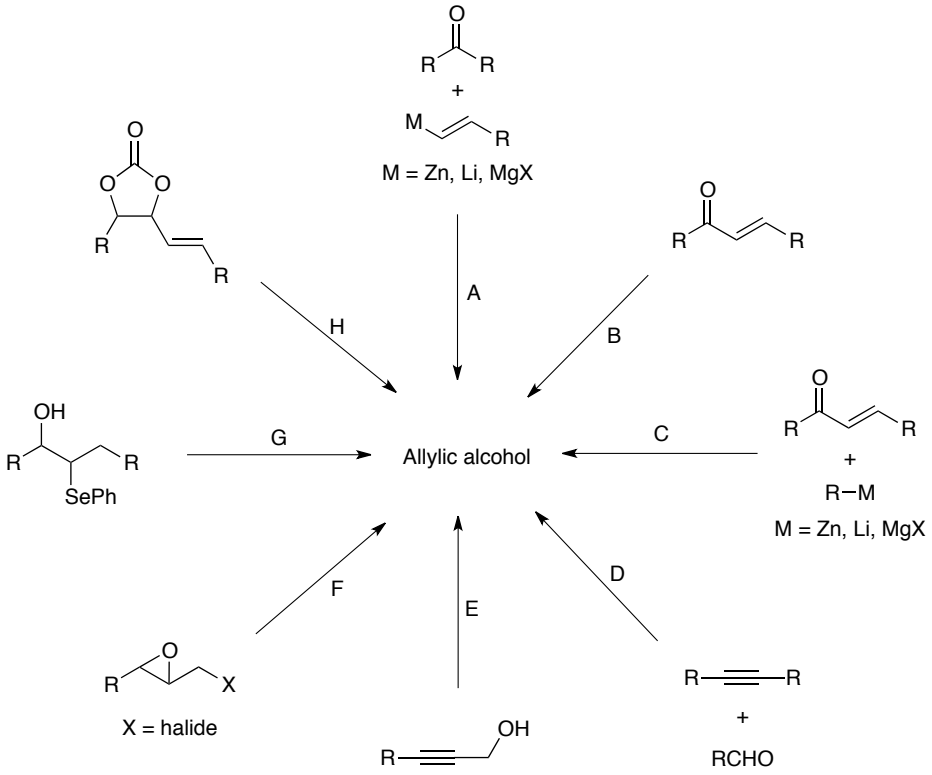
A recent comprehensive overview of synthetic methods available to produce allylic alcohols had been compiled by Hodgson and Humphreys.[18b] A search of the literature

revealed one other method by which two aldehydes can be combined to synthesise 1,2-disubstituted *E*-allylic alcohols.[25] This method involves the synthesis of an *E*-alkenyl halide, from an aldehyde, a haloform and anhydrous $CrCl_2$ in THF; followed, after removal of THF *in vacuo*, by its reaction with a second aldehyde in the presence of a catalytic amount of $NiCl_2$ in DMF (Scheme 2.2). Takai *et al*.[25] reported good *E*-selectivities (81−95% *E*-isomer) for all aldehyde types used as the second aldehyde, apart from α,β-unsaturated aldehydes.



Scheme 2.2

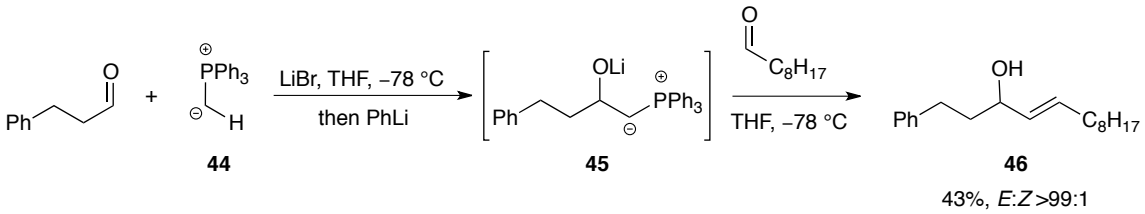
Some other general methods available to synthesise allylic alcohols include (Scheme 2.3): alkenyl anion addition to carbonyl compounds (A), 1,2-reduction of α,β-unsaturated ketones (B), addition of organometallics to α,β-unsaturated carbonyls (C), reductive couplings between alkynes and aldehydes (D), reduction of propargylic alcohols (E), reduction of α-halo epoxides (F), elimination of β-hydroxy selenides (G) and elimination reactions of allylic cyclic carbonates (H).[18*b*, 26]



Scheme 2.3

2.2 Initial findings

As stated earlier (p 22), an interesting observation concerning the chemistry of β-lithiooxy phosphoranes, generated using methylenetriphenylphosphorane and aldehydes, was made by a past DPhil student in the Hodgson group. This researcher noted that one isomer, the *E*-isomer, was produced when β-lithiooxy ylide **45** was reacted with nonanal to yield allylic alcohol **46**. This reaction was repeated following the same experimental procedure used previously and a similar yield (43%) of product and *E*:*Z* selectivity was obtained (Scheme 2.4).



44 **45** **46**

43%, *E*:*Z* >99:1

Scheme 2.4

A solution of anhydrous LiBr (4.0 mmol, 2 equiv) in THF (30 mL) was added to anhydrous methyltriphenylphosphonium bromide (2.0 mmol, 1.0 equiv), then treated with PhLi (2.0 mmol, 1.0 equiv) to make a yellow solution of methylenephosphorane (**44**). A solution of hydrocinnamaldehyde (2.0 mmol, 1 equiv) in THF (10 mL) was added dropwise to this ylide at −78 °C. After complete decolourisation had occurred, PhLi (2.1 mmol,1.05 equiv.) was again added dropwise to this mixture at −78 °C to form a cherry red solution of β-lithiooxy ylide **45.** After stirring for 30 minutes at this temperature, a solution of nonanal (2.1 mmol, 1.05 equiv) in THF (5 mL) was added dropwise. This mixture was then stirred for 2 hours at −78 °C, the temperature was then slowly raised to room temperature over 1 hour and the reaction mixture was stirred for a further 1 hour at room temperature. The mixture was then quenched with saturated aq. ammonium chloride (20 mL), extracted with Et_2O (3 × 15 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by flash column chromatography gave the allylic alcohol in 43% yield.

The product **46** was determined to be the *E*-isomer, from the *J* coupling in the alkene region (15.3 Hz) which was typical for *trans*-alkenes (Figure 2.1).

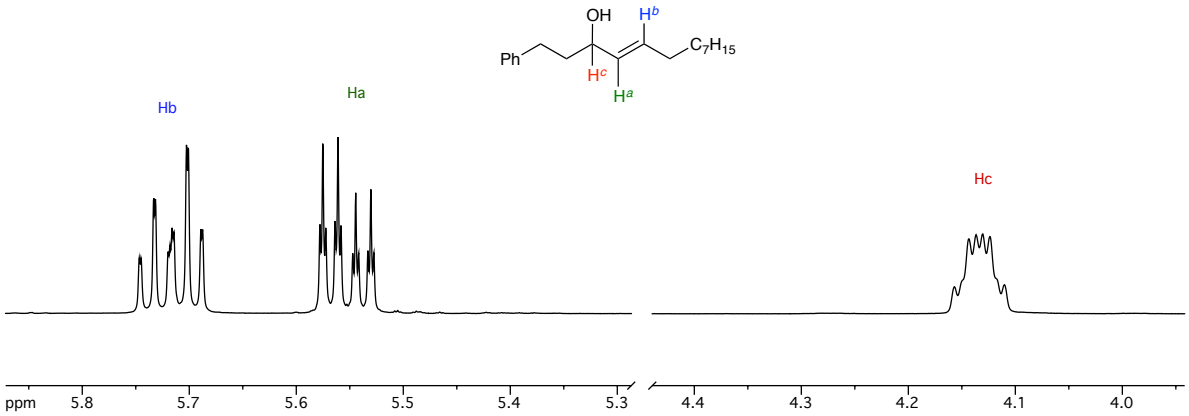


Figure 2.1 ^{1}H NMR (500 MHz) chemical shifts of methine protons of allylic alcohol **46**. See Experimental section for full details.

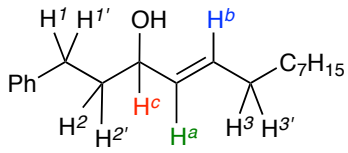


Figure 2.2 Allylic alcohol **46**

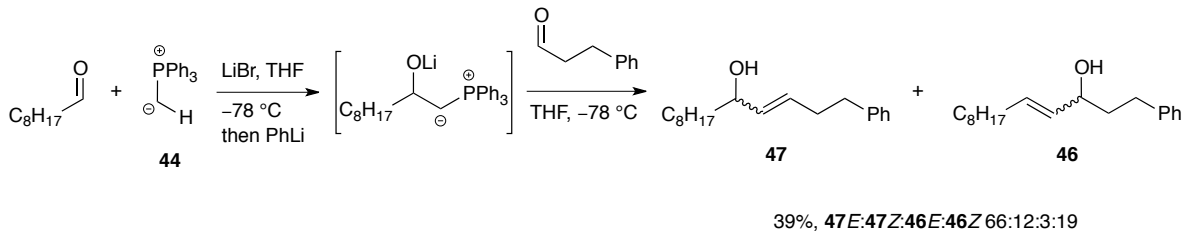
COSY studies showed coupling between H^a and H^b, and H^c; H^a and H^b, and H^3 and $H^{3'}$ (H^3 and $H^{3'}$ coupled to aliphatic protons); H^c, and H^2 and $H^{2'}$; H^2 and $H^{2'}$, and H^1 and $H^{1'}$ (H^1 and $H^{1'}$ coupled to aromatic protons) (Figure 2.2). NOESY studies showed that H^1 and $H^{1'}$, H^2 and $H^{2'}$, H^a, and H^b were spatially close to H^c; H^1 and $H^{1'}$ were spatially close to aromatic protons; and H^a and H^b, and H^3 and $H^{3'}$ were spatially close to aliphatic protons (Figure 2.2).

The fate of ~50% of both starting aldehydes could not be determined, as neither were recovered and carbonyl hydrogen peaks were not observed in the ^{1}H NMR spectrum of the crude product, possibly indicative of complete consumption of starting material.

2.3 Attempted optimisation of original reaction

Efforts then began to optimise this reaction. Hodgson and Arif[16d] noticed that reversing the order of addition of electrophile and β-lithiooxy ylide, that is, adding β-lithiooxy ylide to electrophile *via* cannula, maximized yield of the alkenyl bromides synthesised. Adding the solution of β-lithiooxy ylide **45** to a pre-cooled solution of nonanal at −78 °C led to a significantly higher yield of product (63%). Unfortunately, however, this was a mixture of regio- and stereoisomers. Repeated attempts to determine the isomeric ratio by GC/MS analysis of the crude reaction mixture failed. The ratio of each isomer was therefore determined by ^{1}H NMR analysis of the crude product of the reaction using the C***H*** (OH) proton as the reference since these were each separately distinct. The isomeric ratio was determined to be **46***E*:**46***Z*:**47***E*:**47***Z* 42:24:34:0.

The chemical shift of the C***H***(OH) of **46***E* and its *E*-regioisomer (**47***E*) are very similar: 4.09−4.17 ppm and 4.02−4.11 ppm respectively. The chemical shift of the C***H***(OH) of **45***Z* and the *Z*-regioisomer (**47***Z*) are 4.47−4.55 ppm and 4.26−4.33 ppm, respectively. To confirm that these chemical shifts were indeed characteristic to these isomers, allylic alcohol **47** was synthesised following the original protocol, but reversing the order of addition of the two aldehydes (Scheme 2.5).



Scheme 2.5

In stark contrast to the original result, the product of this reaction was a mixture of regio- and stereoisomers which were chromatographically inseparable. Subtle differences in

the ^{1}H NMR spectra of **47** and **46** were observed. Coupling constants (J = 15.2 Hz) and NOESY studies [C*H*(OH) spatially close to aliphatic protons; C*H*=C*H* spatially close to CH_2CH(OH) and PhCH_2; and CH_2CH(OH) and PhCH_2 spatially close to aromatic protons] confirmed that the major isomer was the desired isomer **47** and chemical shift of the C***H*** (OH) proton as 4.02−4.11 ppm (Figure 2.3). At this point, it was unclear why a mixture of isomers formed.

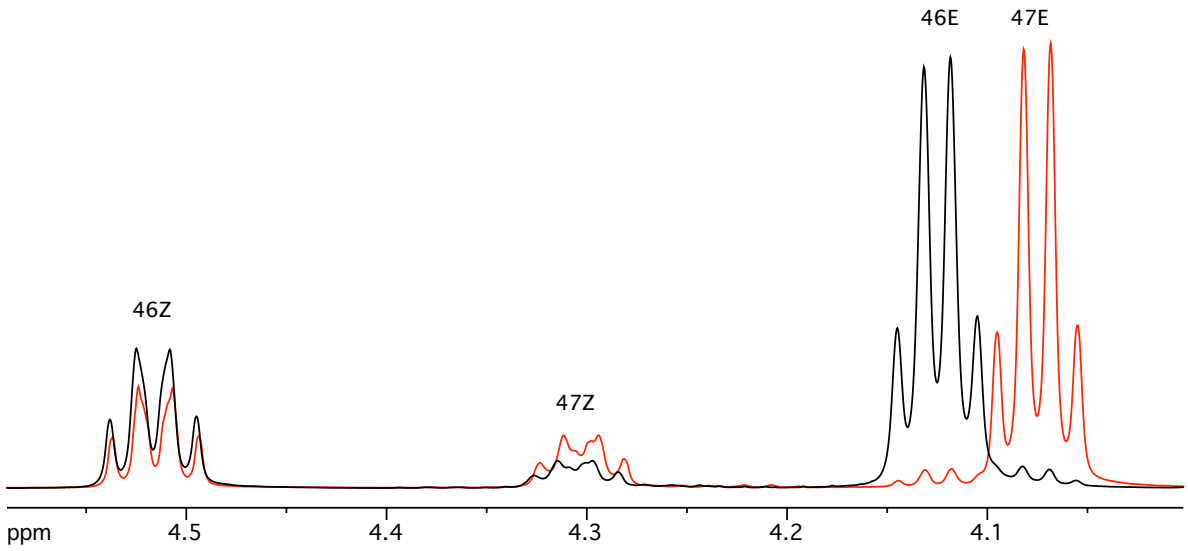
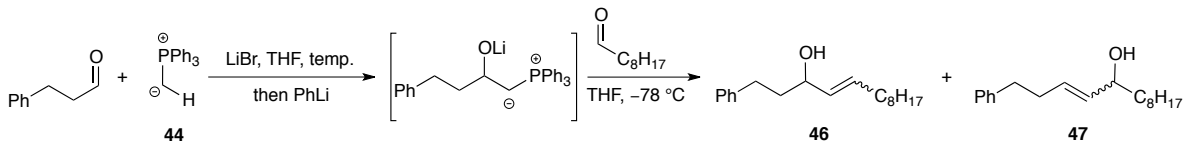


Figure 2.3 Superimposed ^{1}H NMR (500 MHz) spectra showing chemical shifts of C***H***(OH) protons of **46***E*, **46***Z*, **47***E* and **47***Z*.

The reverse order of addition of β-lithiooxy ylide to aldehyde, but now at 0 °C produced, a complex mixture of product along with impurities which was difficult to separate. Adding β-lithiooxy ylide to aldehyde at −90 °C, adding aldehyde to β-lithiooxy ylide at −90 °C, varying the equivalents of LiBr and electrophile added similarly gave a mixture of chromatographically inseparable isomers in various ratios, albeit most often with the desired *E*-allylic alcohol as the major component (Table 2.1).



Entry	temp. (°C)	LiBr (equiv)	Yield (%)	46*E*:46*Z*:47*E*:47*Z*[c]
1	-78	2	43	100:0:0:0
2[a]	**-78**	2	63	40:34:2:24
3[a]	**-90**	2	25	82:3:4:11
4	**-90**	2	50	36:36:4:24
5	-78	**4**	43	30:41:6:23
6	-78	**0**	61	36:32:5:27
7[b]	-78	2	56	51:33:0:16

[a] β-lithiooxy ylide added to aldehyde; aldehyde added to β-lithiooxy ylide for all other entries
[b] 1.5 equiv. nonanal used [c] *E*:*Z* ratios determined by ^{1}H NMR analysis of crude product

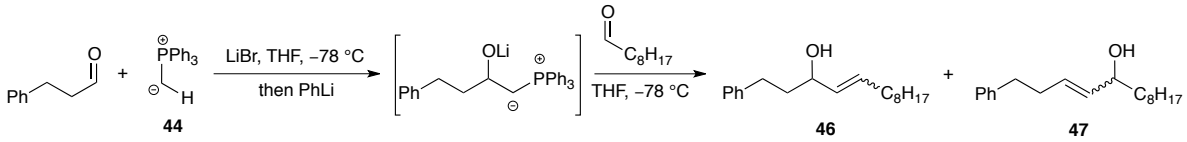
Table 2.1 Effect of varying experimental conditions in attempted optimisation of the synthesis of allylic alcohol **46**.

It was interesting to observe multiple C*H*(OH) peaks (see Figure 2.3) in the ^{1}H NMR spectrum for the purified product obtained form these experiments. These results suggest that the proposed directionof elimination of triphenylphosphine oxide[3b, 15c, 15e] (Scheme 1.23, p 17) may not be as well defined for methylenephosphorane compared with ethylene-phosphorane derived β,β'-di(lithiooxy)phosphonium adducts **35**. Corey and co-workers[15] contend that for maximum stereocontrol to achieved, attention needs to be paid to controlling the temperature of the reaction mixture at −78 °C when both aldehydes and PhLi are added. This is to ensure that the desired *racemic* β,β'-di(lithiooxy) species **35** (Scheme 1.23, p 17) prior to the elimination of Ph_3PO predominates.

In an effort to establish reproducibility, a repeat of the original reaction which furnished **46** (Scheme 1.28) as exclusively the desired isomer, rather perplexingly produced a mixture of stereo- and regioisomers. It was thought that adding reagents in a manner

which resulted in the temperature of the reaction not being controlled at the desired temperature of −78 °C might explain this outcome.

Using the original protocol, the temperature within the reaction vessel was carefully monitored during the entire course of the reaction. The outcome of this reaction was, unfortunately, also a mixture of stereo- and regioisomers (Table 2.2, entry 3). With this result in hand, a look at other conditions which might ensure that only one regioisomer and one stereoisomer be produced began.



44 46 47

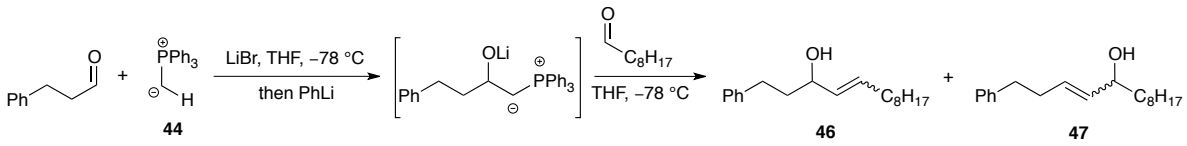
Entry	Yield (%)	46*E*:46*Z*:47*E*:47*Z*[d]
1[a]	43	100:0:0:0
2[b]	43	56:16:13:15
3[c]	41	37:27:9:27

[a] Using original protocol (Scheme 1.28)
[b] Repeat of entry 1 to establish reproducibility of results
[c] Repeat of entry 1 monitoring temperature in reaction vessel
[d] *E*:*Z* ratios determined by ^{1}H NMR analysis of crude product

Table 2.2 Effect of repeating original reaction in efforts to reproduce original result

The effect of varying the concentration of the reaction mixture was next examined to determine its effect on the yield of product and selectivity. The original protocol called for the addition of the first and second aldehydes (1.0 mmol and 1.05 mmol, respectively) as solutions in 10 mL and 5 mL THF, respectively. The reaction (Scheme 2.4) was repeated with the addition of both aldehydes as a less dilute solution in THF (0.5 mL THF/mmol aldehyde was used). Quenching the reaction mixture as per usual (2 h at −78 °C, warm to rt over 1 h, then 1 h at rt, then quenching with saturated aq. NH_4Cl) and after 2 hours after the addition of the second aldehyde at −78 °C showed no apparent difference in the ratios of the stereo- and regioisomers formed (Table 2.3, entries 1 and 2). These results suggest that the

stereochemistry of the β,β'-di(lithiooxy)phosphonium species **35** (Scheme 1.23, p 17) is 'set up' during this time (stirring for 2 h) at −78 °C and that elimination of Ph_3PO is slow, and warming to room temperature is necessary to effect complete elimination of Ph_3PO.



44 **46** **47**

Entry	Yield (%)	46*E*:46*Z*:47*E*:47*Z*[d]
1[a]	64	31:38:6:25
2[b]	38	32:36:5:27
3[c]	60	76:11:8:5

[a] Quench as per usual [b] Quench 2 h after E^+ added at −78 °C
[c] Warm cool cycle (−78 °C, rt., −78 °C)
[d] *E*:*Z* ratios determined by ^1H NMR analysis of crude product

Table 2.3 Effect of varying the concentration of the reaction mixture (addition of aldehydes as a less dilute solution in THF)

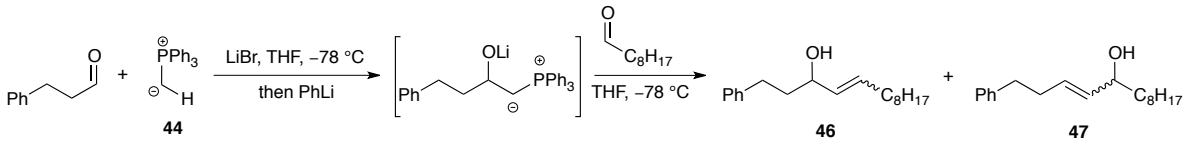
The effect of a warm-cool cycle (30 min at −78 °C, then temperature raised to room temperature over 15 min, then 30 min at room temperature, then cooled to −78 °C) after the generation of the β-lithiooxyphosphonium ylide was next looked at. Such a warm-cool cycle has been shown in the literature to be effective in increasing yield and/or stereoselectvity,[12f, 17] even when using methylenephosphorane.[17] Schlosser and co-workers[12f] posited that a warm-cool cycle allows for equilibration of any diastereomeric forms of β-lithiooxy-phosphonium ylides (diastereoisomers would result when initial phosphorane used is not methylidenephosphorane) (Scheme 1.23, p 17) formed, consequently ensuring the desired 'mode' of elimination of Ph_3PO occurs (Scheme 1.23). Table 2.3, entry 3 shows the effect such a warm-cool cycle has on our system. The yield remained unchanged, but, significantly, the proportion of the desired isomer increased at the expense of the *Z*-isomers of **46** and **47**.

Since it was shown that adding both aldehydes as a less dilute solution in THF (0.5 mL/mmol aldehyde instead of 10 mL/mmol first aldehyde and 5 mL/mmol second aldehyde) did not affect the ratio of the stereo- and regioisomers formed (but only slightly when a warm-cool cycle was used), a further examination of the effect of lowering the concentration of the reaction mixture even further was then done. Schlosser, *et al*.,[12f] in their studies of *trans*-selective Wittig reactions, used approximately 3.5 mL THF/mmol alkyltriphenylphosphorane used. Using this new combination [0.5 mL THF/mmol aldehyde, 3.5 mL THF/mmol Wittig reagent] and following the original experimental procedure had no effect on the yield of product (Table 2.4). More importantly, the ratio of the desired *E*-isomer increased significantly, but again, the original result of exclusively the desired isomer could not be obtained. However, using a warm-cool cycle along with a reduction in the volume of solvent used, pleasingly increased the ratio of the desired isomer: **46***E*:**46***Z*:**47***E*:**47***Z* **90**:4:4:2 (Table 2.4, entry 3).

The effect of adding *t*-BuOK was next examined. There is some literature precedence for the use of this reagent in the synthesis of allylic alcohols.[12f, 13] Schlosser and co-workers [12f, 13] assert that adding *t*-BuOK after the addition of the electrophile effects an exchange of O−Li for O−K, resulting in a freer O^- ion, which then facilitates oxaphosphetane formation, then elimination of Ph_3PO thereby maximising the yield of product. Using either 1 or 2 equivalents of *t*-BuOK was found to degrade stereoselectivity even though, adding 1 equivalent of this reagent at the end of the reaction increased the total yield of product to 70% (Table 2.4).

Using this new concentration, it was noticed that stirring became difficult when the salt prior to the formation of the β-lithiooxyphosphonium ylide by deprotonation with PhLi

was formed and achieving homogeneity of the reaction mixture was difficult, even with very vigorous stirring.



Entry	Yield (%)	46*E*:46*Z*:47*E*:47*Z*[e]
1[a]	52	70:11:11:8
2[a,b]	46	85:9:3:3
3[a,b]	**47**	**90:4:4:2**
4[a,b,c]	71	62:27:3:8
5[a,b,d]	32	81:13:3:3

[a] Quench as per usual [b] Warm cool cycle (−78 °C, rt., −78 °C)
[c] 1 equiv. *t*-BuOK added after electrophile [d] 2 equiv. *t*-BuOK added after electrophile
[e] *E*:*Z* ratios determined by ^{1}H NMR analysis of crude product

Table 2.4 Effect of varying the concentration of the reaction mixture (use of a more concentrated solution of phosphorane along with addition of aldehydes as a less dilute solution in THF)

At this stage, a repeat of the original experiment (Scheme 1.28) by the DPhil student who made the original observation of exclusively one isomer using methylenephosphorane, hydrocinnamaldehyde as the first aldehyde and nonanal as the second aldehyde also failed to replicate the original result. A mixture of chroamtographically inseparable isomers was obtained: desired product **46** *E*:*Z* 76:12; regioisomeric alcohol **47** *E*:*Z* 6:6 in 44% total yield. This result underlines the capricious nature of this reaction.

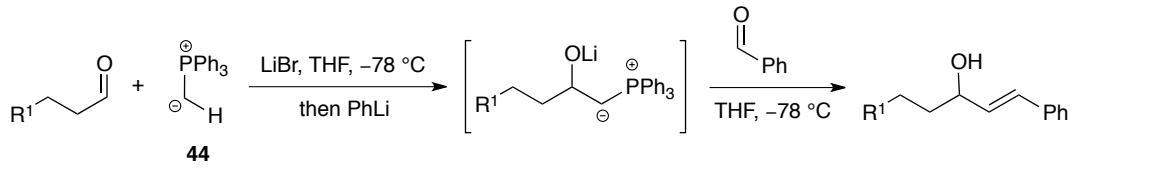
2.4 Synthesis of allylic alcohols

Determining the compatibility of various types of aldehyde electrophiles with these new conditions [which afforded the greatest proportion of the desired regioisomer **45***E* (Table 2.4, entry 3): 0.5 mL THF/mmol aldehyde, 3.5 mL THF/mmol Wittig reagent and

using a warm-cool cycle (30 min at −78 °C, then temperature raised to room temperature over 15 min, then 30 min at room temperature, then cooled to −78 °C)] was then carried out.

2.4.1 Using aromatic aldehydes as the second aldehyde

In examining the suitability of using these new reaction conditions, benzaldehyde was added to β-lithiooxy ylides prepared using an aliphatic aldehyde (nonanal) as well as an aliphatic aldehyde with a tethered aromatic substituent (hydrocinnamaldehyde). Pleasingly, the respective desired *E*-isomers, **48** and **49** were obtained exclusively, albeit in moderate yield (Scheme 2.6).



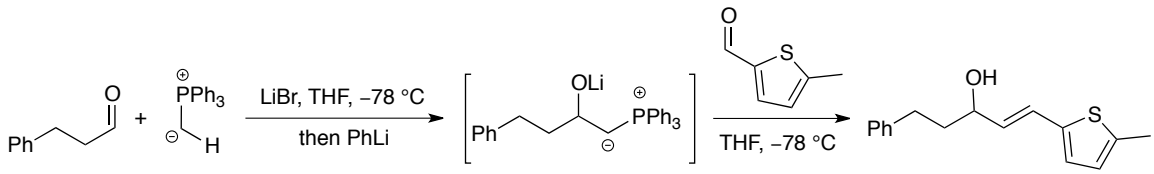
48: R^1 = *n*-hexyl, 46%, *E*:*Z* >99:1

49: R^1 = Ph, 41%, *E*:*Z* >99:1

Scheme 2.6

In order to account for this contrast in experimental outcomes, it was thought that developing conjugation between the C=C double bond formed and the aromatic substituent favours the regioselectivity in the elimination of Ph_3PO.

I then sought to investigate whether any difference in yield of product and/or selectivity would be observed using the above conditions [0.5 mL THF/mmol aldehyde, 3.5 mL THF/mmol Wittig reagent and a warm-cool cycle], compared to using 0.5 mL THF/ mmol aldehyde, 15 mL of THF/mmol Wittig reagent and no warm-cool cycle for a system employing an aromatic aldehyde (5-methylthiophene-2-carboxaldehyde) as the second aldehyde in the reaction sequence. These results are presented in Table 2.5 below.



44 **50**

Entry	Yield (%)	*E*:*Z*[d]
1[a]	60	>99:1
2[b]	57	>99:1
3[c]	57	>99:1

[a] 15 mL THF/ mmol Wittig reagent, 0.5 mL THF/mmol aldehyde, no warm-cool cycle

[b] 15 mL THF/ mmol Wittig reagent, 0.5 mL THF/mmol aldehyde, warm-cool cycle

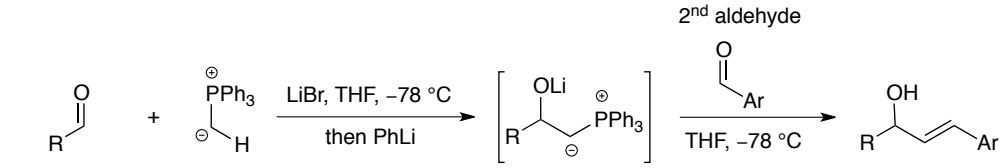
[c] 3.5 mL THF/mmol Wittig reagent, 0.5 mL THF/mmol aldehyde, warm-cool cycle

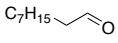
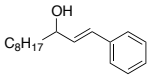
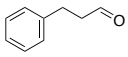
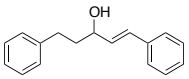
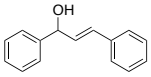
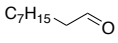
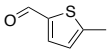
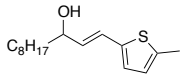
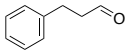
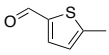
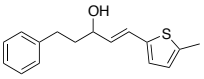
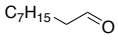
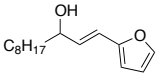
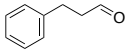
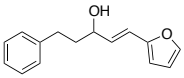
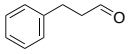
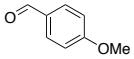
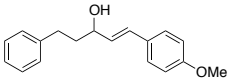
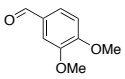
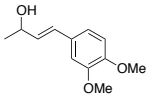
[d] *E*:*Z* ratios determined by ^{1}H NMR analysis of crude product

Table 2.5 Effect of varying the concentration of the reaction mixture and use of a warm-cool cycle using an aromatic second aldehyde.

These results suggested that stereoselectivity and yield are not altered for systems where an aromatic aldehyde is used as the second aldehyde in the reaction sequence when a warm-cool cycle and 3.5 mL THF/mmol Wittig reagent are used compared to when no warm-cool cycle and 15 mL THF/mmol Wittig reagent are used. Therefore, for simplicity of method, these further steps were not followed, and 15 mL THF was used in generating methylenephosphorane, and 0.5 mL THF per mmol aldehyde was used for all subsequent reactions due to the ease in obtaining homogeneity of the reaction mixture.

A range of allylic allylic alcohols, including a simple natural product **56** (entry 9) isolated from the rhizomes of *Zingiber cassumunar*,[26, 27] using aromatic aldehydes as the second aldehyde were synthesised (Table 2.6). These included heteroaromatic, substituted heteroaromatic and electron rich aromatic aldehydes.



Entry	1st aldehyde	2nd aldehyde	Product	Yield (%)b	
1				**48**	46
2				**49**	41
3				**51**	67
4				**52**	59
5				**50**	60
6				**53**	49
7				**54**	56
8				**55**	35
9				**56**	65

[a] *E*:*Z* ratios determined by ^{1}H NMR analysis of crude product [b] total yield of product after purification

Table 2.6 *E*-allylic alcohols from aromatic aldehydes

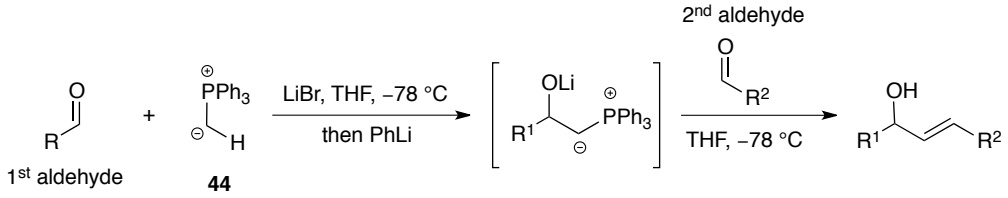
2.5 Probe into substrate influences on selectivity

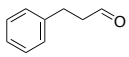
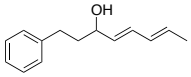
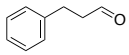
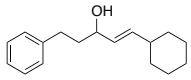
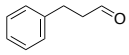
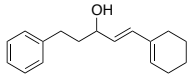
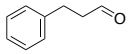
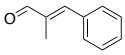
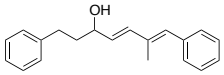
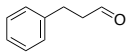
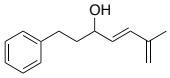
It was previously mentioned that developing conjugation between the C=C double bond formed with the aromatic system was considered to be a potential driving force for the regioselectivity in the formation of the desired *E*-isomer. To further examine this assumption, the effect of using aldehydes with α,β-unsaturation to trap β-lithiooxy-phosphonium ylides generated was studied.

2.5.1 Using α,β-unsaturated and branched α-aldehydes as the second aldehyde

Using crotonaldehyde, a simple α,β-unsaturated aldehyde, (Table 2.7, entry 1) curiously resulted in the formation of a mixture of chromatographically inseparable stereo-isomers. In this case, the newly formed C=C double bond was generated by elimination involving exclusively the oxygen originating from the second aldehyde used in the sequence. This result suggests that α,β-unsaturation is necessary to ensure complete regio-selectivity in the elimination of Ph_3PO in the desired direction, but is not sufficient, in itself, to ensure high *E*-stereoselectivity.

Using an α-branched aldehyde, cyclohexane carboxaldehyde, (Table 2.7, entry 2), was similarly *E*-stereoselective, but was only 90% regioselective. This result suggests that α-branching in the second aldehyde favours the formation of *E*-isomers. Using α-branched-α,β-unsaturated aldehydes produced exclusively the desired *E*-allylic alcohol, albeit, in moderate yields (Table 2.7, entries 3-5). The combination of a substituent in the α-position together with α,β-unsaturation appears key for maximum regio- and stereoselectivity. This chemistry provides a convenient entry to dienols, such as a functionalised isoprene unit **61**, which are potentially useful in cycloadditions.[28]



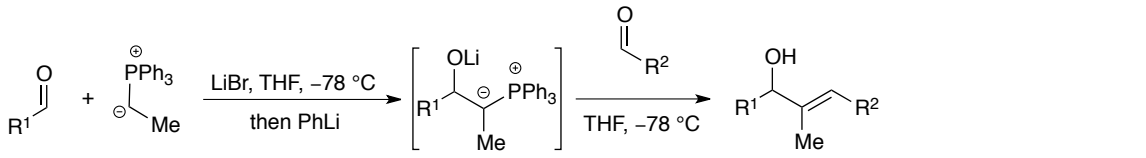
Entry	1st aldehyde	2nd aldehyde	Product	Yield (%)[a]		*E*:*Z*[b]
1				**57**	51	81:19
2				**58**	42	90:0[c]
3				**59**	44	>99:1
4				**60**	39	>99:1
5				**61**	63	>99:1

[a] total isolated yield of product after purification. [b] *E*:*Z* ratios determined by ^{1}H NMR analysis of crude product.
[c] 10:0 *E*/*Z* regioisomeric alcohol also found.

Table 2.7 Allylic alcohols from α,β-unsaturated and α-branched aldehydes

2.6 Using aliphatic aldehydes as the second aldehyde

As previously mentioned, Corey and Yamamoto[15c] were able to achieve the formation of one isomer, the desired *E*-isomer, using ethylidenetriphenylphosphorane and an aliphatic aldehyde as the second aldehyde in the reaction sequence (Scheme 1.19). These reactions were repeated, using nonanal and acetaldehyde, as a check of our experimental procedure (Scheme 2.7). The outcome of these experiments was in complete accordance with Corey and Yamamoto's initial report.

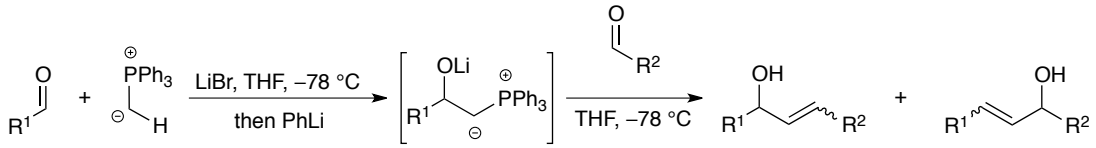


62: $R^1 = CH_3$, R^2 = *n*-octyl, 58%, *E*:*Z* >99:1

63: R^1 = *n*-octyl, $R^2 = CH_3$, 63%, *E*:*Z* >99:1

Scheme 2.7 Reaction of two aliphatic aldehydes and ethylenephosphorane

On the other hand, using methylenetriphenylphosphorane, acetaldehyde and nonanal produced alcohols **64** and **65** as a mixture of chromatographically inseparable isomers in similar yield (Scheme 2.8). These results seem to support Schlosser and Coffinet's[19] earlier assumptions regarding the lower stereoselectivity seen when using methylenetriphenyl-phosphorane as the Wittig reagent. These results also indicate that alkyl substitution on the phosphorane used has a significant influence on the reaction pathway from β-lithiooxy ylide to allylic alcohol.



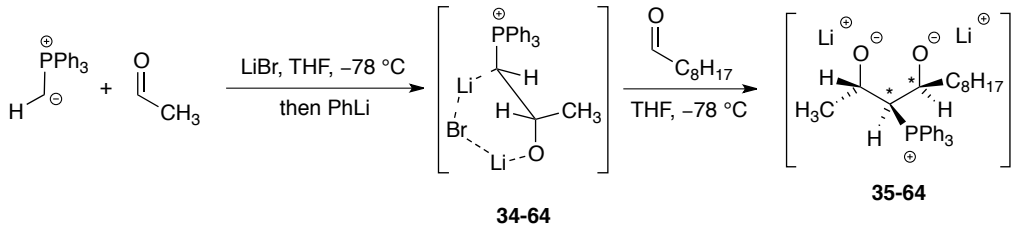
64 **65**

$R^1 = CH_3$, R^2 = *n*-octyl
55%, **64***E*:**64***Z*:**65***E*:**65***Z* 60:33:0:7

R^1 = *n*-octyl, $R^2 = CH_3$
58%, **65***E*:**65***Z*:**64***E*:**64***Z* 46:13:4:37

Scheme 2.8 Reaction of two aliphatic aldehydes and methylenephosphorane

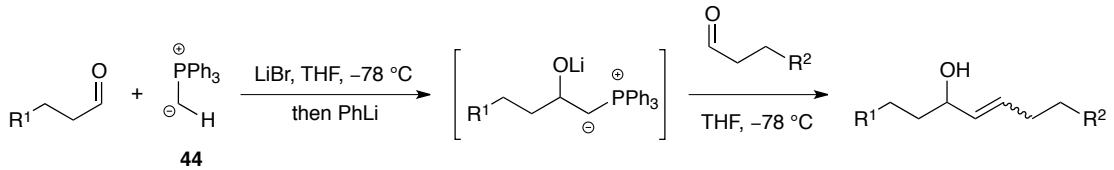
These results (Scheme 2.8) indicate that the aliphatic aldehyde chain length influences regio- and stereoselectivity. For methylenephosphorane with longer chain aliphatic aldehyde and short chain aliphatic second aldehyde, *Z*-elimination is favoured to a greater extent compared to using a shorter chain first aldehyde. This is indicative of a poor diastereoisomeric ratio (at both positions marked '*') of β,β'-di(lithiooxy) phosphonium intermediate **35-64** (Scheme 2.9) which favours *Z*-elimination to furnish the *Z*-regioisomeric allylic alcohols.



Scheme 2.9

Using a shorter chain aliphatic aldehyde as the first aldehyde favours *E*-elimination to a greater extent, as well as elimination in the desired direction compared to using a longer chain aliphatic first aldehyde. Using hydrocinnamaldehyde as the first aldehyde and a long chain aliphatic second aldehyde (in the synthesis of **46**), likewise favours *E*-elimination as well as elimination in the desired direction, but the proportion of *E*-isomer (from elimination in the desired direction) is almost always higher than the *Z*-isomer (from elimination in the desired direction). This is possibly due to a remote effect by the phenyl group which influences regio- and stereoselectivity. These results suggest that stereo-selectivity depends on the nature of both the first and second aldehydes used in the reaction sequence.

Using this method and methylenephosphorane to synthesise symmetric disubstituted allylic alcohols produced a chromatographically inseparable mixture of the *E*- and *Z*-isomers (Scheme 2.10). The presence of the phenyl substituents of the aldehyde used to make allylic alcohol **67** appears to, again, influence the selectivity.



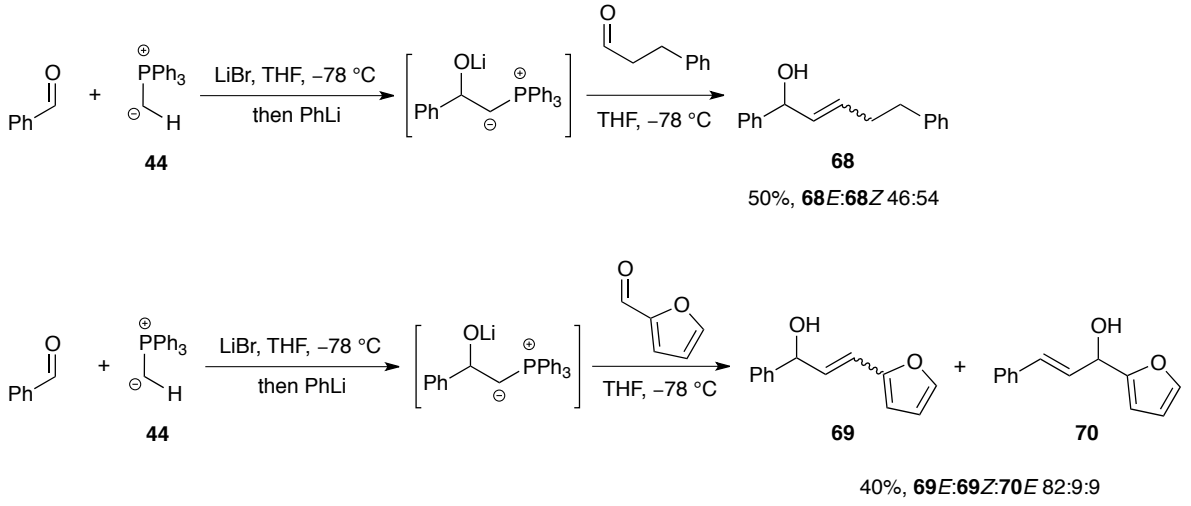
66: $R^1 = R^2 =$ *n*-hexyl, 52%, *E*:*Z* 64:36

67: $R^1 = R^2 =$ Ph, 55%, *E*:*Z* 82:18

Scheme 2.10 Synthesis of symmetric disubstituted allylic alcohols

2.7 Using aromatic aldehydes as the first aldehyde

Interestingly, using benzaldehyde as the first aldehyde and hydrocinnamaldehyde as the second aldehyde in the reaction sequence resulted in the formation of a stereoisomeric mixture of allylic alcohol **68**, with moderate *Z*-selectivity (Scheme 2.11). When benzaldehyde was used first then furfuraldehyde, a mixture of regio- and stereoisomers **69** and **70** was also formed but with greater *E*-selectivity to furnish the desired isomer (Scheme 2.11). It seems that using an aromatic aldehyde as the first aldehyde results in the formation of an isomeric mixture of product, but using an aromatic second aldehyde compared to using an aliphatic second aldehyde (with tethered aromatic substituent) favours formation of the desired *E*-isomer to a greater extent.



Scheme 2.11 Reactions using benzaldehyde as the first aldehyde

It is unclear why a chromatographically inseparable mixture of regio- and stereoisomers was formed when benzaldehyde and furfural were used in the synthesis of alcohol **69**, but this result helps to confirm that stereoselectivity depends on the nature of both the first and second aldehyde used in the reaction sequence. In hindsight, the result of the reaction using methylenephosphorane and furfuraldehyde first, then benzaldehyde after

β-lithiooxy ylide formation (in the synthesis of allylic alcohol **70**) would have been useful for a comparison.

The results presented in this chapter bring into question the mode of elimination of triphenylphosphine oxide previously proposed[3b,15c,15e] (Scheme 1.23, p 17) and suggest that it is not as well defined for methylenephosphorane derived β,β'-di(lithiooxy) phosphonium species of type **35** as it is for ethylenephosphorane derived β,β'-di(lithiooxy) phosphonium species (Scheme 1.23, p 17). Our results show that there is competition between the different modes of elimination of Ph_3PO but the 'desired' mode is still predominant when methylenetriphenylphosphorane (R^2 = H, Scheme 1.23) is used as the Wittig reagent, as opposed to when a more substituted Wittig reagent (R^2 = Me, Scheme 1.23) is used when complete stereocontrol in the elimination of Ph_3PO is observed. Maryanoff *et al*.[3b] along with Speziale and Bissing[29] have discussed the the preference for *E*-isomer formation in terms of a competitive reversible dissociation between β,β'-di(lithiooxy) phosphonium adduct of type **35**, and β-lithiooxy ylide and aldehyde which lends some measure of thermodynamic control to the reaction when aromatic aldehydes are used as the second aldehyde. Whereas, there is no reversibility when saturated aliphatic aldehydes are used.

Work done by Vedejs *et al*.[30] and Anderson and Henrick[31] support this postulate of competitive reversibility when using aromatic aldehydes as the second aldehyde in the reaction sequence. From our results, we believe that competitive reversibility- between β,β'-di(lithiooxy) phosphonium species **35**, and β-lithiooxy ylide and the second aldehyde (aromatic or α,β-unsaturated) used in the reaction sequence- together with the steric influences of α-branching in the second aldehyde used in the reaction sequence are likely important contributing factors toward ensuring maximum selectivity.

2.8 Summary and conclusions

The synthetic method described to produce disubstituted *E*-allylic alcohols in this Chapter is a very straightforward one-pot operation involving the use of widely commercially and economically available starting materials. Stereoselectivity was found to depend on the nature of both the first and second aldehydes used in the reaction sequence with preferential *syn*-elimination of Ph_3PO involving the loss of the oxygen from the second aldehyde used in the reaction sequence. *Syn*-elimination involving loss of the oxygen from the first aldehyde used in the reaction sequence leading to *Z*-stereochemistry is thought to be a process involving a higher energy transition state.

Using an aromatic aldehyde or an α-branched-α,β-unsaturated aldehyde as the second aldehyde in the sequence is robust in ensuring maximum *E*-stereoselectivity and produces one isomer in reasonable yield. The only case when use of these aldehydes as the second aldehyde in the reaction sequence fail to give a single regioisomer is when an aromatic aldehyde is also used as the first aldehyde. In that case, reduced stereoselectivity and a slight loss in regioselectivity are observed.

With two aliphatic aldehydes used as both the first and second aldehydes, the regio- and stereochemical outcome of the reaction is very sensitive to changes in experimental conditions, with reproducibility under seemingly the same conditions being difficult. This class of aldehyde-aldehyde coupling is also sensitive to minor structural variations in the aldehyde. A β-phenyl substituent on the first aldehyde seems to favour the desired regio- and stereoisomer. A short chain aliphatic first aldehyde seems to favour the desired stereochemical course of elimination, while a longer chain first aldehyde seems to favour *E*-elimination the least to give a considerable proportion of the regioisomeric *Z*-allylic alcohols.

α-Branching in conjunction with α,β-unsaturation is key to obtaining one isomer. Substituents on the aromatic ring of the second aldehyde used in the reaction sequence do not affect stereoselectivity. Using an aldehyde with a phenyl substituent further away from the carbonyl functionality, in the β-position, as the first aldehyde used in the reaction sequence (with aliphatic second aldehyde) favours the formation of the desired *E*-isomer to a greater extent, compared to when benzaldehyde is used as the first aldehyde (with aliphatic second aldehyde) when the greater proportion of isomer formed is the *Z*-isomer.

Chapter 3: Studies toward the synthesis of chiral disubstituted *E*-allylic alcohols *via* β-lithiooxyphosphonium ylides

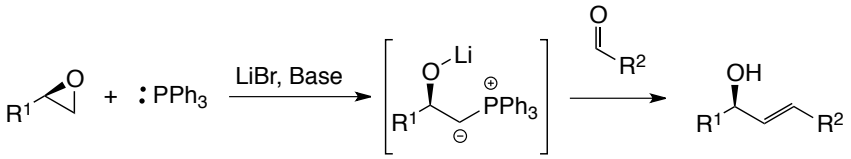
This chapter details my studies toward the synthesis of enantiomerically pure 1,2-disubstituted *E*-allylic alcohols *via* a Wittig-like olefination in which β-lithiooxy-phosphonium ylides, generated by the nucleophilic ring-opening of a terminal epoxide with triphenylphosphine, are trapped with an aldehyde substrate. Three routes for the synthesis of chiral *trans*-1,2-disubstituted allylic alcohols were investigated:

- Lewis acid-promoted ring-opening of a terminal epoxide by triphenylphosphine.
- The ring-opening of α-lithiated terminal epoxides using triphenylphosphine, using LTMP as lithiating agent.
- The ring-opening of α-lithiated terminal epoxides using triphenylphosphine, using organolithiums as lithiating agents.
- A fourth conceptualised method was briefly investigated, and entailed using the experimental procedure outlined in the previous Chapter, with the addition of a chiral, non-racemic ligand to the reaction mixture.

Of the methods requiring an epoxide starting material, only the second showed promise. The fourth method necessitates further work, but also showed promise.

3.1 Lewis acid-promoted ring-opening of a terminal epoxide by triphenylphosphine

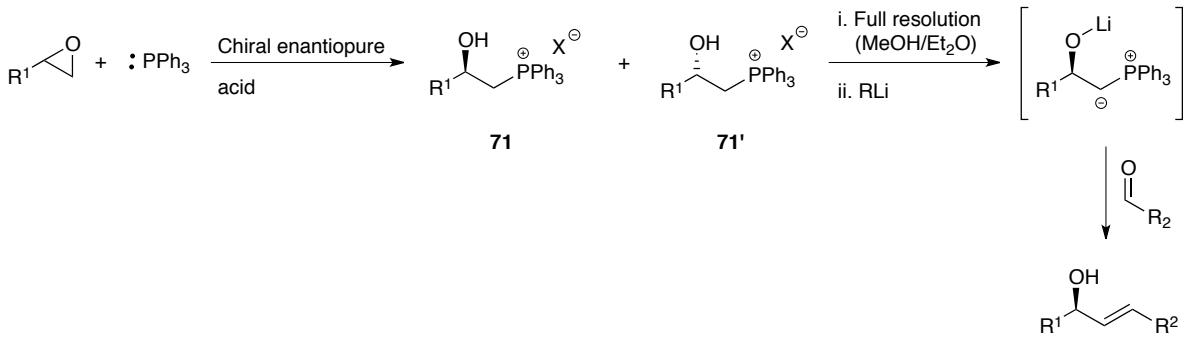
Enantiomerically pure allylic alcohols are important structural motifs found in many natural products and they have versatile utility.[3, 4] There are several methods available to synthesize such systems in good yield and in good to excellent optical purity.[18, 23, 32, 33] We envisaged a one-pot means of accessing allylic alcohols from a terminal epoxide (and ultimately, an enantiopure terminal epoxide) and an aldehyde. The method would use PPh_3 to ring-open the epoxide as an approach to the β-lithiooxy ylide intermediate (Scheme 3.1).



Scheme 3.1

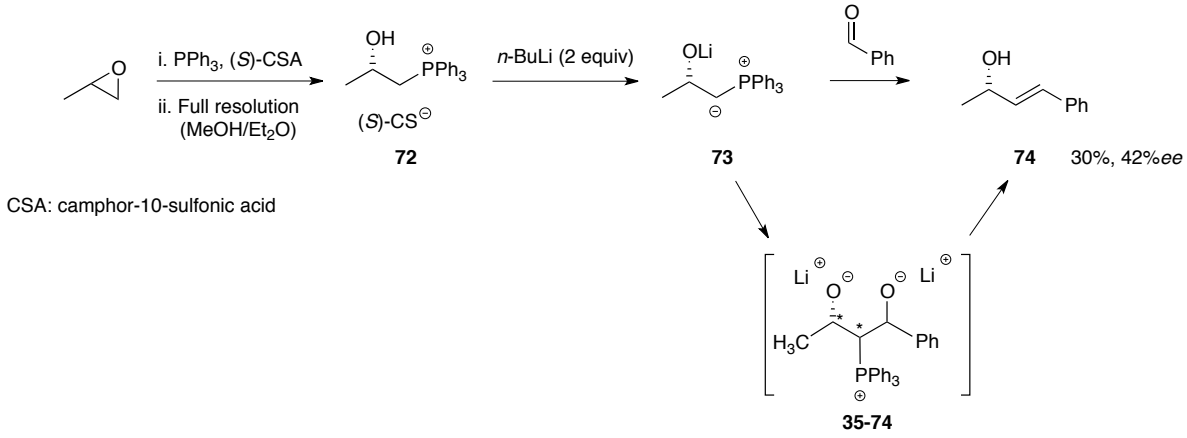
3.1.1 Background

Okuma *et al.*[23i, 34] and Kubota and Yamamoto[23h] have previously synthesised optically active *E*-allylic alcohols in good yield and optical purity using a terminal epoxide and PPh_3 as starting materials. The method used by Okuma and co-workers[23i, 34] was a two-step process (Scheme 3.2). Resolution of the diastereomeric hydroxyphosphonium salts **71** and **71′**, produced from the ring-opening of a terminal epoxide by triphenylphosphine in the presence of chiral enantiopure acid, was necessary prior to the formation of the optically active allylic alcohol.



Scheme 3.2

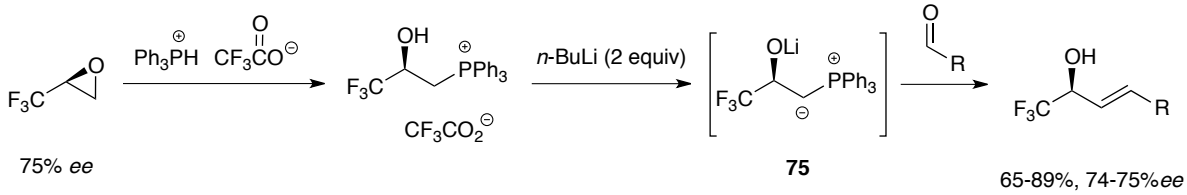
Using this method, Okuma and co-workers[23*i*, 34] synthesised allylic alcohol **74** in moderate yield and optical purity (Scheme 3.3). These researchers posited that the loss of optical purity observed might have occurred before the formation of olefinic product in a reversible retro-Wittig reaction (at positions marked *, **35-74**) before the oxaphosphetane derived from the β-lithiooxyphosphonium ylide **73** and benzaldehyde decomposed to give product and Ph_3PO.



Scheme 3.3

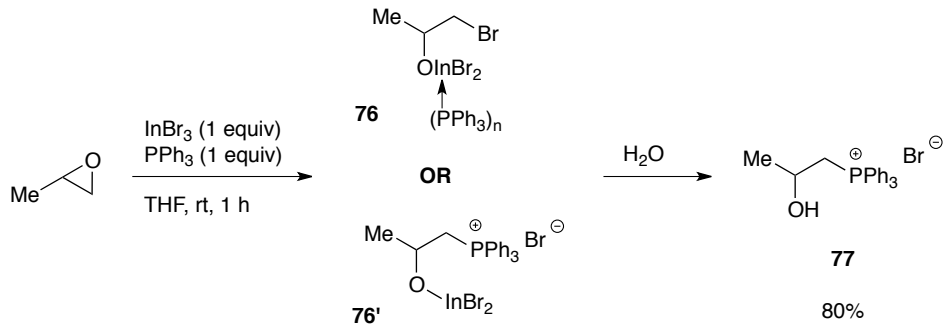
Kubota and Yamamoto[23*h*], on the other hand, used chiral, non-racemic trifluoropropene oxide (75% *ee*) in their synthesis of chiral allylic alcohols (Scheme 3.4). These workers obtained markedly better yields but varying *E*:*Z* selectivity, which depended on the type of aldehyde used to trap the β-lithiooxy ylide formed. In contrast to the results reported by Okuma and co-workers,[23*i*, 34] no degradation in optical purity was reported by

these researchers. With benzaldehyde to trap the trifluoromethylated β-lithiooxy ylide intermediate **75**, these researchers reported the formation of only the *trans*-trifluoromethylated allylic alcohol. Using aliphatic and α,β-unsaturated aldehydes resulted predominantly in the formation of *trans*-isomers.



Scheme 3.4

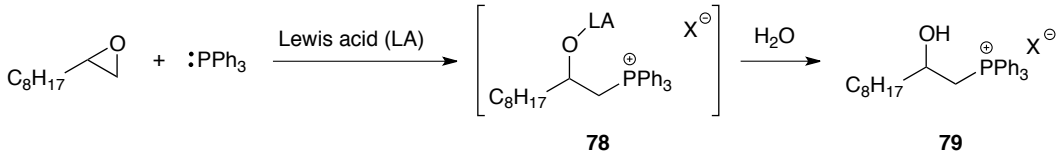
A search of the literature revealed one reaction which was very similar to our planned route of using triphenylphosphine to open the ring of a terminal epoxide in the presence of a Lewis acid. Recently, Shibata *et al.*[35] accomplished the synthesis of hydroxyphosphonium bromide salt **77** in 80% isolated yield (Scheme 3.5). However, no further chemistry was carried using **77** as an olefinating reagent by these workers. Shibata and co-workers proposed that alcohol **77** may be formed *via* one of the two intermediates **76** or **76′** using this metal-mediated pathway. Their studies on the $InBr_3$-catalysed formation of cyclic carbonates from epoxides and CO_2 led them to propose these two structures as intermediates by which product could be derived. However, it seems unlikely that hydroxyphosphonium bromide **77** would be formed via **76** as only 1 equivalent PPh_3 was reported to be used in this reaction.



Scheme 3.5 Synthesis of hydroxyphosphonium bromide **77** by Shibata *et al*.[35]

3.1.2 Findings

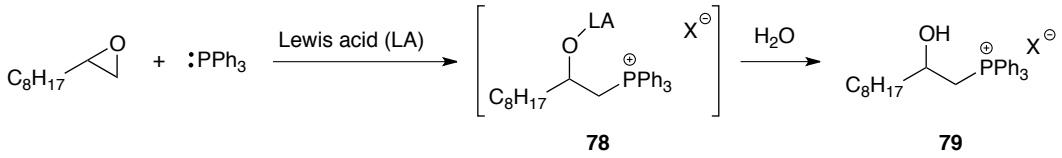
My investigations into this route began with an examination of the suitability of various Lewis acids to aid in ring-opening of 1,2-epoxydecane (Scheme 3.6). To a solution of the epoxide under an inert atmosphere of nitrogen, was added the Lewis acid and the mixture was stirred for 10 min. A solution of PPh_3 (2 equiv) was was then added and the mixture stirred. This mixture was then quenched with saturated aq. ammonium chloride.



Scheme 3.6

The suitability of various Lewis acids (excess LiBr, LiBr with TMSCl, $BF_3.OEt_2$, $TiCl_4$, $AlCl_3$, $FeCl_3$), solvents (THF, toluene) and reaction temperatures were investigated (Table 3.1). Completion of the reaction was determined from the absence of the starting epoxide by TLC analysis of the reaction mixture prior to quenching. Only in the cases where $BF_3.OEt_2$, $TiCl_4$ or $AlCl_3$ were used was the starting epoxide consumed. By ^1H NMR analysis of the crude material, no olefinic protons were observed, indicating that 1-decene was not formed by elimination of Ph_3PO from intermediate **78**. Low resolution mass spectral spectral analysis was used as a means of confirmation of product formation. By

mass spectral analysis, a mass [*m*/*z* 491.19 (85%, M−X)] consistent with the mass of alcohol **79**, less the mass of the halide ion was observed in the instances indicated.



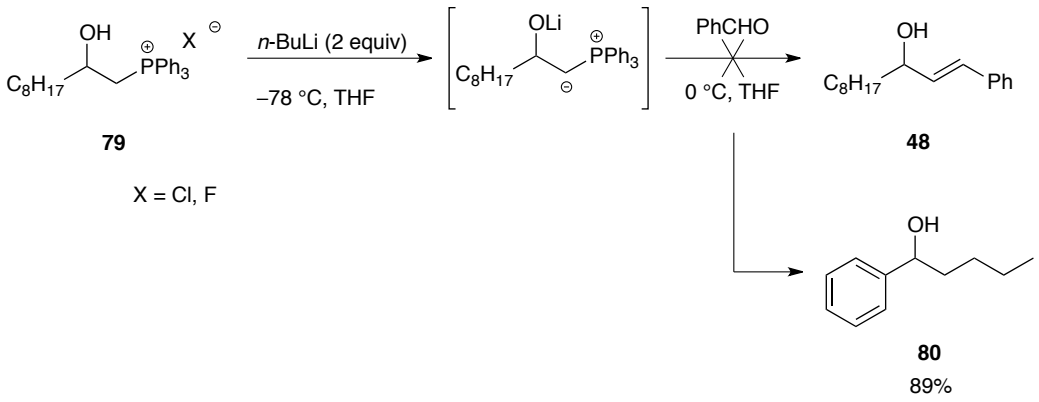
78 **79**

Entry	Lewis acid	Temp (°C)	Solvent	Yield (%)[a]	Comments
1	LiBr (2 equiv)	reflux (4 d)	THF	-	Starting material by TLC
2	TMSCl (1 equiv), LiBr (2 equiv)	reflux (4 d)	THF	-	Starting material by TLC
3	$BF_3.Et_2O$ (1 equiv)	rt (1 h)	Toluene	99%	No decene from ^1H NMR. LRMS (ESI+) found mass consistent with (M−F)
4	$TiCl_4$ (1 equiv)	rt (1 h)	Toluene	97%	^1H, ^{13}C spectra seem to match with with product of entry 3. M−Cl does not appear in LRMS
5	$AlCl_3$ (1 equiv)	rt (24 h)	Toluene	99%	No decene from ^1H NMR. LRMS (ESI+) found mass consistent with (M−Cl)
6	$AlCl_3$ (1 equiv)	rt (24 h)	THF	99%	No decene from ^1H NMR. LRMS (ESI+) found mass consistent with (M−Cl)
7	$FeCl_3$ (1 equiv)	rt (48 h)	Toluene	-	Starting material by TLC
8	$FeCl_3$ (1 equiv)	rt (48 h)	THF	-	Starting material by TLC

[a] yield of crude material

Table 3.1

The presumed hydroxyphosphonium salts **79** formed were then subjected to deprotonation using an organolithium and subsequent aldehyde addition (Scheme 3.7). The methodology used by Okuma *et al*.[23i] was employed: *n*-BuLi (2 equiv) was added dropwise to a solution of the hydroxyphosphonium salt in THF at −78 °C. A solution of the aldehyde in THF was then added after 1 h at 0 °C.

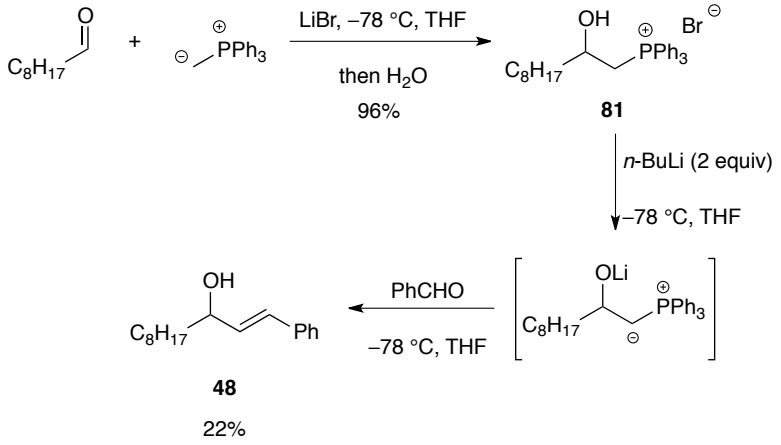


Scheme 3.7

No product, allylic alcohol **48**, was obtained. Instead, alcohol **80**, formed *via* nucleophilic addition of *n*-BuLi to benzaldehyde was formed, in 89% yield. By TLC analysis of the crude reaction product, neither 1-decene nor Ph_3PO was observed indicating that the β-lithiooxyphosphonium species formed as a result of mono-deprotonation of alcohol **79** by *n*-BuLi may not have decomposed by simple Wittig elimination.

In order to determine whether the hydroxyphosphonium bromide salts were indeed being formed using the three Lewis acids ($BF_3.OEt_2$, $TiCl_4$, $AlCl_3$), hydroxyphosphonium bromide **81** was synthesised following the methodology previously described in Chapter 2 (Scheme 3.8), a method which is known to generate species of this type, as a check. To a solution of anhydrous LiBr and methyltriphenylphosphonium bromide in THF at −78 °C, was added *n*-BuLi. This mixture was stirred for 30 min at rt to give a yellow solution of methylenephosphorane. This mixture was then re-cooled to −78 °C, then a solution of nonanal in THF added. After 20 min at this temperature, the mixture was quenched with saturated aq. ammonium chloride. This method afforded 96% product which contained only minor impurities by ^1H NMR analysis. This salt was then subjected to methodology used by Okuma *et al.*[23i] (double-deprotonation using *n*-BuLi to form the corresponding β-lithiooxy ylide, to which a solution of benzaldehyde was then added) to produce allylic alcohol **48**. In contrast to using the presumed hydroxyphosphonium bromide salts **79** (Scheme 3.7), *E*-

allylic alcohol **48** was obtained using **81**, albeit only in a moderate 22% yield (Scheme 3.8). By ^{1}H NMR analysis of the crude reaction product, neither decene nor any other side-products could be discerned.



Scheme 3.8

This result suggests that formation of allylic alcohols via β-lithiooxyphosphonium ylides using the one-pot method developed in Chapter 2 (p 38) is a better way of accessing these systems. The hydroxyphosphonium bromide salt **81** was dried under high vacuum (~1 mbar) for ~4 h prior to using, and not by azeotropic distillation as was carried out in many previous investigations [23] using hydroxyphosphonium halide salts in the synthesis of allylic alcohols, which may have affected the yield.

Upon comparing the ^{1}H NMR spectra of **81** and the presumed hydroxyphosphonium halide salts **79** made using $BF_3.OEt_2$, $TiCl_4$, $AlCl_3$, it was noticed that they did not match, except for the aliphatic protons of the octyl substituent and aromatic protons of the triphenyl substituent. A multiplet at 4.20-3.15 ppm, integrating to 2 H, was present in the ^{1}H NMR spectra in all of the three presumed hydroxyphosphonium halide salts **79**. Analysis of the three presumed hydroxyphosphonium halide salts **79** by IR spectroscopy showed a broad, weak peak at 3458 cm^{-1} and 3432 cm^{-1}, indicative of an alcohol substituent for the presumed hydroxyphosphonium chloride (from $AlCl_3$) and the presumed hydroxyphosphonium

fluoride salts respectively. This observation seems to suggest that nucleophilic attack by PPh_3 may have occurred, instead, at the internal, more substituted carbon of the oxirane ring to form the primary hydroxyphosphonium species.

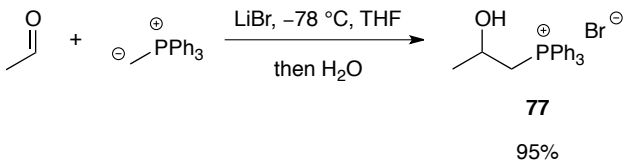
3.1.2.1 Using $InBr_3$

My attention then turned to the recent work carried out by Shibata *et al*.[35] (Scheme 3.5). Initially, repeating this reaction following the experimental procedure given by these researchers proved unsuccessful. A low yield (43%) of crude material was obtained and by ^1H NMR analysis, PPh_3 was seen to be present. Also, only some of the ^1H chemical shifts of remainder of the material matched the data reported by these researchers. Additionally, numerous other unidentifiable peaks were observed in the ^1H NMR spectrum of this material. The reason for this poor result was thought to be due to the quality of the $InBr_3$ used, which was slightly discoloured. Prior to use, the salt was dried under vacuum (~1 mbar) overnight (~12 h).

This reaction was then repeated using fresh anhydrous $InBr_3$ (reagent contained in an ampoule which was opened immediately prior to use under a flow of argon, then subsequently stored under argon), on three separate occasions. Again, the reported result could not be reproduced in my hands. The highest total yield of crude material obtained, which included unreacted PPh_3, was only 46%. After stirring the reaction mixture for the prescribed 1 h at room temperature (20 °C), the presence of PPh_3 was indicated by TLC analysis. Its presence was detected even after stirring the reaction mixture overnight (~16 h). Additionally, only some of the minor peaks in the ^1H NMR spectrum of the crude material matched the literature data (Table 3.2). Also, numerous other unidentifiable impurity peaks were present in the ^1H NMR spectrum of the crude product.

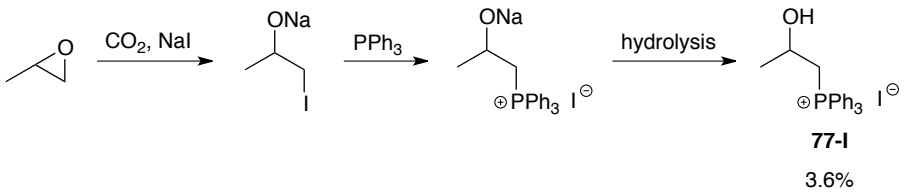
Contact was then made with the original authors asking for any additional details about the experimental procedure which might have enabled me to repeat the reported outcome of the reaction. However, none was given, except that this reaction was carried out in the summer/autumn period in which temperatures were about 25-30 °C.

Hydroxyphosphonium bromide **77** was then made following the methodology used to prepare **81**, outlined in Scheme 3.8, from methylenephosphorane and acetaldehyde (Scheme 3.9). This method afforded 95% product which contained only minor impurities. The ^{1}H NMR spectrum of this material, however, did not match the reported literature data (Table 3.2).[35]



Scheme 3.9 Synthesis of hydroxyphosphonium bromide salt using methylenephosphorane

The corresponding iodide salt **77-I** was previously made by Huang and Shi,[36] in 3.6% yield (Scheme 3.10).



Scheme 3.10

A comparison of the reported ^{1}H NMR data by Shibata and co-workers, the data of the product obtained using Shibata's reported method, the method outlined in Scheme 3.9 and the reported data of **77-I** are presented below.

Assignment	**77-I** (300 MHz, $CDCl_3$)	**77 (reported)**	**77 (Scheme 3.9)** (400 MHz, $CDCl_3$)
CH_3	1.51 (3 H, dd, *J* = 5.7, 2.4)	1.51 (3 H, dd, *J* = 5.84, 2.67)	1.43 (3 H, dd, *J* = 6.1, 2.5)
CH_aH_b	3.46 (1 H, ddd, *J* = 15.3, 12.6, 2.7)	3.24 (1 H, ddd, *J* = 15.63, 12.70, 2.93)	3.24−3.11 (1 H, m)
CH_aH_b	3.81 (1 H, ddd, *J* = 21.0, 15.3, 10.5)	3.45 (1 H, ddd, *J* = 15.63, 10.74, 10.74)	3.86 (1 H, dt, *J* = 15.4, 10.6)
CH	4.33−4.20 (1 H, m)	4.22 (1 H, m)	4.20−4.05 (1 H, m)
OH	4.05 (1 H, d, *J* = 6.6)	2.23 (1 H, m)	5.63 (1 H, d, *J* = 7.1)
Ph	7.83−7.64 (15 H, m)	7.90−7.60 (15 H, m)	7.79−7.51 (15 H, m)

Table 3.2: Comparison of ^{1}H NMR chemical shifts of hydroxyphosphonium bromide and iodide salts

The areas of difference in ^{1}H spectral data for product obtained following the method reported by Shibata and co-workers and that reported by these researchers are:

^{1}H (400 MHz) δ = 4.98 (1 H, d, *J* = 6.3), 3.88 (1 H, dt, *J* = 15.3, 10.5), 3.44−3.33 (0.5 H, m), 2.29 (0.2 H, dt, *J* = 6.6, 1.9), 1.46 (3 H, dd, *J* = 6.2, 2.7).

Inaccurate recording of the data could possibly account for the discrepancies between the ^{1}H NMR data reported by Shibata and co-workers and the data obtained by myself. No further contact was made with Shibata and co-workers about these differences in ^{1}H NMR data.

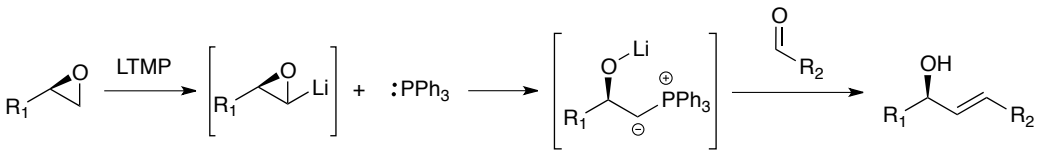
3.1.3 Summary and conclusions

The results presented in this section indicate that the Lewis acid mediated ring-opening of terminal epoxides does not result in the formation of the desired secondary hydroxyphosphonium intermediate. Instead, ring-opening at the more substituted carbon of the oxirane ring seems to have occurred using $AlCl_3$ and $BF_3.OEt_2$. Use of $InBr_3$ seems to

result in the formation of the desired secondary hydroxyphosphonium intermediate. However, this method is low yielding and the product formed is highly impure. Further investigations into this route were therefore abandoned.

3.2 Ring-opening of α-lithiated terminal epoxides using triphenylphosphine, use of LTMP as lithiating agent

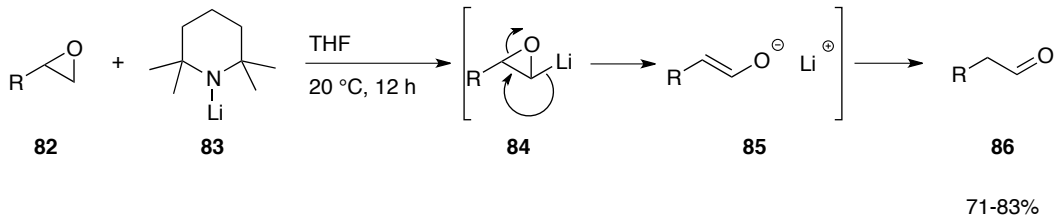
The second of the routes envisaged to chiral *E*-allylic alcohols involved the use of triphenylphosphine to ring-open α-lithiated terminal epoxides to form β-lithiooxy-phosphonium ylides to which aldehyde electrophiles would then be added (Scheme 3.11). Conceptually, this route was considered a more attractive way into chiral allylic alcohols than the route presented in the previous section (Scheme 3.1), as the β-lithiooxy-phosphonium ylides are formed from epoxides *in situ*.



Scheme 3.11

3.2.1 Previous work on lithiation of terminal epoxides using lithium amides

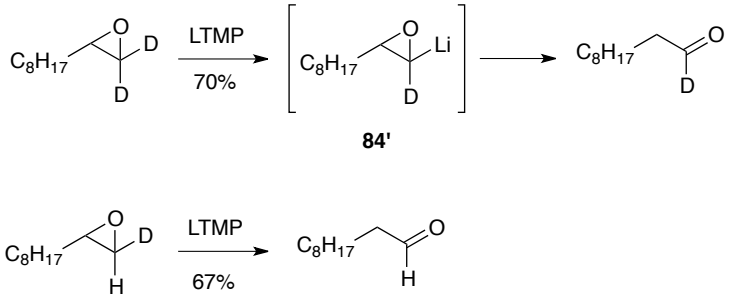
In 1994, Yamamoto *et al*,[37] reported very selective and high-yielding isomerisations of terminal epoxides **82** to aldehydes **86** using sterically hindered lithium amides. This was observed particularly with the use of lithium 2,2,6,6-tetramethylpiperidide (LTMP, **83**), generated from commercially available 2,2,6,6-tetramethylpiperidine (TMP) and *n*-BuLi at 0 °C (Scheme 3.12).



82 83 84 85 86

Scheme 3.12 Proposed reaction pathway by Yamamoto *et al*.[36]

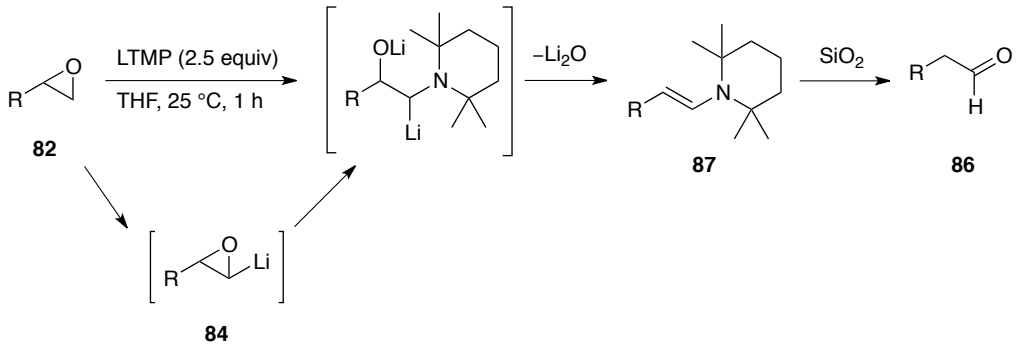
Through various experiments using deuterium-labeled terminal epoxides (Scheme 3.13), these researchers determined that aldehyde formation proceeded via α-deprotonation, removal of the proton *trans* to the alkyl substituent on the oxirane ring, to form an α-lithiated epoxide **84**. They proposed that aldehyde formation proceeded *via* an aldehyde enolate **85** formed by β-elimination to ring-open α-lithiated oxirane species **84**.



84'

Scheme 3.13 Lithiation experiments by Yamamoto *et al*.[36]

Further investigation by Hodgson and co-workers[38] into the pathway of this reaction revealed that the lithiated epoxide **84** actually undergoes a further reaction with LTMP, which acts as a nucleophile, followed by the elimination of Li_2O to form an enamine **87** which can then be isolated, or hydrolysed to the corresponding aldehyde **86** (Scheme 3.14). LTMP has since been used in similar chemistry by several researchers including the Hodgson Group.[38, 39]

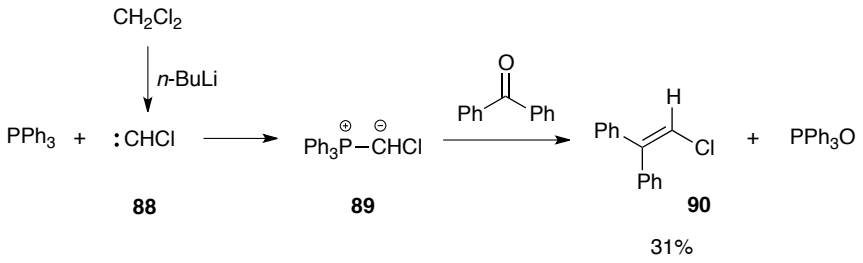


Scheme 3.14

3.2.2 Generation of ylides from carbenes and PPh_3

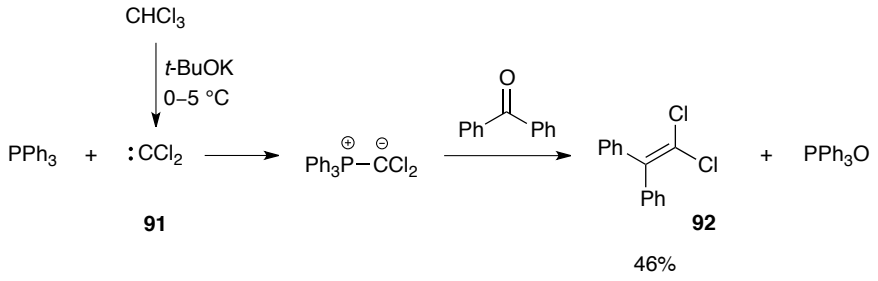
Lithiated epoxides are highly electrophilic species and have carbenoid character, due to a combination of the strain in the three-membered ring of the α-lithiated epoxide and the weakening of the α C−O bond because of its now greater polarisation.[38] There is some literature precedence for the formation of ylides from carbenes and carbenoids and a considerable amount of work has been carried out on the reaction of phosphines and carbenoids in the synthesis of olefins by the Wittig reaction.[40-44] These studies indicate that trialkyl- and triarylphosphines are mild carbene trapping agents. Excellent reviews on the use of phosphorus containing compounds to trap carbenes are given by Padwa and Hornbuckle,[40] Kashin *et al*.[41] and Aggarwal *et al*.[42]

Wittig and Schlosser[43] generated olefin **90** in 31% yield from the reaction of chloro ylide **89**, the latter being obtained from PPh_3 and chlorocarbene **88**, with benzophenone (Scheme 3.15).



Scheme 3.15

Speizale *et al*.[44] obtained similar results using dichlorocarbene (**91**) in the formation of olefin **92** (Scheme 3.16). Similar work has since been done by a number of other researchers.[45]



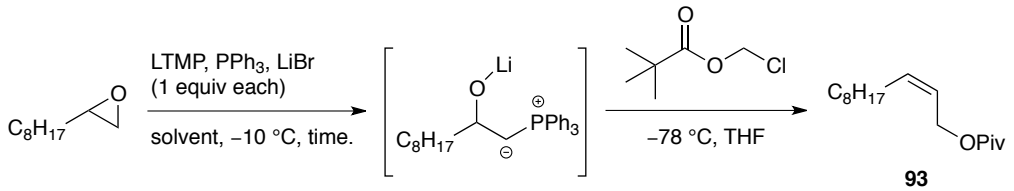
Scheme 3.16

3.2.3 Initial findings

My initial investigations into this route began with test reactions to produce disubstituted allylic ester **93**, a known compound[17*b*] using 1,2-epoxydecane as starting epoxide and chloromethyl pivalate as the electrophile (Table 3.3). Chloromethyl pivalate was used as it is a reactive electrophile and would therefore hopefully efficiently trap the β-lithiooxy ylide if generated. Hodgson and Arif[17*b*] obtained high yields of product **93** using this electrophile to trap β-lithiooxy ylides generated from methylenephosphorane and aldehydes (Scheme 1.13).

LTMP was straightforwardly generated from commercially available 2,2,6,6-tetramethylpiperidine (TMP) using *n*-BuLi in solvent at 0 °C and to which a solution of PPh_3 was added, followed immediately by a solution of epoxide, and stirred until the epoxide was no longer visible by TLC analysis. A solution of the electrophile was then added to this mixture, cooled to −78 °C. The solvent used varied between using THF and *t*-BuOMe. Hodgson and Salik[39] noticed that *t*-BuOMe functioned better as a reaction medium compared to THF, in their studies on the intramolecular cyclopropanation of terminal

unsaturated epoxides. A study done by Kopka *et al*.[46] showed that LTMP has a half life of 12 h in THF at 24 °C, so the suitability of both solvents in this instance warranted examination.



Entry	Epoxide (equiv)	Solvent	Time (h)	Yield (%)[b]	*Z*:*E*
1[a]	0.33	*t*-BuOMe	4	-	
2[a]	1	*t*-BuOMe	4	-	
3	0.33	THF	24	21	>99:1

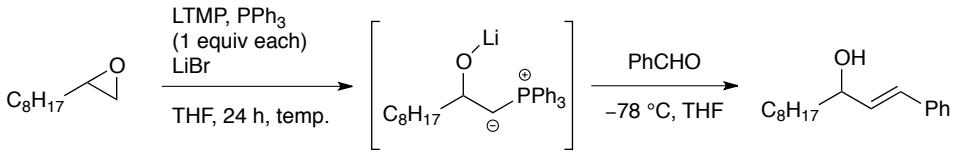
[a] No LiBr used. LiBr is not soluble in *t*-BuOMe. [b] yield of product after purification

Table 3.3 Initial findings

The results of these investigations revealed that THF was the more suitable solvent, even though, the mixture was stirred for one day at −10 °C to generate ylide, and before the electrophile could be added. During this time, the red-orange colour characteristic of the β-lithiooxyphosphonium ylide gradually developed, becoming very intense after about three hours of stirring. However, epoxide was still visible by TLC after stirring for 24 h. On the other hand, the crude product obtained using *t*-BuOMe was very difficult to purify; but, epoxide was no longer visible by TLC after only four hours of stirring at −10 °C. Analysis of the ^{1}H spectrum of the product obtained in entry 3 (Table 3.3) showed that only the *Z*-isomer was formed (NMR data was consistent with that reported)[17b] indicating that, by this method of generating β-lithiooxyphosphonium ylides, *E*/*Z* selectivities are not altered.

3.2.4 Attempted optimisation of reaction

With this encouraging, but promising result (Table 3.3, entry 3), I then investigated the effect of using an aldehyde as the ylide-trapping electrophile to produce an allylic alcohol (Table 3.4). Benzaldehyde was chosen since, as outlined in Chapter 2, it was shown that using aromatic aldehydes to trap β-lithiooxyphosphonium ylides results in only one stereoisomer and regioisomer being produced.



48, *E*:*Z* >99:1[a]

Entry	Epoxide (equiv)	LiBr (equiv)	Temp (°C)	Yield (%)
1	0.33	0	−10	6
2	0.33	1	−10	7
3	1	0	−10	8
4	1	1	−10	9
5	1	0	0	15
6	**1**	**1**	**0**	**22**
7	**1**	**2**	**0**	**20**
8[b]	1	1	0	6
9[b]	1	0	rt	9
10	1	2	10	14

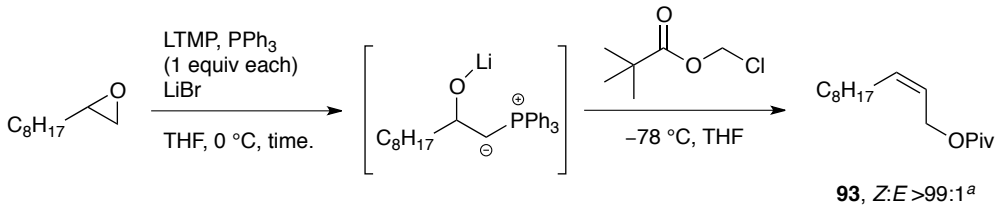
[a] *E*:*Z* ratios determined by ^{1}H NMR analysis of crude product. [b] mixture stirred for 6 h to form ylide

Table 3.4 Effect of varying experimental conditions in attempted optimisation of the synthesis of allylic alcohol **48**.

Using the same experimental conditions and procedure, only a minimal amount of product was obtained when benzaldehyde was used as the ylide-trapping electrophile. From the results shown in Table 3.4, it was determined that a temperature of 0 °C was more

suitable for ylide formation. At lower temperatures, lithiation of the epoxide, and hence β-lithiooxy ylide formation, is slow, and at higher temperatures, it seems that the β-lithiooxy ylide formed decomposes. Also, added LiBr seemed to be necessary. In each of these reactions, epoxide was still visible by TLC after stirring for the lithiation/nucleophile trapping time indicated; and a red-orange colour, characteristic of the β-lithiooxy ylide, persisted for this time.

Using chloromethyl pivalate as the ylide-trapping electrophile, it was shown that allowing the ylide to form over 2 h produced significantly less product **93**, compared to allowing the ylide to form over 24 hours, then adding the electrophile. These results are shown in Table 3.5 below. The importance of the use of LiBr in this instance could not be determined from the results of these experiments as yield of product after purification varied only minimally.



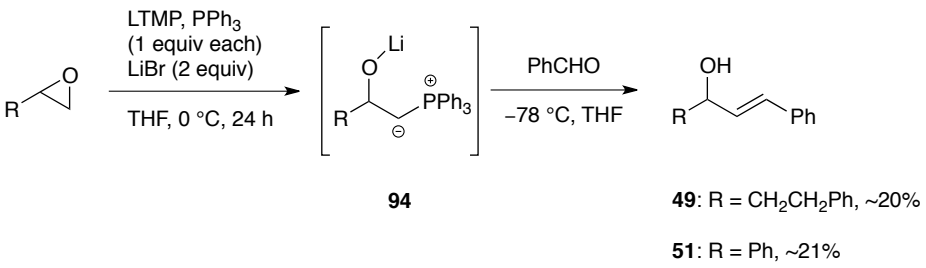
93, *Z*:*E* >99:1[a]

Entry	LiBr (equiv)	Time (h)	Yield (%)
1	0	24	23
2	1	24	26
3	1	2	10

[a] *E*:*Z* ratios determined by ^{1}H NMR analysis of crude product.

Table 3.5 Effect of varying lithiation time

Using these conditions, *E*-allylic alcohols **49** and **51** were obtained in similar yields, but minor impurities were visible in the ^{1}H NMR spectrum of both compounds (Scheme 3.17).



Scheme 3.17

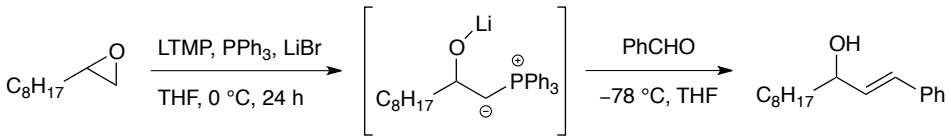
It was previously inferred, from the studies carried out by Schlosser and co-workers[12] and Corey and co-workers[20-23] using β-lithiooxyphosphonium ylides of type **94**, that ylides of this type have limited stability at temperatures above −78 °C, which may have been why Schlosser *et al.*,[12f] in their warm-cool cycle, allowed the β-lithiooxyphosphonium ylide to warm at room temperature for only 30 minutes before immediately being cooled back to −78 °C. It was thought that if left for longer than 24 hours at 0 °C, the β-lithiooxy-phosphonium ylide would decompose fully. It was noticed that a red-orange colour, characteristic of β-lithiooxyphosphonium ylides, persisted after the mixture of epoxide, LTMP and PPh_3 was left to stir at this temperature for 24 h. This observation suggested that the ylide may be more stable than is suggested, or that the presence of TMP in the reaction mixture may be impeding the progress of the reaction.

3.2.4.1 Increasing the equivalents of PPh_3 used

The effect of using an excess of PPh_3 in comparison to LTMP was examined to determine whether increasing the concentration of this nucleophile would result in more efficient trapping of the lithiated epoxide. The results of this investigation were interesting (Table 3.6). Increasing the amount of PPh_3 used to 2 equivalents increased the yield of product to 31% (entry 2). Again, the importance of the use of LiBr could not be determined as the difference in yield was only minimal. Using no LiBr, as opposed to 2 equiv LiBr,

resulted in the formation of 24% product. However, using a five-fold excess of PPh_3 resulted in no increase in the yield of product, as compared to using 2 equiv PPh_3. Using a three-fold excess of PPh_3 compared to LTMP also resulted in no variation in the yield of product.

The effect of reversing the addition, that is adding LTMP to a solution of PPh_3, LiBr and epoxide was next examined (entries 4 and 7). LTMP was straightforwardly generated from commercially available TMP using *n*-BuLi in THF at 0 °C. This mixture was then cooled to −78 °C and added to a cooled mixture (at 0 °C) of PPh_3, LiBr and epoxide *via* cannula very slowly over 1 h. Unfortunately, the yield of product did not improve using both 1 and 3 equiv LTMP; ~55% PPh_3 was recovered in each case.



48, *E*:*Z* >99:1[a]

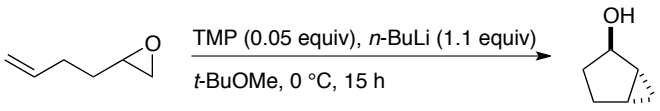
Entry	PPh_3 (equiv)	LTMP (equiv)	LiBr (equiv)	Yield (%)
1	2	1	0	24
2	**2**	**1**	**2**	**31**
3	**5**	**1**	**2**	**33**
4[b]	2	1	2	16
5[c]	9	3	2	30
6[c]	2	3	2	24
7[b, c]	2	3	2	20

[a] *E*:*Z* ratios determined by ^{1}H NMR analysis of crude product.
[b] reverse addition: LTMP added to solution of epoxide and PPh_3 over 1 h.
[c] 4 equiv PhCHO used. For all other experiments, 1.05 equiv PhCHO was used.

Table 3.6 Effect of varying the equivalents of PPh_3 used

3.2.4.2 Using a catalytic amount of TMP

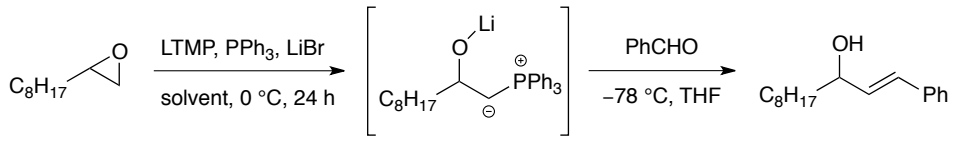
It was thought that if the original conditions used to synthesise racemic *E*-allylic alcohols (described in Chapter 2) could be more closely mimicked in this instance, that is, keeping the amount of TMP present in the reaction mixture to a minimum, then better yields of product may be obtained. Hodgson *et al.*[38a] examined the effect of using a catalytic amount of TMP on the intramolecular cyclopropanation of 1,2-epoxy-5-hexene (**95**) and found that using a substoichiometric amount of TMP produces equally satisfactory results as using 1 equiv (95%) (Scheme 3.18).



95 **96** 63%

Scheme 3.18 Intramolecular cyclopropanation using catalytic TMP by Hodgson *et al.*[38a]

My investigations using catalytic amounts of TMP were disappointing and showed that a stoichiometric amount of the lithium amide base is necessary (Table 3.7). To a mixture of PPh_3, LiBr, epoxide and TMP at the specified temperature was added *n*-BuLi very slowly dropwise over 3 h with vigorous stirring. This mixture was then stirred for 24 h at the indicated temperature, then cooled to −78 °C and a solution of benzaldehyde added. In examining whether it was necessary to wait for 24 hours before adding the electrophile, it was shown that stirring for only 2 hours produced similar results. Also, the yield increased only slightly when using an excess of PPh_3. From these results, it could not be determined whether 1 or 2 equivalents of LiBr was necessary as yields varied only slightly.



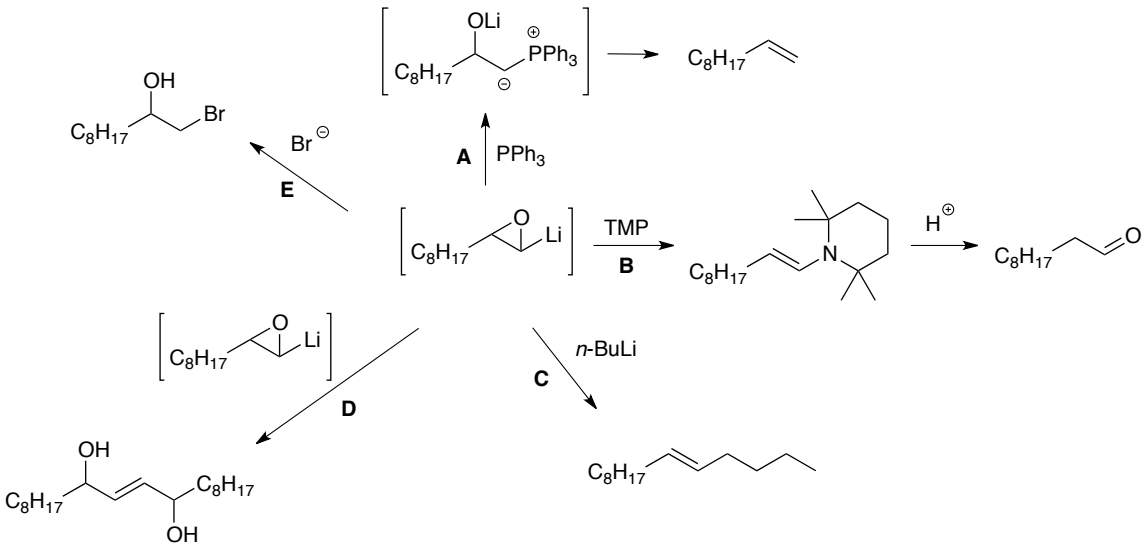
48, *E*:*Z* >99:1[a]

Entry	Solvent	LTMP (equiv)	PPh_3 (equiv)	LiBr (equiv)	Yield (%)
1	THF	0.25	1	1	10
2	THF	0.25	1	2	15
3[b]	THF	0.25	1	1	11
4[b]	THF	0.25	1	2	16
5	THF	0.25	2	1	20
6	*t*-BuOMe	0.1	2	0	16
7[c]	*t*-BuOMe	0.1	2	0	20

[a] *E*:*Z* ratios determined by ^{1}H NMR analysis of crude product. [b] Stirred for 2 h before benzaldehyde added.
[c] Mixture stirred at −30 °C to make ylide

Table 3.7 Effect of using catalytic TMP

None of the obvious byproducts from possible competing side reactions (Scheme 3.19): 1-decene form Wittig elimination of Ph_3PO from the β-lithiooxy ylide intermediate (A), 1-decanal from the hydrolysis of the aldehyde/enamine (B), the alkene due to reductive alkylation of the epoxide by *n*-BuLi (C), the alkenediol due to dimerization of the α-lithiated terminal epoxide (D), or the bromohydrin from the nucleophilic ring-opening of the lithiated epoxide by Br^- (E), were observed in the ^{1}H NMR spectrum of the crude product in each of these reactions.



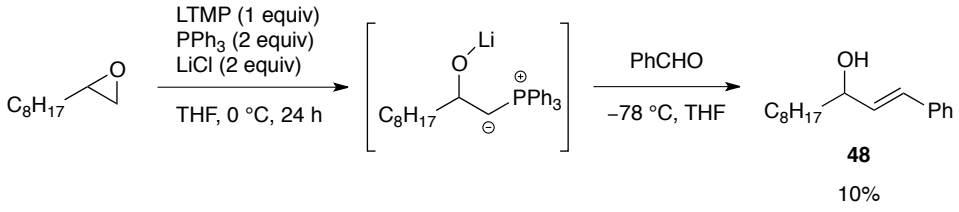
Scheme 3.19 Possible competing side reactions

3.2.4.3 Using a more nucleophilic phosphine

The use of more nucleophilic phosphines to trap the lithiated epoxide formed was next examined. It was thought that PPh_3 may not have been sufficiently nucleophilic to open the ring of the lithiated terminal epoxide to any appreciable extent as the average yield of product was 20%, and that using more nucleophilic phosphines[47] might produce better yields of product. Using both PBu_3 and PCy_3 did not result in formation of product. In fact, in both instances, no colour development to the characteristic red-orange colour of β-lithiooxyphosphonium ylides was seen. In both cases, a yellow mixture was observed after the 24 h lithiation time. TLC analyses of the reaction mixtures after 4 h and 6 h lithiation showed only starting material present. It is not clear why use of these phosphines failed to give product. These results, however, suggest that the phenyl groups of PPh_3 may have some influence on the trapping of the α-lithiated epoxide to form β-lithiooxyphosphonium ylides.

3.2.4.4 Using LiCl

It was thought that the bromide ion might be a competing nucleophile in the ring-opening of the lithiated epoxide to form the corresponding bromohydrin as a possible competing side reaction. No evidence of the formation of this species was discerned from ^{1}H NMR analysis of the crude reaction product. Nevertheless, a reaction was carried out to examine what effect using a lithium salt with a less nucleophilic counter-ion would have. Using LiCl, however, resulted in a significantly lower yield (10%) of product (Scheme 3.20).



Scheme 3.20

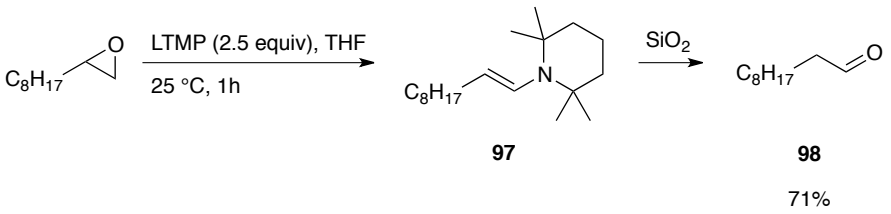
3.2.5 Determining fate of starting material

Throughout my investigation into this route, consistently low yields of product were obtained. By ^{1}H NMR analysis of the crude material, only product and starting material were discernible. No obvious by-products of this reaction were visible. None-the-less, confirmatory experiments were done to rule out all possibilities.

3.2.5.1 Aldehyde/enamine formation

It is known that the experimental conditions used are ideal for enamine formation, which can be hydrolysed to the aldehyde under the acidic conditions of the work-up (quench with saturated aq. ammonium chloride). However, neither carbonyl nor enanime protons of **98** and **97**, respectively, were observed in the ^{1}H NMR spectrum of the crude reaction

mixtures. A simple test experiment was carried out to form decanal (**98**) from the hydrolysis of enamine **97** (Scheme 3.21). The Hodgson method of enamine formation was followed.[38]



97 **98**

71%

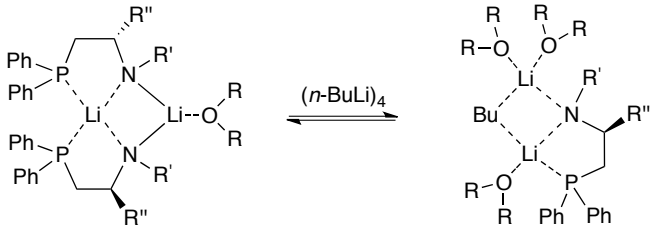
Scheme 3.21

The result of this experiment is consistent with that obtained by Yamamoto *et al*.[37] (67% yield, Scheme 3.13) and helps to confirm that experimental procedure was being carried out accurately. In addition, this shows that decanal does not azeotrope with solvent and therefore is not removed during the work-up procedure. To determine whether lithiation of the epoxide was affected by the presence of LiBr, this reaction was repeated in the presence of 1 equivalent LiBr. The yield of decanal (65%) in this case was also similar to the yield reported by Yamamoto and co-workers. Importantly, no unreacted epoxide was observed. These results suggest that the presence of LiBr does not have any effect on the lithiation of a terminal epoxide, and lithiation followed by trapping with nucleophilic TMP occurs relatively quickly. It appears that it is the presence of PPh_3 in the reaction mixture which slows lithiation considerably, possibly by coordinating with the Li of LTMP, as starting epoxide was visible by ^1H NMR analysis of the crude reaction product.

3.2.5.2 Li−P interactions

An interesting recent study done by Rönnholm and Hilmersson[48] lends some support to this observation. These researchers, in their studies on the use of chiral lithium amides with a chelating diphenylphosphine substituent in asymmetric additions of alkyllithiums to benzaldehyde, showed that Li−amide−phosphine chelates are possible in coordinating

ethereal solvents such as THF (Scheme 3.22). The results of their study suggest that the Li −P interactions in these chelates are strong enough to resist solvation (addition) by THF, a much better ligand for Li than phosphorus. Also, $^{6}Li–^{31}P$ couplings obtained from low temperature NMR studies suggest that in THF solutions of these chelates, there exists substantial steric hindrance which may force Li and P close together, shortening lithium-phosphine distances.



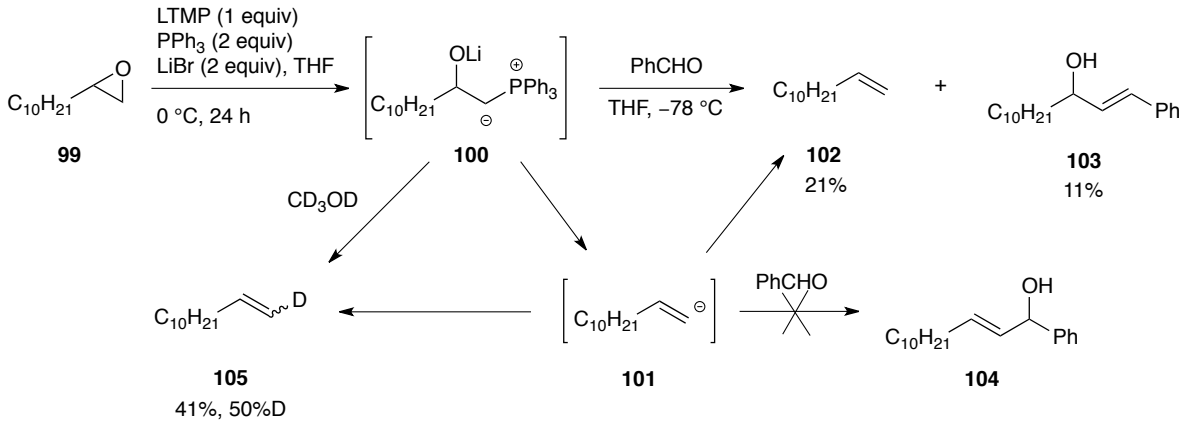
Scheme 3.22 Proposed equilibrium between lithium amide−phosphine (*n*-BuLi)$_4$ mixed complexes in ethereal solvents by Rönnholm and Hilmersson[48]

A test was carried out to determine whether the red-orange colour change seen was due to some interaction between PPh_3 and LTMP. Upon stirring these two reagents in THF at 0°C for 24 h, no colour change was observed. After 24 h the mixture was yellow. Only when the epoxide is present does the red-orange colour develop. However, the intensity of this colour is clearly not an accurate indication of the amount of β-lithiooxy ylide formed. The formation of a chelate, or a coordination-species between PPh_3, LTMP and the epoxide may account for the intense red-orange colour seen when LTMP is used as the lithiating agent.

3.2.5.3 Alkene formation

Using a higher molecular weight epoxide, 1,2-epoxydodecane (**99**), the reaction was repeated to determine whether there was any decomposition of the β-lithiooxy ylide **100**

formed to the corresponding terminal olefin **102** (Scheme 3.23). This compound was observed in the ^{1}H NMR spectrum of the crude product and isolated in 21% yield. Olefin **102** is presumed to be formed via the alkenyl anion **101** which abstracts a proton from the solvent. Allylic alcohol **104** was not observed in ^{1}H NMR spectrum of the crude product, indicating that nucleophilic addition of this anion to benzaldehyde was not a competing side reaction.



Scheme 3.23

A test reaction was done using CD_3OD (Scheme 3.23) as the electrophile to trap β-lithiooxy ylide **100** to form deuterated olefin **105**. This reaction seems to confirm that alkenyl anion **101** is formed. Deuterated alkene **105** was formed in 41% yield with 50% deuterium incorporation [^{1}H (400 MHz, $CDCl_3$) δ = 5.75−5.91 (1 H, m), 5.05−5.88 (0.99 H, m), 2.05 (2 H, q, *J* = 6.6) (Figure 3.1). It is unclear why the yield using this electrophile is higher than the yields obtained using benzaldehyde or chloromethyl pivalate, but this result seems to indicate that, by this method, β-lithiooxy ylides are produced to an appreciable extent. However, the rate of formation is very slow and over time, decomposition occurs.

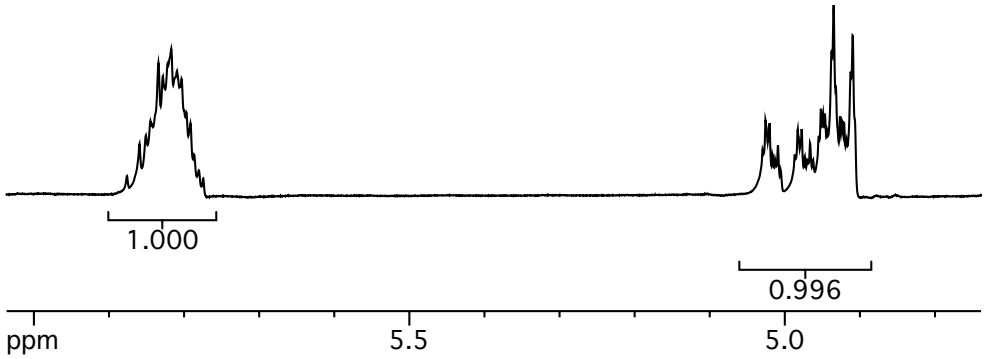
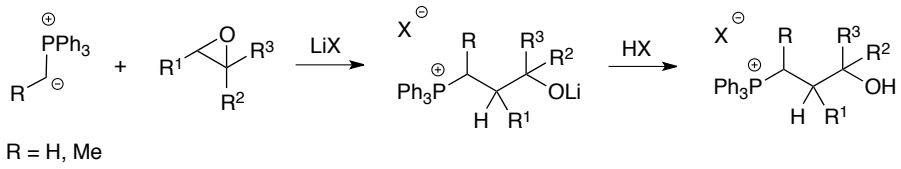


Figure 3.1 Integration and ^{1}H NMR (400 MHz) chemical shifts of the olefinic protons of deuterated alkene **105**

3.2.5.4 Other possible side reactions

Since the presence of neither enamine nor aldehyde was observed, it was thought that lithiation of PPh_3 by LTMP may be a competing reaction, using up the base in this way instead of lithiating the epoxide. A search of the literature revealed one study done by Gilman and Brown,[49] which indicates that PPh_3 can be metalated, in a *meta* position. In their work, a mixture of *n*-BuLi (3.2 equiv) and PPh_3 in Et_2O were refluxed, with stirring, for 46 h. This mixture was then poured onto dry ice. Analysis of the product formed showed the formation of *m*-carboxyphenyl diphenylphosphine. Based on comparison of pK_a values of *n*-BuLi (~50) and LTMP (~37)[50], consumption of LTMP in this way seems unlikely.

Work carried out by Schlosser *et al*.[51] and Heath *et al*.[52] have shown that triphenyl-phosphonium ylides can react with oxiranes (32−61%). Schlosser and co-workers contend that these reactions occur only in the presence of soluble lithium halide salts and that the interaction between Li and O constitutes the major driving force for the reaction (Scheme 3.24).

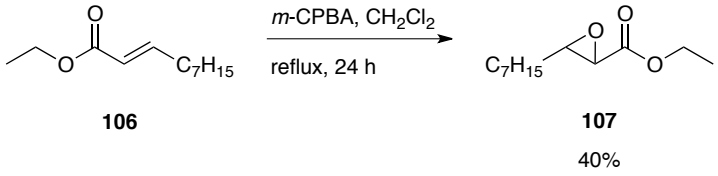


Scheme 3.24

In the reactions carried out, the hydroxyphosphonium salt which would arise from the reaction of β-lithiooxyphosphonium ylides and terminal epoxides was not observed in the ^{1}H NMR spectrum of the crude reaction product, even though LiBr was present in many of these reactions. This suggests that ylides of this type may not be capable of reacting with epoxides (methylenetriphenylphosphorane and ethylenetriphenylphosphorane were used in Schlosser's and Heath's studies, respectively), or the presence of LTMP and/or PPh_3 prevents this reaction from occurring.

3.2.6 Using a 2,3-disubstituted epoxide

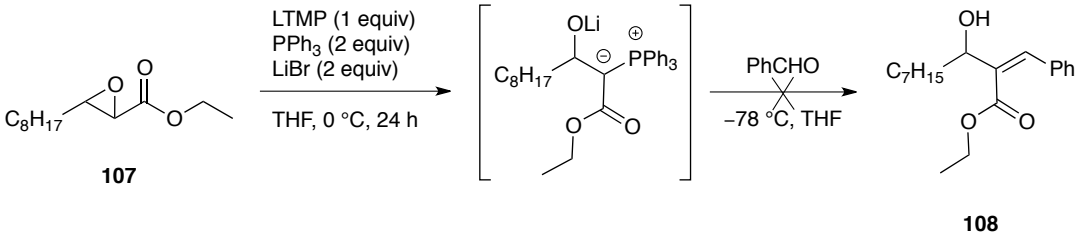
A brief investigation was then carried out to examine what effect, if any, using a 2,3-disubstituted epoxide bearing an acidic hydrogen would have on the experimental outcome. Epoxide **107** was obtained from unsaturated ester **106** by oxidation using *m*-CPBA in refluxing CH_2Cl_2, in 40% yield (Scheme 3.25).



Scheme 3.25

Subjecting epoxide **107** to the reaction conditions resulted in the formation of no product, even with a shorter (6 h) lithiation time (Scheme 3.26). TLC analysis of the reaction mixture after these lithiation times, and after the addition of benzaldehyde to the reaction mixture showed that the starting epoxide was still present. Alcohol **108**, a known

compound,[53] has very distinctive chemical shifts of the alkene (6.9 ppm) and C*H*(OH) (4.42−4.36) protons, which were not observed in the ^{1}H NMR spectrum of the crude product.



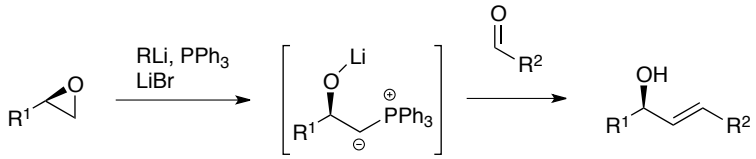
Scheme 3.26

3.2.7 Summary and conclusions

The study described in this section to produce enantiopure disubstituted *E*-allylic alcohols via β-lithiooxyphosphonium ylides formed *in situ*, using LTMP to α-lithiate terminal epoxides and PPh_3 to trap the lithiated species, provides a route into these systems, albeit, only in moderate yield. β-Lithiooxyphosphonium ylides can be formed in this way to an appreciable extent, but rather slowly and during this time, decomposition to the corresponding olefin via an alkenyl anion occurs. Importantly, the regioselectivity and stereoselectivity in allylic alcohol formation remains unchanged when using aromatic aldehydes as the ylide trapping electrophile. It is presumed that the regio- and stereoselectivities observed when using aliphatic, α-branched, α,β-unsaturated aldehydes to trap β-lithiooxyphosphonium ylides generated *via* this route will also remain unchanged from those using β-lithiooxyphosphonium ylides generated *via* methylenephosphorane and aldehydes.

3.3 Ring-opening of α-lithiated terminal epoxides using triphenylphosphine, use of organolithiums as lithiating agent

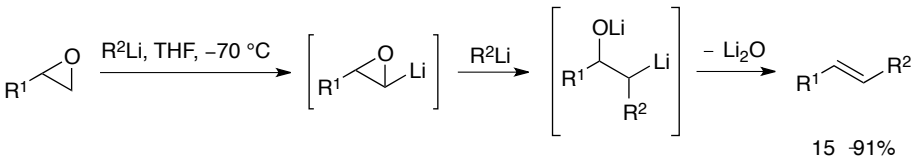
It was thought that the yield of product may improve if the experimental conditions were kept similar to those by which we can form racemic allylic alcohols in moderate yield (Chapter 2). This was partially examined, as outlined in the previous section, using sub-stoichiometric amounts of TMP. Unfortunately, this examination had led to no improvement in yield. We were curious to know what would be the effect of having no amine present in the reaction mixture (Scheme 3.27).



Scheme 3.27

3.3.1 Background

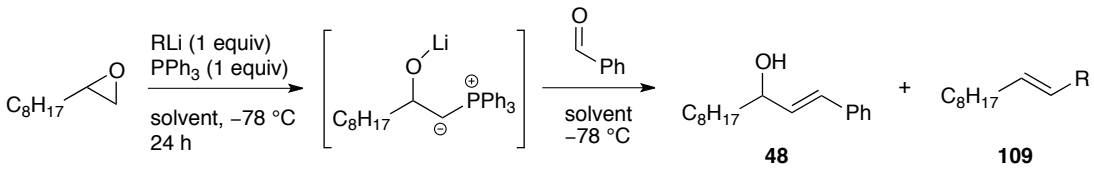
Mioskowski and co-workers[54] examined the 'reductive alkylation' of epoxides using various organolithiums (Scheme 3.28). Their results showed that various terminal and 2,3-disubstituted epoxides can be lithiated to a good extent using organolithiums such as MeLi, PhLi and the BuLi's.



Scheme 3.28

3.3.2 Findings

My investigations into this route began with determining the organolithium which would afford product formation (Table 3.8). In many of the experiments carried out, the alkene due to reductive alkylation of the terminal epoxide was formed. The organolithium was added to a cooled solution of epoxide and PPh_3 very slowly, dropwise over approximately 10 min. The reaction mixture was then analysed by TLC to determine consumption of the starting epoxide. In all cases, the starting epoxide was present after the time allowed for lithiation, and in the instances where the reductive alkylation product was formed, its presence was detected within the first 2 h of the time allowed for lithiation. One major difference observed between the current route and the route described in the previous section (using LTMP as the lithiating agent) is that the intensity of the red-orange colour developed, possibly indicative of the ylide formed, was greater for the latter route. In most cases in the present route, the colour of the mixture after the time allowed for lithiation was yellow or orange.



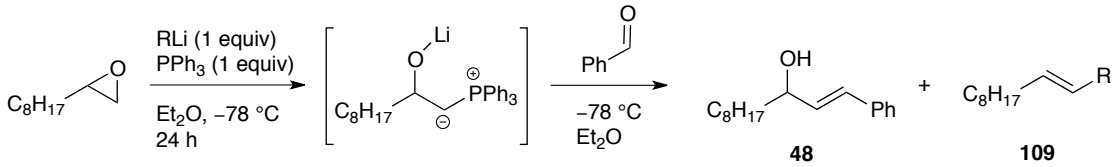
Entry	RLi	Solvent	Yield (%)	
			48	**109**
1[a]	*s*-BuLi	THF	2	45
2[a]	*t*-BuLi	THF	0	28
3[a]	MeLi	THF	Only starting material by crude ^{1}H NMR analysis	
4[a, b]	*s*-BuLi	THF	4	40
5	*s*-BuLi	*t*-BuOMe	10	20
6	*t*-BuLi	*t*-BuOMe	8.5	16
7	*s*-BuLi	toluene	1	10
8	*t*-BuLi	toluene	4	12
9[c]	*s*-BuLi	hexane	6	36
10[c]	*t*-BuLi	hexane	13	21

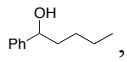
[a] 2 Equiv LiBr. [b] 2 Equiv PPh_3. [c] Volume of solvent doubled.

Table 3.8 Effect of varying organolithium and solvent

It seemed that using THF as the solvent favours formation of the reductive alkylation product. These results also seem to suggest that relatively non-polar ethereal solvents favour product formation and decreases yield of side product **109**. Of the solvents examined, diethyl ether was found to be the most suitable (Table 3.9). Also, the results presented in Tables 3.8 and 3.9 seem to suggest that *s*-BuLi was the most suitable organolithium. The best yield of product was obtained using *s*-BuLi, diethyl ether and a 24 h lithiation time (entry 1, Table 3.9). Increasing the lithiation time (entries 3 and 4, Table 3.9) served only to decrease the amount of product formed. This could possibly be due to degradation of the ylide over the extended time.

Increasing the lithiation temperature to −40 °C decreased the yield of product and increased the yield of the reductive alkylation product. On the other hand, decreasing the lithiation temperature to −90 °C did not seem to affect the yield of product or side product.



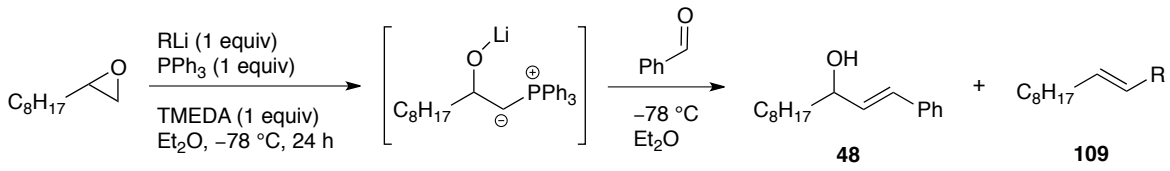
Entry	RLi	Yield (%)	
		48	**109**
1	***s*-BuLi**	**18**	**25**
2	*t*-BuLi	11	31
3[a]	*s*-BuLi	7	28
4[a]	*t*-BuLi	4	32
5[b]	*s*-BuLi	8	21
6[b]	*t*-BuLi	6	21
7	*n*-BuLi	 , 66%	
8	PhLi	 , 83%	
9[c]	*s*-BuLi	5	45
10[c]	*t*-BuLi	4	33
11[d]	*s*-BuLi	12	20
12[d]	*t*-BuLi	9	28

[a] 48 h Lithiation time. [b] 2 Equiv PPh_3. [c] −40 °C Lithiation temperature.
[d] −90 °C Lithiation temperature.

Table 3.9 Effect of varying organolithium

3.3.2.1 Using a TMEDA/organolithium complex

In the results presented above, there is evidence of a greater extent of lithiation of the terminal epoxide using organolithiums. However, reductive alkylation out-competes ylide formation. It was thought that using TMEDA would de-aggregate the organolithiums, thereby reducing the amount of reductive alkylation product, and consequently increase yield of product. However, this was not found to be the case (Table 3.10). The yield of the reductive alkylation product **109** remained constant but after a 24 h lithiation time, the yield of product decreased (entries 1 and 2). Interestingly, using a shorter lithiation time of 3 h afforded similar yields of product.



Entry	RLi	Yield (%)	
		48	**109**
1	*s*-BuLi	6	19
2	*t*-BuLi	7	31
3[a]	*s*-BuLi	10	19
4[a]	*t*-BuLi	8.5	27

[a] using a 3 h lithiation time

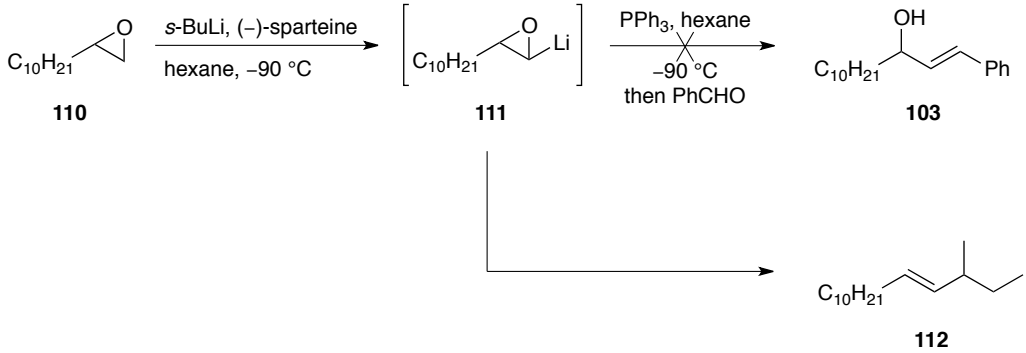
Table 3.10 Effect of using a TMEDA/organolithium complex

In all of the above cases, ~30% of the starting epoxide and ~60% of PPh_3 were recovered.

3.3.2.2 Using (−)-sparteine/*s*-BuLi complex

Investigations into the routes outlined in the previous two sections have indicated that lithiation of terminal epoxides is slowed considerably in the presence of PPh_3. Formation of the lithiated epoxide first, followed by trapping with PPh_3 was thought to be a viable circumvention. Work carried out by Hodgson and co-workers[55] has shown that lithiation of terminal epoxides can be effected at low temperatures (−90 °C) using diamine/*s*-BuLi complexes. However, these reactions are quite sensitive to the quality of the organolithium used, very slight variations in temperature, and are generally quite mercurial in nature.

A test reaction was carried out to form the lithiated terminal epoxide at −90 °C, followed by the addition of a solution of PPh_3 then benzaldehyde to determine whether allylic alcohols could be accessed in this way (Scheme 3.29). Unfortunately, no product was detected by ^{1}H NMR analysis of the crude material. Instead, alkene **112** was observed.

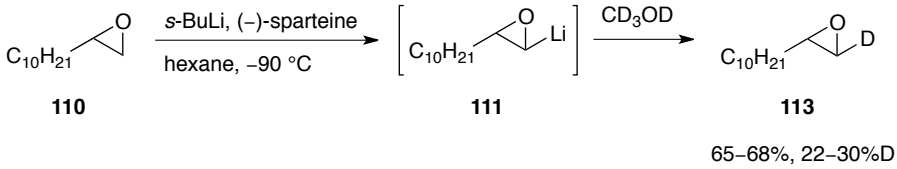


110 **111** **103** **112**

Scheme 3.29

Several test reactions, (−)-sparteine/*s*-BuLi-mediated lithiation of the terminal epoxide followed by deuteration, were then carried out to ensure that the experimental procedure was being carried out accurately using the method outlined by Hodgson and Norsikian[55a] (Scheme 3.30). Unfortunately, only a maximum of 30% deuterium incorporation could be achieved [^{1}H (400 MHz, $CDCl_3$) δ = 2.91−2.87 (1 H, m), 2.77−2.71

(0.7 H, m), 2.50−2.42 (1 H, m)]. These researchers, by contrast, obtained 70% yield with a maximum of 70% D incorporation.



Scheme 3.30

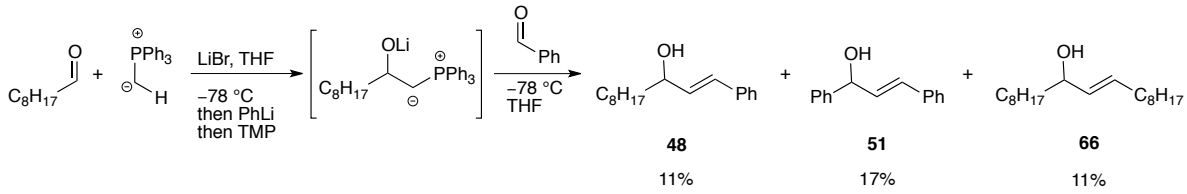
3.3.3 Summary and conclusions

The method of disubstituted *E*-allylic alcohol formation described in this section, using β-lithiooxy ylides generated from an organolithium-effected deprotonation of terminal epoxides followed by trapping with PPh_3, is not as suitable for β-lithiooxy ylide generation compared to using LTMP to effect α-deprotonation. Only with the use of *s*-BuLi and *t*-BuLi was *E*-allylic alcohol formed. Reductive alkylation of the starting epoxide by the organolithium (*s*-BuLi and *t*-BuLi) used outcompetes formation of the desired product. When PhLi, MeLi and *n*-BuLi are used, no product or reductive alkylation of the epoxide is observed. Again, the selectivity of the reaction of β-lithiooxy ylides, generated using methylenephosphorane and aldehydes, and aromatic aldehydes previously observed remained unchanged using β-lithiooxy ylides generated by this means.

3.4 Effect of presence of an amine on formation of allylic alcohols

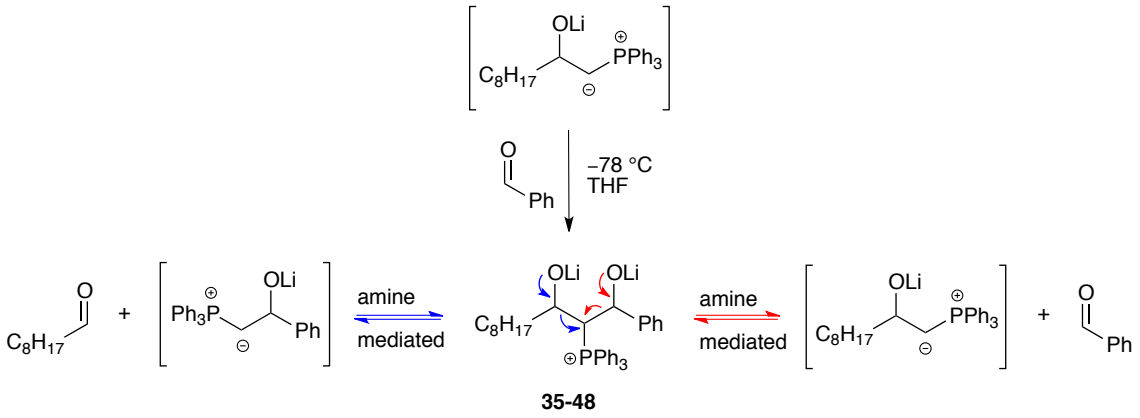
As a test to determine whether the presence of an amine affects the formation of allylic alcohols formed from the reaction of β-lithiooxy ylides with aldehydes, a reaction was carried out using β-lithiooxy ylides generated from methylenephosphorane and aldehydes. The β-lithiooxy ylide from nonanal and methylenephosphorane was generated in

the usual way, as outlined in Chapter 2. Prior to the addition of benzaldehyde to this β-lithiooxy ylide, TMP was added at −78 °C (Scheme 3.31). The result of this experiment was interesting.



Scheme 3.31

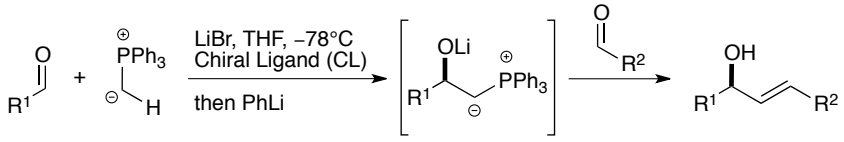
Upon warming the mixture of β-lithiooxy ylide, amine and aldehyde to room temperature, the red-orange colour which is characteristic to β-lithiooxy ylides intensified greatly and this colour persisted until the work-up. Additionally, the yield (11%) of product **48** obtained after purification by flash column chromatography was poor. Curiously, symmetric allylic alcohols **51** and **66** were also isolated, 17% and 11%, respectively. This is possibly due to reversibility between the β,β'-di(lithiooxy) phosphonium adduct **35-48** formed after the addition of benzaldehyde, and β-lithiooxy ylide and aldehydes, aided in some way by the amine (Scheme 3.32).



Scheme 3.32 Possible amine-mediated reversibility

3.5 The fourth conceptualised method into chiral *E*-allylic alcohols

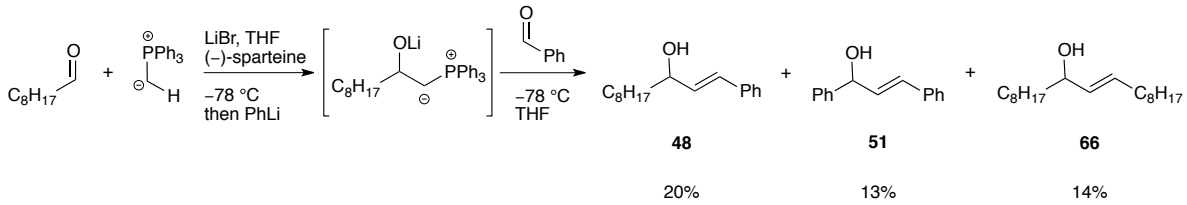
A fourth route into chiral *E*-allylic alcohols was conceptualised, but was not investigated in any detail. It entailed using a variation of the methodology outlined in Chapter 2, with the addition of a chiral ligand to the reaction mixture prior to the addition of the second aldehyde so that a 'chiral environment' may necessarily be 'set up' around the oxygen originating from the first aldehyde used in the reaction sequence (Scheme 3.33).



Scheme 3.33

This conceptualised route bears similar procedural similarities to the to the method outlined in Scheme 3.31. I decided to look at the effect, if any, that the presence of (−)-sparteine may have on the outcome of the reaction, both as a test of this route into chiral allylic alcohols and to confirm whether a similar experimental outcome, that is formation of a mixture of product and symmetric allylic alcohols, possibly due to an amine-induced reversibility (Scheme 3.32), would result as was seen with the presence of TMP in the reaction mixture (Scheme 3.31).

The experimental procedure outlined in Chapter 2 was followed, but (−)-sparteine was added after methylenephosphorane was generated and before the addition of the first aldehyde in the reaction sequence (Scheme 3.34). Interestingly enough, a similar change in the intensity if the colour of the reaction mixture upon warming to room temperature after the second aldehyde was added was seen. Similarly, a mixture of product **48** and symmetric allylic alcohols **51** and **66** were obtained, all in poor yield.



Scheme 3.34

We were curious to know whether any induction of chirality had occurred in the desired product **48** of the reaction. The specific rotation of (*S*)-**48** is known to be +6.6 (0.72, $CHCl_3$).[56] Surprisingly, the $[\alpha]_D^{20}$ of the product **48** obtained from the reaction using (−)-sparteine, using the same concentration of material and solvent, was calculated to be −4.0, suggesting that the product formed in this case is optically active. Further work in this area is necessitated.

3.6 Summary and conclusions

The investigations described in this chapter showed that, potentially, chiral 1,2-disubstituted *E*-allylic alcohols can be accessed *via* β-lithiooxyphosphonium ylides generated from α-lithiated terminal epoxides and PPh_3 *in situ*, followed by trapping with an aldehyde electrophile. α-Lithiation of terminal epoxides and trapping with PPh_3 in the generation of β-lithiooxyphosphonium ylides was showed to be effected to a greater extent using LTMP, a hindered lithium amide, compared to using other organolithiums (PhLi, MeLi and the BuLi's). However, β-lithiooxyphosphonium ylides generated in this way (using LTMP) was shown to be unstable, decomposing to the simple terminal olefin. The regio- and stereoselectivity of the reaction of β-lithiooxy ylides and aromatic aldehydes, previously observed (Chapter 2), remained unchanged. Even though a synthetically useful method to access 1,2-disubstituted *E*-allylic alcohols could not be developed, the

investigations presented in this Chapter represent the first examples of phosphonium ylides generated by the trapping of metalated epoxides with a phosphine.

Chapter 4: Experimental data

4.1 General details

All reactions requiring anhydrous conditions were carried out under an atmosphere of nitrogen in flame-dried glassware. Cannulas were oven-dried.

Materials: THF was distilled from sodium and benzophenone under nitrogen. Diethyl ether, hexane and toluene were degassed then dried over activated alumina under argon. Petrol refers to the fraction of petroleum ether that boils at 30−40 ºC. Anhydrous *tert*-butyl methyl ether was obtained from Sigma Aldrich®. Other solvents were used as obtained. PhLi (2.0 M in Bu_2O) was obtained from Acros Organics®. Benzaldehyde, furfural, *p*-methoxybenzaldehyde were distilled under reduced pressure (64 °C, 20 mbar, 61 °C, 33 mbar, 115 °C, 13 mbar, respectively) prior to use. 2,2,6,6-Tetramethylpiperidine was distilled from CaH_2 under reduced pressure (60 °C, 43 mbar). LiBr was made anhydrous by heating under nitrogen until it melted then cooled and dissolved in THF before using. Methyltriphenylphosphonium bromide and triphenylphosphine were dried overnight (~12 h) under high vacuum (~1 mbar). Other starting materials were obtained commercially and were used without further purification unless otherwise indicated.

Chromatography: Thin Layer Chromatography was carried out on aluminum-backed plates pre-coated with silica (60 F_{254}, Merck) and visualised by irradiation under UV light (λ = 254 nm) and by immersion in phosphomolybdic acid (PMA) or $KMnO_4$ solutions followed by heating. Purification of reaction products was carried out by flash chromatography using silica gel (40-63μm) in the solvent systems indicated. Optical rotations were recorded on a

Perkin-Elmer 241 polarimeter, with a path length of 10 cm in $CHCl_3$. $[\alpha]_D$ values are reported in 10^{-1} deg cm^2 g^{-1}. Concentrations are given in grams per 100 cm^3.

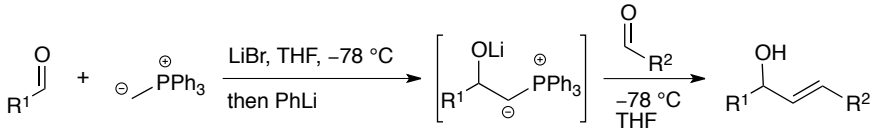
IR spectra were recorded as thin films using a 1750 Perkin-Elmer Paragon Fourier Transform spectrometer. The strength of absorbance is designated by the following abbreviations: br, s, m, and w, which refer to broad, strong, medium and weak, respectively.

^{1}H and ^{13}C NMR spectra were recorded using Brücker AV400 and AVC500 spectrometers. Chemical shifts are reported in ppm and referenced to internal residual $CHCl_3$ at 7.27 ppm for ^{1}H NMR spectra, and to the central line of the $CDCl_3$ triplet at 77.0 for ^{13}C NMR spectra. Coupling constants, *J*, are given in Hz to the nearest 0.1 Hz. The ^{13}C NMR peaks were assigned by standard methods using HSQC and DEPT experiments. *E*:*Z* ratios of allylic alcohols were determined by ^{1}H NMR analysis of crude products.

Mass spectra were obtained by field ionisation (FI; Micromass GCT) or by electrospray ionisation (ESI; LCT Premier Reflectron TOF and Brücker MicroTOF) using tetraoctyl-ammonium bromide or sodium dodecyl sulfate as lock mass; values are quoted as ratios of mass:charge (*m*/*z*) in Daltons, and relative intensities of assignable peaks observed are quoted as a percentage value.

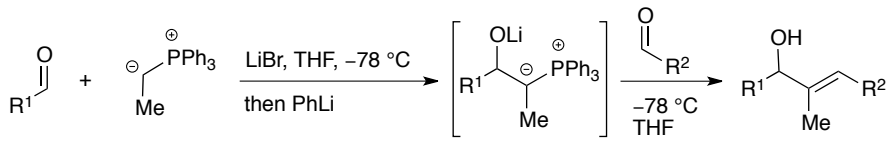
4.2 General procedures and data for Chapter 2

4.2.1 General Procedure A: Synthesis of disubstituted *E*-allylic alcohols



A solution of anhydrous LiBr (2 equiv) in THF (7.5 mL/mmol LiBr) was added to anhydrous methyltriphenylphosphonium bromide (1.0 equiv) at room temperature. The mixture was stirred for 10 min before cooling to −78 ºC. PhLi (2.0 M in Bu_2O, 1.0 equiv) was then added dropwise at −78 ºC. The cooling bath was removed, and the mixture allowed to warm to rt over 15 min during which time a clear-yellow solution formed. After 30 min at rt, the mixture was re-cooled to −78 ºC and a solution of the first aldehyde (1.0 equiv) in THF (0.5 mL/mmol aldehyde) was added dropwise. After 20 min, when complete decolourisation had occurred, PhLi (2.0 M in Bu_2O, 1.05 equiv) was added dropwise resulting in a cherry-red solution. This solution was stirred for 30 min at −78 ºC, after which time a solution of the second aldehyde (1.05 equiv) in THF (0.5 mL/mmol aldehyde) was added dropwise at −78 ºC. The reaction mixture was stirred at −78 ºC for 2 h. The reaction mixture was then warmed to rt over 1 h and stirring continued for a further 1 h. The mixture was quenched with saturated aq. ammonium chloride (20 mL), extracted with Et_2O (3 × 15 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by flash chromatography in the solvent system indicated gave the disubstituted *E*-allylic alcohol.

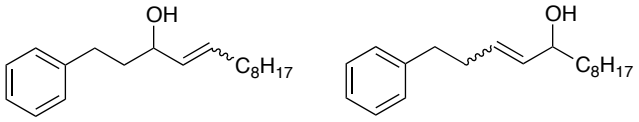
4.2.2 General Procedure B: Synthesis of trisubstituted *E*-allylic alcohols



A solution of anhydrous LiBr (2 equiv) in THF (7.5 mL/mmol LiBr) was added to anhydrous ethyltriphenylphosphonium bromide (1.0 equiv) at room temperature, The mixture was stirred for 10 min before cooling to −78 ºC. PhLi (2.0 M in Bu_2O, 1.0 equiv) was then added dropwise at −78 ºC. The cooling bath was removed, and the mixture allowed to warm to rt over 15 min during which time a clear-yellow solution formed. After 30 min at rt, the mixture was re-cooled to −78 ºC and a solution of the first aldehyde (1.0 equiv) in THF (0.5 mL/mmol aldehyde) was added dropwise. After 20 min, when complete decolourisation had occurred, PhLi (2.0 M in Bu_2O, 1.05 equiv) was added dropwise resulting in a cherry-red solution. This solution was stirred for 30 min at −78 ºC, after which time a solution of the second aldehyde (1.05 equiv) in THF (0.5 mL/mmol aldehyde) was added dropwise at −78 ºC. The reaction mixture was stirred at −78 ºC for 2 h. The reaction mixture was then warmed to rt over 1 h and stirring continued for a further 1 h. The mixture was quenched with saturated aq. ammonium chloride (20 mL), extracted with Et_2O (3 × 15 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by flash chromatography in the solvent system indicated gave the trisubstituted *E*-allylic alcohol.

4.2.3 Data for disubstituted and trisubstituted allylic alcohols synthesised

1-phenyltridec-4-en-3-ol (46) and 1-phenyltridec-3-en-5-ol (47)



Following **General Procedure A**, methyltriphenylphosphonium bromide (714 mg, 2.0 mmol) was first reacted with 3-phenylpropanal (268 mg, 2.0 mmol) and then nonanal (299 mg, 2.1 mmol) to give allylic alcohols **46** and **47** as a mixture of chromatographically inseparable isomers (236 mg, 43% **46***E*:**46***Z*:**47***E*:**47***Z* 56:16:13:15 by ^{1}H NMR integration of C*H*(OH)) as a pale yellow oil; R_f 0.26 (20% Et_2O/petrol);

IR (neat) /cm^{-1}: 3345br, m, 3027w, 2925s, 2854s, 1603w, 1496w, 1455m, 1030w, 969m, 745w, 698m.

LRMS (ESI+): 304.27 (95), 585.55 (100); (ESI−): 280.26 (100), 281.29 (30); HRMS (FI+): 274.2297 calculated for $C_{19}H_{30}O$, found 274.2291.

Data for **46***E*:

^{1}H NMR (500 MHz) δ = 7.32−7.17 (5 H, m, Ph), 5.67 (1 H, dtd, *J* = 15.3, 6.6, 0.9, =C*H*CH$_2$), 5.51 (1 H, ddt, *J* = 15.3, 6.6, 1.5, CH(OH)C*H*), 4.13 (1 H, qd, *J* = 6.6, 3.5, C*H*(OH)), 2.76−2.64 (2 H, m, PhCH$_2$), 2.05 (2 H, q, *J* = 6.9, CH=CHC*H*$_2$), 1.94−1.77 (2 H, m, C*H*$_2$CH(OH)), 1.48 (1 H, br. s, OH), 1.42−1.35 (2 H, m, CH$_2$), 1.35−1.24 (10 H, m, 5 × CH$_2$), 0.89 (3 H, t, *J* = 1.0, CH$_3$).

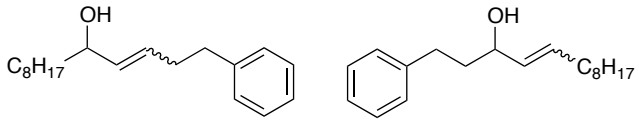
^{13}C NMR (125 MHz) δ = 142.0 (Ph), 132.7 (*C*H=*C*H), 128.4 (2 × Ph), 128.3 (2 × Ph), 125.8 (Ph), 72.5 (CH(OH)), 38.8 (*C*H$_2$CH(OH)), 32.2 (CH$_2$), 31.9 (CH$_2$), 31.8 (Ph*C*H$_2$), 29.4 (CH$_2$), 29.3 (CH$_2$), 29.2 (CH$_2$), 22.7 (CH$_2$), 14.1 (CH$_3$).

Discernible data for **46***Z*:

^{1}H NMR (500 MHz) δ = 7.32−7.17 (5 H, m, Ph), 5.58−5.34 (2 H, m, C*H*=C*H*), 4.51 (1 H, app. q, *J* = 7.3, C*H*(OH)), 2.76−2.64 (2 H, m, PhCH_2), 2.53−2.34 (2 H, m, =CHCH_2) 1.94−1.77 (2 H, m, CH_2CH(OH)), 1.46−1.18 (12 H, m, 6 × CH_2), 0.91 (3 H, t, *J* = 1.0, CH_3).

^{13}C NMR (125 MHz) δ = 133.6 (CH), 132.5 (CH), 67.1 (CH(OH)), 38.8 (*C*H_2CH(OH), 37.2 (PhCH_2), 32.2 (=CH*C*H_2)

1-phenyltridec-3-en-5-ol (47) and 1-phenyltridec-4-en-3-ol (46)



Following **General Procedure A**, methyltriphenylphosphonium bromide (714 mg, 2.0 mmol) was first reacted with nonanal (284 mg, 2.0 mmol) and then 3-phenylpropanal (282 mg, 2.1 mmol) to give allylic alcohols **47** and **46** as a mixture of chromatographically inseparable isomers (214 mg, 39% **47***E*:**47***Z*:**46***E*:**46***Z* 66:12:3:19 by ^{1}H NMR integration of C*H*(OH)) as a pale yellow oil; R_f 0.28 (20% Et_2O/petrol);

IR (neat) /cm^{-1}: 2923m, 2853w, 1454w, 968w, 743m, 697m.

LRMS (ESI+): 297.21 (100, M+Na), 337.28 (65), 441.32 (92); HRMS (ESI+): (M+Na) 297.2189 calculated for $C_{19}H_{30}ONa$, found 297.2193.

Data for **47***E*:

^{1}H (500 MHz) δ = 7.35−7.18 (5 H, m, Ph), 5.69 (1 H, dt, *J* = 15.4, 6.6, =C*H*CH_2), 5.51 (1 H, ddt, *J* = 15.4, 6.6, 1.3, CH(OH)C*H*), 4.07 (1 H, app. q, *J* = 6.8, C*H*(OH)), 2.81−2.63 (2 H,

m, $PhCH_2$), 2.54−2.35 (2 H, m, =CHCH_2), 1.71 (1 H, br. s, OH), 1.62−1.42 (2 H, m, CH(OH)CH_2), 1.42−1.11 (12 H, m, 6 × CH_2), 0.98−0.86 (3 H, m, CH_3).

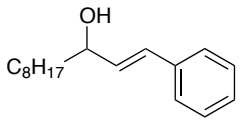
^{13}C (125 MHz) δ = 141.7 (Ph), 133.9 (CH(OH)*C*H), 130.8 (=*C*HCH_2), 128.5 (2 × Ph), 128.3 (2 × Ph), 125.9 (Ph), 73.1 (CH(OH)), 37.3 (CH_2), 35.7 (CH_2), 34.0 (CH_2), 31.9 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 25.5 (CH_2), 22.7 (CH_2), 14.1 (CH_3).

Discernible data for **47***Z*:

^{1}H (500 MHz) δ = 7.35−7.18 (5 H, m, Ph), 5.58−5.34 (2 H, m, C*H*=C*H*), 4.33−4.26 (1 H, m, C*H*(OH)), 2.81−2.63 (2 H, m, $PhCH_2$), 2.54−2.35 (2 H, m, =CHCH_2), 1.62−1.42 (2 H, m, CH(OH)CH_2), 1.42−1.11 (12 H, m, 6 × CH_2), 0.98−0.86 (3 H, m, CH_3).

^{13}C (125 MHz) δ = 133.8 (CH), 132.5 (CH), 67.5 (CH(OH)), 37.2 (*C*H_2CH(OH), 37.1 ($PhCH_2$), 32.2 (=CH*C*H_2)

(*E*)-1-Phenylundec-1-en-3-ol (48)



Following **General Procedure A**, methyltriphenylphosphonium bromide (714 mg, 2 mmol) was reacted with nonanal (284 mg, 2 mmol) and benzaldehyde (223 mg, 2.1 mmol) to give allylic alcohol **48**[57] (197 mg, 40%) as a pale yellow oil; R_f 0.41 (30% Et_2O/petrol);

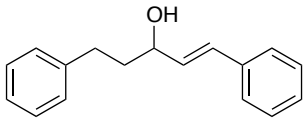
IR (neat) /cm^{-1}: 3351br. w, 2924m, 2853m, 1494w, 1450w, 964m, 746s, 691s.

^{1}H (400 MHz) δ = 7.43−7.22 (5 H, m, Ph), 6.58 (1H, d, *J* = 15.8, CH(OH)CH=C*H*), 6.24 (1 H, dd, *J* = 15.8, 6.8, CH(OH)C*H*), 4.29 (1 H, q, *J* = 6.6, C*H*(OH)), 1.80 (1 H, br. s, OH), 1.71−1.56 (2 H, m, C*H*$_2$CH(OH)), 1.50−1.22 (12 H, m, 6 × CH_2), 0.94−0.87 (3 H, t, *J* = 1.1, CH_3).

^{13}C (100 MHz) δ = 136.7 (Ph), 132.6 (CH(OH)CH=C*H*), 130.1 (CH(OH)C*H*), 128.5 (2 × Ph), 127.5 (Ph), 126.4 (2 × Ph), 73.1 (CH(OH)), 37.4 (CH(OH)*C*H$_2$), 31.8 (CH$_2$), 29.6 (CH$_2$), 29.5 (CH$_2$), 29.2 (CH$_2$), 25.4 (CH$_2$), 22.6 (CH$_2$), 14.1 (CH$_3$).

LRMS (ESI+): 269.19 (80, M+Na), 301.22 (55), 413.32 (55), 515.39 (100); HRMS (ESI+): (M+Na) 269.1876 calculated for $C_{17}H_{26}ONa$; found 269.1868.

(*E*)-1,5-Diphenylpent-1-en-3-ol (49)



Following **General Procedure A**, methyltriphenylphosphonium bromide (714 mg, 2.0 mmol) was first reacted with 3-phenylpropanal (268 mg, 2.0 mmol) and then benzaldehyde (223 mg, 2.1 mmol) to give allylic alcohol **49**[58] (190 mg, 40%) as a pale yellow oil; R_f 0.25 (30% Et_2O/petrol);

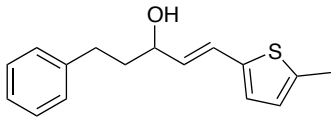
IR (neat) /cm^{-1}: 3346br. w, 3025w, 2924w, 1601w, 1494w, 1452w, 965m, 745s, 692s.

^{1}H (400 MHz) δ = 7.50−7.13 (10 H, m, 2 × Ph), 6.61 (1H, d, *J* = 15.9, PhC*H*), 6.28 (1 H, dd, *J* = 15.9, 6.8, CH(OH)C*H*), 4.33 (1 H, app. q, *J* = 6.5, C*H*(OH)), 2.91−2.68 (2 H, m, PhC*H*$_2$), 2.12−1.91 (2 H, m, CH(OH)C*H*$_2$), 1.86 (1 H, br. s, OH).

^{13}C (100 MHz) δ =141.7 (Ph), 136.6 (Ph), 132.1 (CH(OH)*C*H), 130.5 (CH(OH)CH=*C*H), 128.6 (2 × Ph), 128.4 (2 × Ph), 128.4 (Ph), 127.7 (Ph), 126.4 (Ph), 125.8 (Ph), 72.3 (CH(OH)), 38.7 (PhCH$_2$), 31.6 (CH(OH)*C*H$_2$).

LRMS (ESI+): 261.14 (100, M+Na), 493.24 (80); HRMS (ESI+): (M+Na) 261.1250 calculated for $C_{17}H_{18}ONa$; found 261.1248.

(*E*)-1-(5-Methylthiophen-2-yl)-5-phenylpent-1-en-3-ol (50)



Following **General Procedure A**, methyltriphenylphosphonium bromide (714 mg, 2.0 mmol) was first reacted with 3-phenylpropanal (268 mg, 2.0 mmol) and then 5-methylthiophene-2-carboxaldehyde (225 mg, 2.1 mmol) to give allylic alcohol **50** (309 mg, 60%) as a yellow oil; R_f 0.20 (20% Et_2O/petrol);

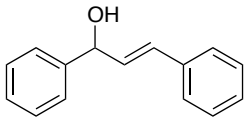
IR (neat) /cm^{-1}: 3371br. w, 3025w, 2918w, 2858w, 1644w, 1602w, 1543w, 1495m, 1453m, 1156m, 1029s, 954s, 793s, 744s, 697s.

^1H (400 MHz) δ = 7.36−7.19 (5 H, m, Ph), 6.76 (1 H, d, *J* = 3.5, CH thiophenyl), 6.64 (1 H, d, *J* = 15.7, CH(OH)CH=C*H*), 6.64 (1 H, dq, *J* = 3.6, 1.2, CH thiophenyl), 5.98 (1 H, dd, *J* = 15.7, 6.8, CH(OH)C*H*), 4.25 (1 H, app. q, *J* = 6.3, C*H*(OH)), 2.85−2.68 (2 H, m, PhCH_2), 2.48 (3 H, d, *J* = 0.8, CH_3), 2.06−1.88 (2 H, m, CH(OH)CH_2), 1.85 (1 H, br. s, OH).

^{13}C (100 MHz) δ = 141.7 (Ph), 139.6 (thiophenyl), 139.2 (thiophenyl), 130.4 (CH(OH)*C*H), 128.4 (2 × Ph), 128.3 (2 × Ph), 126.1 (thiophenyl), 125.8 (Ph), 125.4 (thiophenyl), 124.1 (CH(OH)CH=*C*H), 72.0 (*C*H(OH)), 38.7 (CH(OH)*C*H_2), 31.6 (PhCH_2), 15.5 (CH_3).

LRMS (ESI+): 281.11 (100, M+Na); HRMS (ESI+): (M+Na) 281.0971 calculated for $C_{16}H_{18}OSNa$; found 281.0964.

(*E*)-1,3-Diphenylprop-2-en-1-ol (51)



Following **General Procedure A**, methyltriphenylphosphonium bromide (714 mg, 2.0 mmol) was first reacted with benzaldehyde (212 mg, 2.0 mmol) and then benzaldehyde (223

mg, 2.1 mmol) to give allylic alcohol **51**[57] (274 mg, 65%) as a pale yellow oil; R_f 0.26 (30% Et_2O/petrol);

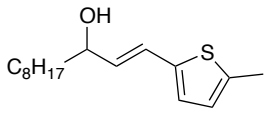
IR (neat) /cm^{-1}: 3329br. w, 3027w, 1493w, 1449w, 1494w, 964m, 742s, 692s.

^1H (400 MHz) δ = 7.53−7.20 (10 H, m, 2 × Ph), 6.71 (1H, d, *J* = 15.9, PhCH), 6.41 (1 H, dd, *J* = 15.9, 6.6, CH(OH)C*H*), 5.40 (1 H, d, *J* = 6.3, C*H*(OH)), 2.24 (1 H, br. s, OH).

^{13}C (100 MHz) δ = 142.7 (Ph), 136.5 (Ph), 131.5 (CH(OH)C*H*), 130.5 (PhCH), 128.6 (2 × Ph), 128.5 (2 × Ph), 127.7 (Ph), 126.6 (Ph), 126.3 (2 × Ph), 75.1 (CH(OH)).

LRMS (ESI+): 233.09 (100, M+Na), 265.13 (75), 443.23 (55); HRMS (ESI+): (M+Na) 233.0937 calculated for $C_{15}H_{14}ONa$; found 233.0943.

(*E*)-1-(5-Methylthiophen-2-yl)-undec-1-en-3-ol (52)



Following **General Procedure A**, methyltriphenylphosphonium bromide (714 mg, 2.0 mmol) was first reacted with nonanal (284 mg, 2.0 mmol) and then 5-methylthiophene-2-carboxaldehyde (225 mg, 2.1 mmol) to give allylic alcohol **52** (317 mg, 59%) as a pale yellow oil; R_f 0.36 (20% Et_2O/petrol);

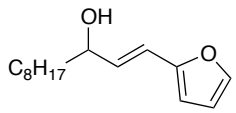
IR (neat) /cm^{-1}: 3340br. w, 2922s, 2853m, 2360s, 1645s, 1464w, 1040w, 952s, 789s, 721w.

^1H (400 MHz) δ = 6.73 (1 H, d, *J* = 3.3, Ar), 6.60 (1 H, d, *J* = 15.7, CH(OH)CH=C*H*), 6.60 (1 H, dq, *J* = 3.4, 1.1, Ar), 5.93 (1 H, dd, *J* = 15.7, 6.8, (CH(OH)C*H*), 4.19 (1 H, app. q, *J* = 6.7, C*H*(OH)), 2.51−2.42 (3 H, m, SCC*H*$_3$), 2.11 (1 H, br. s, OH), 1.69−1.50 (2 H, m, CH(OH)C*H*$_2$), 1.50−1.18 (12 H, m, 6 × CH_2), 0.97−0.83 (3 H, m, CH_3).

^{13}C (100 MHz) δ = 139.8 (Ar), 139.0 (Ar), 130.9 (CH(OH)*C*H), 125.9 (Ar), 125.4 (Ar), 123.8 (CH(OH)CH=*C*H), 72.9 (CH(OH)), 37.3 (CH(OH)*C*H$_2$), 31.8 (CH$_2$), 29.5 (CH$_2$), 29.2 (CH$_2$), 25.4 (CH$_2$), 22.6 (CH$_2$), 15.5 (SC(*C*H$_3$)), 14.1 (CH$_3$).

LRMS (ESI+): 289.18 (25, M+Na); HRMS (ESI+): (M+Na) 289.1597 calculated for $C_{16}H_{26}OSNa$; found 289.1589.

(*E*)-1-(Furan-2-yl)-undec-1-en-3-ol (53)



Following **General Procedure A**, methyltriphenylphosphonium bromide (714 mg, 2.0 mmol) was first reacted with nonanal (284 mg, 2.0 mmol) and then furfuraldehyde (202 mg, 2.1 mmol) to give allylic alcohol **53** (235 mg, 49%) as a red-orange oil; R_f 0.37 (25% Et_2O/ petrol);

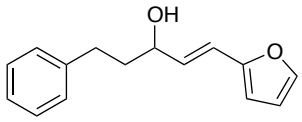
IR (neat) /cm^{-1}: 3352br. w, 2924w, 2854w, 1465w, 1011w, 960w, 793w, 728w.

^{1}H (400 MHz) δ = 7.35 (1 H, d, *J* = 1.5, Ar), 6.41 (1 H, d, *J* = 15.9, CH(OH)CH=C*H*), 6.37 (1 H, dd, *J* = 3.3, 1.8, Ar), 6.24 (1 H, d, *J* = 3.0, Ar), 6.18 (1 H, dd, *J* = 15.9, 6.6, CH(OH) C*H*), 4.24 (1 H, app. q, *J* = 6.4, C*H*(OH)), 1.76 (1 H, br. s, OH), 1.67−1.53 (2 H, m, CH (OH)C*H*$_2$), 1.48−1.18 (12 H, m, 6 × CH$_2$), 0.89 (3 H, t, *J* = 6.7, CH$_3$).

^{13}C (100 MHz) δ = 152.4 (Ar), 141.9 (Ar), 131.0 (CH(OH)*C*H), 118.4 (CH(OH)CH=*C*H), 111.2 (Ar), 107.9 (Ar), 72.6 (CH(OH)), 37.4 (CH(OH)*C*H$_2$), 31.8 (CH$_2$), 29.6 (CH$_2$), 29.5 (CH$_2$), 29.3 (CH$_2$), 25.4 (CH$_2$), 22.6 (CH$_2$), 14.1 (CH$_3$).

LRMS (ESI−): 251.18 (45), 469.36 (40) 533.37 (100); (ESI+): 477.36 (100), 511.37 (40); HRMS (FI+): 236.1776 calculated for $C_{15}H_{24}O_2$; found 236.1774.

(*E*)-1-(Furan-2-yl)-5-phenylpent-1-en-3-ol (54)



Following **General Procedure A**, methyltriphenylphosphonium bromide (714 mg, 2.0 mmol) was first reacted with 3-phenylpropanal (268 mg, 2.0 mmol) and then furfuraldehyde (202 mg, 2.1 mmol) to give allylic alcohol **54** (258 mg, 56%) as a red-orange oil; R_f 0.32 (30% Et_2O/petrol);

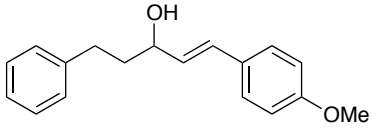
IR (neat) /cm^{-1}: 3363br. w, 2923w, 1602w, 1493w, 1454w, 1254w, 1150w, 1011m, 960m, 926m, 883w, 798w, 732s, 697s.

^{1}H (400 MHz) δ = 7.39−7.35 (1 H, app. d, CH furanyl), 7.35−7.17 (5 H, m, Ph), 6.44 (1 H, d, *J* = 15.9, CH(OH)CH=C*H*), 6.40 (1 H, dd, *J* = 3.2, 1.9, CH furanyl), 6.26 (1 H, d, *J* = 4.0, CH furanyl), 6.23 (1 H, dd, *J* = 15.9, 6.6, CH(OH)C*H*), 4.29 (1 H, app. q, *J* = 6.3, C*H*(OH)), 2.85−2.69 (2 H, m, $PhCH_2$), 2.04−1.88 (2 H, m, CH(OH)CH_2), 1.77 (1 H, br. s, OH).

^{13}C (100 MHz) δ = 152.3 (furanyl), 141.9 (furanyl), 141.7 (Ph), 130.8 (CH(OH)*C*H), 128.4 (2 × Ph), 128.3 (2 × Ph), 125.8 (Ph), 118.7 (CH(OH)CH=*C*H), 111.3 (furanyl), 108.1 (furanyl), 71.8 (CH(OH)), 38.7 (CH(OH)*C*H_2), 31.6 ($PhCH_2$).

LRMS (ESI+): 251.12 (20, M+Na); HRMS (ESI+): (M+Na) 251.1043 calculated for $C_{15}H_{16}O_2Na$ found 251.1038.

(*E*)-1-(4-methoxyphenyl)-5-phenylpent-1-en-3-ol (55)



Following **General Procedure A**, methyltriphenylphosphonium bromide (714 mg, 2.0 mmol) was first reacted with 3-phenylpropanal (268 mg, 2.0 mmol) and then *p*-

methoxybenzaldehyde (286 mg, 2.1 mmol) to give allylic alcohol **55** (189 mg, 35%) as a red-orange oil; R_f 0.28 (30% Et_2O/petrol);

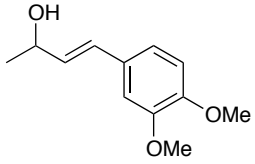
IR (neat) /cm^{-1}: 3367 br. w, 3026 w, 2932 w, 2836 w, 1606 m, 1510 s, 1454 m, 1300 m, 1245 s, 1174 s, 1031 s, 966 s, 816 m, 732 m, 698 s.

^1H (400 MHz) δ = 7.38−7.20 (7 H, m, Ph, Ar), 6.92−6.86 (2 H, m, Ar), 6.54 (1 H, d, *J* = 15.9, ArC*H*=), 6.14 (1 H, dd, *J* = 15.9, 7.1, CH(OH)C*H*), 4.30 (1 H, app. q, *J* = 6.6, C*H*(OH)), 3.83 (1 H, s, OCH_3), 2.86−2.71 (2 H, m, $PhCH_2$), 2.08−1.89 (3 H, m, CH(OH)CH_2, OH).

^{13}C (100 MHz, $CDCl_3$) δ = 159.2 (Ar), 141.8 (Ph), 130.1 (ArCH=), 130.0 (CH(OH)*C*H), 129.3 (Ar), 128.4 (2 × Ph), 128.3 (2 × Ph), 127.6 (2 × Ar), 125.8 (Ph), 114.0 (2 × Ar), 72.4 (CH(OH)), 55.2 (OCH_3), 38.7 (*C*H_2CH(OH)), 31.7 ($PhCH_2$).

LRMS (ESI+): 291.14 (100, M+Na), 292.16 (35), 559.31 (52, 2M+Na); HRMS (ESI+): (M +Na) 291.1361calculated for $C_{18}H_{20}O_2Na$, found 291.1356.

(*E*)-4-(3,4-Dimethoxyphenyl)-but-3-en-2-ol (56)



Following **General Procedure A**, methyltriphenylphosphonium bromide (714 mg, 2.0 mmol) was first reacted with acetaldehyde (112 μL, 2.0 mmol) and then 3,4-dimethoxybenzaldehyde (349 mg, 2.1 mmol) to give allylic alcohol **56**[27a] (271 mg, 65%) as a pale yellow oil; R_f 0.16 (30% Et_2O/petrol);

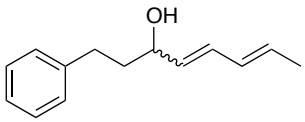
IR (neat) /cm^{-1}: 3372br. w, 2967w, 2836w, 1513m, 1463w, 1262m, 1136m, 1024m, 965w, 911w, 800w, 728m.

^{1}H (400 MHz) δ = 6.89 (1 H, d, *J* = 1.8, Ar), 6.85 (1 H, dd, *J* = 8.4, 1.8, Ar), 6.76 (1 H, d, *J* = 8.4, Ar), 6.44 (1 H, d, *J* = 15.9, CH(OH)CH=C*H*), 6.09 (1 H, dd, *J* = 15.9, 6.3, CH(OH) C*H*), 4.42 (1 H, quin d, *J* = 6.3, 0.8, C*H*(OH)), 3.84 (3 H, s, OCH_3), 3.82 (3 H, s, OCH_3), 2.32 (1 H, br. s, OH), 1.33 (3 H, d, *J* = 6.3, CH_3).

^{13}C (100 MHz) δ = 148.8 (OCH_3), 148.6 (OCH_3), 131.6 (CH(OH)*C*H), 129.6 (Ar), 128.9 (CH(OH)CH=*C*H), 119.5 (Ar), 110.9 (Ar), 108.6 (Ar), 68.7 (CH(OH)), 55.7 (Ar), 55.6 (Ar), 23.3 (CH_3).

LRMS (ESI+): 231.10 (25, M+Na), 391.28 (30), 413.24 (91), 803.44 (96); HRMS (ESI+): (M+Na) 231.0992 calculated for $C_{12}H_{16}O_3Na$; found 231.0997.

(6*E*)-1-Phenylocta-4,6-dien-3-ol (57)



Following **General Procedure A**, methyltriphenylphosphonium bromide (357 mg, 1.0 mmol) was first reacted with 3-phenylpropanal (134 mg, 1.0 mmol) and then crotonaldehyde (74 mg, 1.05 mmol) to give allylic alcohol **57** as a mixture of chromatographically inseparable isomers (103 mg, 51%, **57***E*:**57***Z* 81:19 by ^{1}H NMR integration of C*H*(OH)) as a pale yellow oil; R_f 0.23 (20% Et_2O/petrol);

IR (neat) /cm^{-1}: 3366br. w, 3024w, 2915w, 1495w, 1453w, 986s, 745m, 697s.

LRMS (ESI+): 225.14 (55, M+Na), 301.09 (100), 579.19 (67); HRMS (ESI+): (M+Na) 225.1250 calculated for $C_{14}H_{18}ONa$; found 225.1244.

Data for **57***E*:

^{1}H (400 MHz) δ = 7.34−7.17 (5 H, m, Ph), 6.21 (1 H, dd, *J* = 15.2, 10.6, CH(OH)CH=C*H*), 6.14−6.02 (1 H, m, C*H*=CHCH$_3$), 5.74 (1 H, dq, *J* = 15.0, 6.8, =C*H*CH$_3$), 5.62 (1 H, dd, *J* = 15.2, 7.1, CH(OH)C*H*=CH), 4.15 (1 H, app. q, *J* = 6.6, C*H*(OH)), 2.80−2.64 (2 H, m, PhC*H*$_2$), 2.02−1.82 (2 H, m, CH(OH)C*H*$_2$), 1.79 (3 H, d, *J* = 6.6, CH$_3$), 1.77 (1 H, br. s, OH).

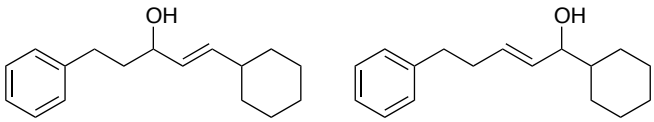
^{13}C (100 MHz) δ =141.9 (Ph), 133.0 (CH(OH)*C*H), 131.1 (CH(OH)CH=*C*H), 130.7 (*C*H=CHCH$_3$), 130.0 (=*C*HCH$_3$), 128.4 (2 × Ph), 128.3 (2 × Ph), 125.7 (Ph), 72.0 (CH(OH)), 38.7 (CH(OH)*C*H$_2$), 31.7 (Ph*C*H$_2$), 18.1 (CH$_3$)

Discernible data for **57***Z*:

^{1}H (400 MHz) δ = 7.34−7.17 (5 H, m, Ph), 6.33−6.23 (1 H, m, C*H*=CHCH$_3$), 6.14−6.02 (1 H, m, CH(OH)CH=C*H*), 5.78 (1 H, dq, *J* = 15.0, 6.8, =C*H*CH$_3$), 5.38−5.29 (1 H, m, CH(OH)C*H*=CH), 4.60 (1 H, app. q, *J* = 7.5, C*H*(OH)), 2.80−2.64 (2 H, m, PhC*H*$_2$), 2.02−1.82 (2 H, m, CH(OH)C*H*$_2$), 1.79 (3 H, d, *J* = 6.6, CH$_3$), 1.77 (1 H, br. s, OH).

^{13}C (100 MHz) δ = 141.8 (Ph), 131.8 (=*C*HCH$_3$), 130.8 (CH(OH)CH=*C*H), 130.5 (CH(OH)*C*H), 128.4 (Ph), 128.3 (Ph), 126.5 (*C*H=CHCH$_3$), 125.9 (Ph), 67.3 (CH(OH)), 38.9 (CH(OH)*C*H$_2$), 31.6 (PhCH$_2$), 18.2 (CH$_3$).

(*E*)-1-cyclohexyl-5-phenylpent-1-en-3-ol (58a) and (*E*)-1-cyclohexyl-5-phenylpent-2-en-1-ol (58b)



Following **General Procedure A**, methyltriphenylphosphonium bromide (714 mg, 2.0 mmol) was first reacted with 3-phenylpropanal (268 mg, 2.0 mmol) and then cyclohexanecarboxaldehyde (236 mg, 2.1 mmol) to give *E*-allylic alcohols **58a** and **58b**[59] as a mixture of chromatographically inseparable isomers (206 mg, 42%, **58a**:**58b** 90:10 by ^{1}H NMR integration of C*H*(OH)) as a pale yellow oil; R_f 0.28 (20% Et_2O/petrol);

IR (neat) /cm^{-1}: 3364br. w, 2922m, 2851m, 1495w, 1449m, 1030w, 969m, 907m, 730s, 697s.

LRMS (ESI+): 267.17 (100, M+Na), 268.20 (38), 511.38 (24, 2M+Na); HRMS (ESI+): (M+Na) 267.1725 calculated for $C_{17}H_{24}ONa$; found 267.1720.

Data for **58a**:

^{1}H (400 MHz) δ = 7.35−7.19 (5 H, m, Ph), 5.64 (1 H, dd, *J* = 15.7, 6.6, CH(OH)CH=C*H*), 5.49 (1 H, ddd, *J* = 15.7, 7.0, 1.1, CH(OH)C*H*), 4.09 (1 H, app. q, *J* = 6.7, C*H*(OH)), 2.80−2.65 (2 H, m, (PhC*H*$_2$), 2.10−1.58 (8 H, m, CH cyclohexyl, 2 × CH_2 cyclohexyl, CH(OH)C*H*$_2$ and OH), 1.42−1.05 (6 H, m, 3 × CH_2 cyclohexyl).

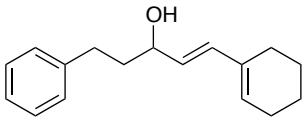
^{13}C (100 MHz) δ = 142.0 (Ph), 138.0 (CH(OH)CH=*C*H), 130.1 (CH(OH)*C*H), 128.3 (2 × Ph), 128.2 (2 × Ph), 125.6 (Ph), 72.4 (CH(OH)), 40.2 (CH=CH*C*H), 38.7 (CH(OH)*C*H$_2$), 32.8 (CH_2 cyclohexyl), 32.7 (CH_2 cyclohexyl), 31.7 (Ph*C*H$_2$), 26.0 (CH_2 cyclohexyl), 25.9 (2 × CH_2 cyclohexyl).

Data for **58b**:

^{1}H (400 MHz) δ = 7.35−7.19 (5 H, m, Ph), 5.66 (1 H, dt, *J* = 15.5, 6.4, CH(OH)CH=C*H*), 5.49 (1 H, ddt, *J* = 15.5, 7.3, 1.2, CH(OH)C*H*), 3.79 (1 H, t, *J* = 6.9, C*H*(OH)), 2.80−2.65 (2 H, m, PhCH_2), 2.42 (2 H, q, *J* = 7.4, PhCH$_2$CH_2), 2.10−1.58 (5 H, m, C*H* cyclohexyl, CH$_2$ cyclohexyl, OH), 1.42−1.05 (5 H, m, CH$_2$ cyclohexyl), 1.03−0.88 (2 H, m, CH$_2$ cyclohexyl).

^{13}C (100 MHz) δ = 141.5 (Ph), 132.2 (CH(OH)*C*H=CH), 131.5 (CH(OH)CH=*C*H), 128.2 (2 × Ph), 128.1 (2 × Ph), 125.7 (Ph), 77.4 (CH(OH)), 43.5 (CH cyclohexyl), 35.5 (Ph*C*H$_2$), 33.9 (PhCH$_2$*C*H$_2$), 28.6 (CH$_2$ cyclohexyl), 28.5 (CH$_2$ cyclohexyl), 26.4 (CH$_2$ cyclohexyl), 25.9 (CH$_2$ cyclohexyl).

(*E*)-1-(Cyclohex-1-en-1-yl)-5-phenylpent-1-en-3-ol (59)



Following **General Procedure A**, methyltriphenylphosphonium bromide (714 mg, 2.0 mmol) was first reacted with 3-phenylpropanal (268 mg, 2.0 mmol) and then 1-cyclohexene-1-carboxaldehyde (231 mg, 2.1 mmol) to give allylic alcohol **59** (215 mg, 44%) as a pale yellow oil; R_f 0.31 (20% Et$_2$O/petrol);

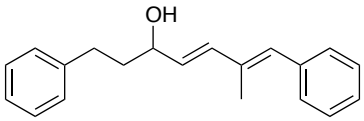
IR (neat) /cm^{-1}: 3334br. w, 2926w, 1649w, 1495w, 1453w, 1027m, 964m, 744m, 698s.

^{1}H (400 MHz) δ = 7.35−7.18 (5 H, m, Ph), 6.23 (1 H, d, *J* = 15.7, CH(OH)CH=C*H*), 5.79 (1 H, app. br. s, C=C*H*CH$_2$), 5.60 (1 H, dd, *J* = 15.7, 7.2, CH(OH)C*H*), 4.18 (1 H, app. q, *J* = 6.7, C*H*(OH)), 2.82−2.66 (2 H, m, PhCH_2), 2.21−2.11 (4 H, m, 2 × CH$_2$ cyclohexenyl), 2.03−1.81 (3 H, m, CH(OH)CH_2 and OH), 1.76−1.67 (2 H, m, CH$_2$ cyclohexenyl), 1.67−1.59 (2 H, m, CH$_2$ cyclohexenyl).

^{13}C (100 MHz) δ = 141.9 (Ph), 134.9 (*C*=CH), 134.4 (CH(OH)CH=*C*H), 130.0 (C=*C*HCH$_2$), 128.4 (2 × Ph), 128.2 (2 × Ph), 128.0 (CH(OH)*C*H), 125.6 (Ph), 72.5 (CH(OH)), 38.8 (CH(OH)*C*H$_2$), 31.7 (PhCH$_2$), 25.8 (=C*C*H$_2$), 24.4 (CH$_2$), 22.4 (CH$_2$), 22.3 (CH$_2$).

LRMS (ESI+): 265.15 (100, M+Na), 266.18 (70), 389.24 (48), 507.35 (63, 2M+Na); HRMS (ESI+): (M+Na) 265.1568 calculated for $C_{17}H_{22}ONa$; found 265.1567.

(4*E*,6*E*)-6-Methyl-1,7-diphenylhepta-4,6-dien-3-ol (60)



Following **General Procedure A**, methyltriphenylphosphonium bromide (357 mg, 1.0 mmol) was first reacted with 3-phenylpropanal (134mg, 1.0 mmol) and then α-methyl-*trans*-cinnamaldehyde (154 mg, 1.05 mmol) to give allylic alcohol **60** (110 mg, 39%) as a pale yellow oil; R_f 0.21 (20% Et$_2$O/petrol);

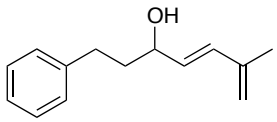
IR (neat) /cm^{-1}: 3024w, 2919w, 2858w, 1601w, 1494m, 1453m, 1101w, 1030m, 1004m, 964s, 916m, 826w, 746s, 696s.

^{1}H (400 MHz) δ = 7.41−7.15 (10 H, m, Ph), 6.55 (1 H, s, PhC*H*=C), 6.44 (1 H, d, *J* = 15.5, CC*H*=CH), 5.82 (1 H, dd, *J* = 15.5, 6.8, CH(OH)C*H*), 4.28 (1 H, app. q, *J* = 6.5, C*H*(OH)), 2.85−2.70 (2 H, m, CH(OH)C*H*$_2$), 2.02 (3 H, s, CH$_3$), 2.06−1.88 (2 H, m, PhC*H*$_2$), 1.69 (1 H, br. s, OH).

^{13}C (100 MHz) δ = 141.8 (Ph), 137.6 (Ph), 136.0 (C*C*H=CH), 135.0 (*C*(CH$_3$)), 131.7 (Ph*C*H=C), 131.4 (CH(OH)*C*H), 129.1 (Ph), 128.4 (2 × Ph), 128.4 (2 × Ph), 128.1 (2 × Ph), 126.6 (Ph), 125.8 (Ph), 72.4 (CH(OH)), 38.9 (PhCH$_2$), 31.7 (CH(OH)*C*H$_2$), 13.9 (CH$_3$).

LRMS (ESI+): 301.17 (100, M+Na); HRMS (ESI+): (M+Na) 301.1563 calculated for $C_{20}H_{22}ONa$; found 301.1561.

(*E*)-6-Methyl-1-phenylhepta-4,6-dien-3-ol (61)



Following **General Procedure A**, methyltriphenylphosphonium bromide (714 mg, 2.0 mmol) was first reacted with 3-phenylpropanal (268 mg, 2.0 mmol) and then methacrylaldehyde (147 mg, 2.1 mmol) to give allylic alcohol **61** (254 mg, 63%) as a pale yellow oil; R_f 0.29 (20% Et_2O/petrol);

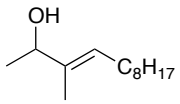
IR (neat) /cm^{-1}: 3354br. w, 2922w, 2360w, 1608w, 1495w, 1453w, 966w, 907m, 729m, 698m.

^1H (400 MHz) δ = 7.37−7.19 (5 H, m, Ph), 6.35 (1 H, d, *J* = 15.8, =CC*H*), 5.72 (1 H, dd, *J* = 15.8, 6.9, CH(OH)C*H*), 5.09−5.01 (2 H, m, C=CH_2), 4.23 (1 H, app. q, *J* = 6.6, C*H*(OH)), 2.85−2.67 (2 H, m, PhCH_2), 2.13 (1 H, br. s, OH), 2.03−1.84 (5 H, m, CH(OH)CH_2 and CH_3).

^{13}C (125 MHz) δ = 141.8 (Ph), 141.3 (*C*=CH_2), 133.5 (=C*C*H), 132.1 (CH(OH)*C*H), 128.4 (2 × Ph), 128.3 (Ph), 125.8 (Ph), 116.9 (Ph), 72.2 (CH(OH)), 38.8 (CH(OH)*C*H_2), 31.7 (PhCH_2), 18.6 (CH_3).

LRMS (ESI−): 112.99 (100), 203.11 (25, M+Na); HRMS (ESI+): (M+Na) 255.1250 calculated for $C_{14}H_{18}ONa$; found 255.1244.

(*E*)-3-Methyldodec-3-en-2-ol (62)



Following **General Procedure B**, ethyltriphenylphosphonium bromide (371 mg, 1.0 mmol) was first reacted with acetaldehyde (56 μL, 1.0 mmol) and then nonanal (149 mg, 1.05 mmol) to give allylic alcohol **62** (115 mg, 58%) as a pale yellow oil; R_f 0.35 (20% Et_2O/ petrol);

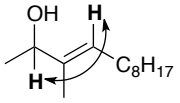
IR (film) /cm^{-1}: 3340w, 2922m, 2854m, 2360w, 1717w, 1457w, 1368w, 1077m, 887w.

^1H (400 MHz) δ = 5.40 (1 H, t, *J* = 7.1, C=C*H*), 4.20 (1 H, q, *J* = 6.3, C*H*(OH)), 2.00 (2 H, q, *J* = 7.1, =CHC*H*$_2$), 1.62 (3 H, s, =CCH_3), 1.56 (1 H, br. s, OH), 1.38−1.21 (15 H, m, 6 × CH_2 and C*H*$_3$CH(OH)), 0.88 (3 H, t, *J* = 6.8, CH_2C*H*$_3$).

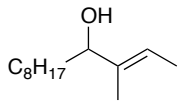
^{13}C (100 MHz) δ = 138.2 (=*C*CH_3), 125.4 (C=*C*H), 73.5 (CH(OH)), 31.9 (CH_2), 29.5 (2 × CH_2), 29.3 (CH_2), 29.2 (CH_2), 27.5 (=CH*C*H_2), 22.65 (CH_2), 21.6 (=C*C*H_3), 14.1 (CH_2*C*H_3), 11.4 (*C*H_3CH(OH)).

LRMS (ESI+): 221.3 (15, M+Na), 253.3 (45), 413.3 (100); HRMS (ESI+): (M+Na) 221.1876 calculated for $C_{13}H_{26}ONa$; found 221.1879.

NOEs observed for **62**:



(*E*)-3-Methyldodec-2-en-4-ol (63)



Following **General Procedure B**, ethyltriphenylphosphonium bromide (371 mg, 1.0 mmol) was first reacted with nonanal (142 mg, 1.0 mmol) and then acetaldehyde (59 μL, 1.05 mmol) to give allylic alcohol **63**[60] (126 mg, 64%) as a pale yellow oil; R_f 0.35 (20% Et_2O/ petrol);

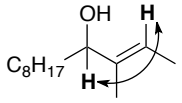
IR (neat) /cm^{-1}: 3343w, 2923m, 2855m, 1457w, 1378w, 1000w, 828w.

^1H (400 MHz) δ = 5.44 (1 H, q, *J* = 6.3, C=C*H*), 3.96 (1 H, app. t, *J* = 6.8, C*H*(OH)), 1.56−1.65 (6 H, m, 2 × CH_3), 1.55−1.46 (2 H, m, CH(OH)C*H*$_2$), 1.35−1.14 (12 H, m, 6 × CH_2), 0.87 (3 H, t, *J* = 6.8, CH_2CH_3).

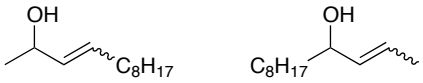
^{13}C (100 MHz) δ = 138.0 (=*C*CH_3), 120.7 (=CH), 78.1 (CH(OH)), 34.8 (*C*H_2CH(OH)), 31.8 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 25.8 (CH_2), 22.6 (CH_2), 14.1 (CH_2CH_3), 13.0 (CH_3), 10.7 (CH_3).

LRMS (ESI+): 142.3 (20), 235.3 (45), 413.3 (100); HRMS (FI+): 198.1984 calculated for $C_{13}H_{26}O$; found 198.1991.

NOEs observed for **63**:



Dodec-3-en-2-ol (64) and Dodec-2-en-4-ol (65)



Following **General Procedure A**, methyltriphenylphosphonium bromide (357 mg, 1.0 mmol) was first reacted with acetaldehyde (56 μL, 1.0 mmol) and then nonanal (149 mg, 1.05 mmol) to give allylic alcohols **64** and **65** as a mixture of chromatographically inseparable isomers (102 mg, 55% **64***E*[61]:**64***Z*[62]:**65***Z* 60:33:7 by ^{1}H NMR integration of C*H*(OH)) as a pale yellow oil; R_f 0.32 (25% Et_2O/petrol);

IR (neat) /cm^{-1}: 3339w, 2923m, 2854m, 2360w, 1457w, 1367w, 1059m, 967m, 721w.

LRMS (ESI+): 207.1 (25, M+Na), 281.3 (100), 413.3 (100); HRMS (ESI+): (M+Na) 207.1723 calculated for $C_{12}H_{24}ONa$; found 207.1719.

Data for **64***E*:

^{1}H (400 MHz) δ = 5.63 (1 H, dt, *J* = 15.4, 6.8, =C*H*CH$_2$), 5.50 (1 H, dd, *J* = 15.4, 6.8, CH(OH)C*H*), 4.25 (1 H, app. quin, *J* = 6.4, C*H*(OH)), 2.01, (2 H, quin, *J* = 6.9, =CHC*H*$_2$), 1.60 (1 H, br. s, OH), 1.40−1.21 (15 H, m, 6 × CH$_2$ and CH(OH)C*H*$_3$), 0.88 (3 H, t, *J* = 6.7, CH$_2$C*H*$_3$).

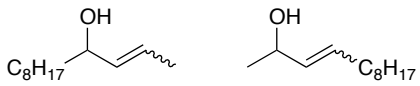
^{13}C (100 MHz) δ = 134.0 (CH(OH)*C*H), 131.2 (=*C*HCH$_2$), 69.0 (CH(OH)), 32.1 (CH$_2$), 31.9 (CH$_2$), 29.4 (CH$_2$), 29.2 (CH$_2$), 29.2 (CH$_2$), 23.4 (*C*H$_3$CH(OH)), 22.6 (CH$_2$), 14.1 (CH$_3$).

Discernible data for **64***Z*:

^{1}H (400 MHz, $CDCl_3$) δ = 5.44−5.37 (2 H, m, C*H*=C*H*), 4.64 (1 H, app. quin, *J* = 6.5, C*H*(OH)), 2.07 (2 H, ddd, *J* = 12.8, 6.3, 2.1, =CHC*H*$_2$), 1.60 (1 H, br. s, OH), 1.40−1.21 (15 H, m, 6 × CH$_2$ and CH(OH)C*H*$_3$), 0.88 (3 H, t, *J* = 6.7, CH$_2$C*H*$_3$).

^{13}C (100 MHz, $CDCl_3$) δ = 133.7 (CH(OH)*C*H), 131.4 (=*C*HCH_2), 63.9 (CH(OH)), 31.9 (CH_2), 29.7(CH_2), 29.4 (CH_2), 29.2 (CH_2), 29.2 (CH_2), 27.5 (CH_2), 23.6 (*C*H_3CH(OH)), 22.6 (CH_2), 14.1 (CH_3).

Dodec-2-en-4-ol (65) and Dodec-3-en-2-ol (64)



Following **General Procedure A**, methyltriphenylphosphonium bromide (357 mg, 1.0 mmol) was first reacted with nonanal (142 mg, 1.0 mmol) and then acetaldehyde (59 μL, 1.05 mmol) to give allylic alcohols **8** and **7** as a mixture of chromatographically inseparable isomers (106 mg, 58%, **65***E*[63]:**65***Z*:**64***E*[61]:**64***Z*[62] 46:13:4:37 by ^{1}H NMR integration of C*H*(OH)) as a pale yellow oil; R_f 0.32 (25% Et_2O/petrol);

IR (neat) /cm^{-1}: 3355w, 2924m, 2854m, 2360w, 1456w, 1377w, 1109w, 908m, 732s.

LRMS (ESI+): 207.1 (15, M+Na), 253.3 (30), 413.3 (100); HRMS (ESI+): (M+Na) 207.1723 calculated for $C_{12}H_{24}ONa$; found 207.1718.

Data for **65***E*:

^{1}H (400 MHz) δ = 5.64 (1 H, dq, *J* = 15.5, 6.0, =C*H*CH_3), 5.47 (1 H, dd, *J* = 15.5, 6.9, CH(OH)C*H*), 4.01 (1 H, app. q, *J* = 6.6, C*H*(OH)), 1.72−1.64 (4 H, m, =CHC*H*$_3$, OH), 1.60−1.40 (2 H, m, CH(OH)C*H*$_2$), 1.39−1.17 (12 H, m, 6 × CH_2), 0.87 (3 H, t, *J* = 6.7, CH_3).

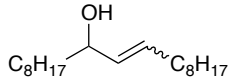
^{13}C (100 MHz) δ = 134.4 (CH(OH)*C*H), 126.6 (=*C*HCH_3), 73.1 (CH(OH)), 37.2 (CH_2CH(OH)), 31.9 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 25.5 (CH_2), 22.6 (CH_2), 17.6 (=CH*C*H_3), 14.1 (CH_3).

Discernible data for **65***Z*:

^{1}H (400 MHz, $CDCl_3$) δ = 5.42−5.34 (2 H, m, C*H*=C*H*), 4.49−4.41 (1 H, m, C*H*(OH)), 1.72−1.64 (4 H, m, CHCH_3, OH), 1.59−1.40 (2 H, m, CH(OH)CH_2), 1.39−1.17 (12 H, m, 6 × CH_2), 0.87 (3 H, t, *J* = 6.7, (CH_3).

^{13}C (100 MHz, $CDCl_3$) δ = 133.6 (CH(OH)*C*H), 126.1 (=*C*HCH$_3$), 67.3 (CH(OH)), 37.4 (*C*H$_2$CH(OH)), 29.6 (CH_2), 27.5 (CH_2), 25.3 (CH_2), 17.6 (CH_3), 13.2 (=CH*C*H$_3$).

Nonadec-10-en-9-ol (66)



Following **General Procedure A**, methyltriphenylphosphonium bromide (714 mg, 2.0 mmol) was first reacted with nonanal (284 mg, 2.0 mmol) and then nonanal (299 mg, 2.1 mmol) to give allylic alcohol **66** as a mixture of chromatographically inseparable isomers (294 mg, 52%, **66***E*:**66***Z* 64:36 by ^{1}H NMR integration of C*H*(OH)) as a colourless oil; R_f 0.33 (20% Et_2O/petrol);

IR (neat) /cm^{-1}: 2922m, 2853m, 1464w, 1004w, 967w, 721w.

LRMS (ESI+): 142.17 (100), 420.28 (55), 579.21 (45); (ESI−): 797.20 (45), 871.23 (70), 945.25 (100); HRMS (FI+): 282.2923 calculated for $C_{19}H_{38}O$, found 282.2912.

Data for **66***E*:

^{1}H (500 MHz) δ = 5.63 (1 H, dt, *J* = 15.4, 6.9, =C*H*CH$_2$), 5.45 (1 H, ddt, *J* = 15.4, 7.2, 1.3, CH(OH)C*H*), 4.04 (1 H, app. q, *J* = 6.7, C*H*(OH)), 2.03 (2 H, q, *J* = 7.3, =CHCH_2), 1.57 (1 H, s, OH), 1.40−1.20 (26 H, m, 13 × CH_2), 0.92−0.85 (6 H, m, 2 × CH_3).

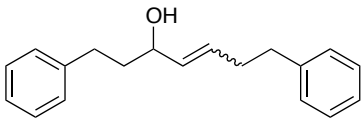
^{13}C (125 MHz) δ = 133.0 (CH(OH)*C*H), 132.2 (=*C*HCH$_2$), 73.3 (CH(OH)), 37.3 (CH$_2$), 32.2 (CH$_2$), 31.9 (CH$_2$), 29.6 (CH$_2$), 29.5 (CH$_2$), 29.3 (CH$_2$), 29.2 (CH$_2$), 29.2 (CH$_2$), 29.1 (CH$_2$), 25.5 (CH$_2$), 22.7 (2 × CH$_2$), 14.1 (2 × CH$_3$)

Data for **66***Z*:

^{1}H (400 MHz) δ = 5.49 (1 H, dd, *J* = 10.8, 7.3, =C*H*CH$_2$), 5.40−5.32 (1 H, m, CH(OH)C*H*), 4.42 (1 H, app. q, *J* = 7.3, C*H*(OH)), 2.16−2.06 (2 H, m, =CHC*H*$_2$), 1.75−1.16 (27 H, m, 13 × CH$_2$ and OH), 0.95−0.83 (6 H, m, 2 × CH$_3$).

^{13}C (100 MHz) δ = 132.6 (CH(OH)*C*H), 132.2 (=*C*HCH$_2$), 67.7 (CH(OH)), 37.5 (CH$_2$), 29.7 (CH$_2$), 29.6 (CH$_2$), 29.6 (CH$_2$), 29.4 (CH$_2$), 29.3 (CH$_2$), 29.2 (CH$_2$), 29.2 (CH$_2$), 27.7 (CH$_2$), 25.4 (CH$_2$), 22.7 (2 × CH$_2$), 14.1 (2 × CH$_3$).

1,7-Diphenylhept-4-en-3-ol (67)



Following **General Procedure A**, methyltriphenylphosphonium bromide (714 mg, 2.0 mmol) was first reacted with 3-phenylpropanal (268 mg, 2.0 mmol) and then 3-phenylpropanal (282 mg, 2.1 mmol) to give allylic alcohol **67** as a mixture of chromatographically inseparable isomers (293 mg, 55%, **67***E*:**67***Z* 82:18 by ^{1}H NMR integration of C*H*(OH)) as a pale yellow oil; R$_f$ 0.30 (30% Et$_2$O/petrol);

IR (neat) /cm^{-1}: 3025w, 2924w, 2856w, 1602w, 1495w, 1453w, 1030w, 969w, 912w, 743m, 696s.

LRMS (ESI+): 154.17 (100); (ESI−): 291.21 (35), 349.27 (70), 397.31 (100), 603.55 (95);

HRMS (FI+): 266.1671 calculated for C$_{19}$H$_{22}$O, found 266.1679.

Data for **67***E*:

^{1}H (500 MHz) δ = 7.35−7.11 (10 H, m, 2 × Ph), 5.72 (1 H, dt, *J* = 15.2, 6.8, =C*H*CH$_2$), 5.54 (1 H, ddt, *J* = 15.2, 7.0, 1.2, CH(OH)C*H*), 4.09 (1 H, app. q, *J* = 6.6, C*H*(OH)), 2.77−2.56 (4 H, m, 2 × PhCH$_2$), 2.44−2.32 (2 H, m, =CHC*H*$_2$), 1.94−1.74 (2 H, m, CH(OH)C*H*$_2$), 1.43 (1 H, br. s, OH).

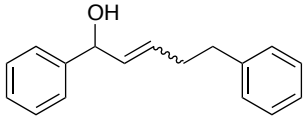
^{13}C (125 MHz) δ = 142.0 (Ph), 141.6 (Ph), 133.5 (CH(OH)*C*H), 131.4 (=*C*HCH$_2$), 128.4 (2 × Ph), 128.3 (2 × Ph), 128.3 (2 × Ph), 125.9 (2 × Ph), 125.8 (2 × Ph), 72.3 (CH(OH)), 38.7 (CH$_2$), 35.5 (CH$_2$), 33.9 (CH$_2$), 31.7 (CH$_2$)

Data for **67***Z*:

^{1}H (400 MHz) δ = 7.37−7.14 (10 H, m, 2 × Ph), 5.57 (1 H, dd, *J* = 10.8, 7.8, =C*H*CH$_2$), 5.49−5.40 (1 H, m, CH(OH)C*H*), 4.26 (1 H, app. q, *J* = 7.3, C*H*(OH)), 2.54−2.82 (4 H, m, 2 × PhCH$_2$), 2.44−2.32 (2 H, m, =CHC*H*$_2$), 1.71−1.59 (2 H, m, CH(OH)C*H*$_2$), 1.05 (1 H, br. s, OH).

^{13}C (100 MHz) δ = 141.8 (Ph), 141.4 (Ph), 133.3 (CH(OH)*C*H), 130.8 (=*C*HCH$_2$), 128.6 (2 × Ph), 128.3 (2 × Ph), 128.3 (2 × Ph), 126.0 (2 × Ph), 125.7 (2 × Ph), 66.8 (CH(OH)), 38.7 (CH$_2$), 35.6 (CH$_2$), 31.5 (CH$_2$), 29.6 (CH$_2$).

1,5-Diphenylpent-2-en-1-ol (68)



Following **General Procedure A**, methyltriphenylphosphonium bromide (357 mg, 1.0 mmol) was first reacted with benzaldehyde (106 mg, 1.0 mmol) and then 3-phenylpropanal (141 mg, 1.05 mmol) to give allylic alcohol **68** as a mixture of chromatographically

inseparable isomers (120 mg, 50%, **68***E*[57]:**68***Z* 46:54 by ^{1}H NMR integration of C*H*(OH)) as a pale yellow oil; R_f 0.39 (30% Et_2O/petrol);

LRMS (ESI+): 261.14 (100, M+Na); HRMS (ESI+): (M+Na) 261.1250 calculated for $C_{17}H_{18}ONa$; found 261.1248.

Data for **68***E*:

^{1}H (500 MHz) δ = 7.44−7.11 (10 H, m, 2 × Ph), 5.82 (1 H, dtt, *J* = 15.2, 6.6, 0.6, =C*H*CH_2), 5.70 (1 H, ddt, *J* = 15.2, 6.6, 1.2, (CH(OH)C*H*), 5.17 (1 H, dd, *J* = 6.6, 2.8, C*H*(OH)), 2.75 (2 H, quin d, *J* = 14.5, 7.3, PhCH_2), 2.42 (2 H, q, *J* = 7.1, C*H*$_2$CH(OH)), 1.94, (1 H, s, OH).

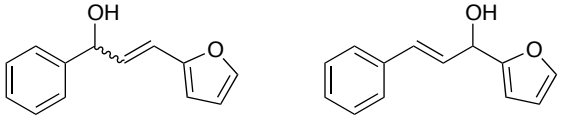
^{13}C (125 MHz) δ = 143.1 (Ph), 141.6 (Ph), 133.0 (CH(OH)C*H*), 131.5 (=C*H*CH_2), 128.4 (2 × Ph), 128.3 (2 × Ph), 128.2 (Ph), 127.5 (Ph), 126.1 (Ph), 125.8 (Ph), 75.0 (CH(OH), 35.4 (CH_2), 33.9 (CH_2).

Data for **68***Z*:

^{1}H (500 MHz) δ = 7.44−7.11 (10 H, m, 2 × Ph), 5.67−5.58 (2 H, m, C*H*=C*H*), 5.39 (1 H, dd, *J* = 7.3, 2.5, C*H*(OH)), 2.75 (2 H, quin d, *J* = 14.5, 7.3, PhCH_2), 2.67−2.58 (1 H, m, C$H_a$$H_b$CH(OH)), 2.57−2.48 (1 H, m, C$H_a$$H_b$CH(OH)), 1.53 (1 H, s, OH).

^{13}C (125 MHz) δ = 143.3 (Ph), 141.4 (Ph), 132.9 (CH(OH)*C*H), 130.7 (=C*H*CH_2), 128.6 (2 × Ph), 128.4 (2 × Ph), 127.3 (Ph), 126.1 (Ph), 125.7 (2 × Ph), 69.4 (CH(OH)), 35.6 (CH_2), 29.6 (CH_2).

3-(furan-2-yl)-1-phenylprop-2-en-1-ol (69) and (*E*)-1-(furan-2-yl)-3-phenylprop-2-en-1-ol (70)



Following **General Procedure A**, methyltriphenylphosphonium bromide (714 mg, 2.0 mmol) was first reacted with benzaldehyde (212 mg, 2.0 mmol) and then furfuraldehyde (202 mg, 2.1 mmol) to give allylic alcohols **69** and **70**[64] as a mixture of chromatographically inseparable isomers (160 mg, 40%, **69***E*[65]:**69***Z*:**70** 82:9:9 by ^{1}H NMR integration of C*H* (OH)) as a red-orange oil; R_f 0.29 (20% Et_2O/petrol);

IR (neat) /cm^{-1}: 3366br. w, 3028w, 2923w, 2854w, 1491w, 1452w, 1150w, 1067w, 1011m, 960w, 926w, 883m, 735m, 698m.

LRMS (ESI+): 405.17 (100), 406.17 (30), 787.35 (40), (ESI–): 215.09 (70), 381.17 (100), 413.19 (35); HRMS (FI+): 200.0837 calculated for $C_{13}H_{12}O_2$; found 200.0829.

Data for **69***E*:

^{1}H (400 MHz) δ = 7.53−7.29 (6 H, m, Ph and CH furanyl), 6.52 (1 H, dd, *J* = 16.0, 1.3, CH (OH)CH=C*H*), 6.38 (1 H, dd, *J* = 3.4, 1.9, CH furanyl), 6.36 (1 H, dd, *J* = 16.0, 5.8, (CH (OH)C*H*), 6.28 (1 H, d, *J* = 3.3, CH furanyl), 5.36 (1 H, d, *J* = 6.3, C*H*(OH)), 2.14 (1 H, br. s, OH).

^{13}C (100 MHz) δ = 152.2 (furanyl), 142.5 (Ph), 142.0 (furanyl), 130.1 (CH(OH)*C*H), 128.6 (2 × Ph), 127.8 (2 × Ph), 126.4 (Ph), 118.7 (CH(OH)CH=*C*H), 111.3 (furanyl), 108.4 (furanyl), 74.7 (CH(OH)).

Discernible data for **69***Z*:

^{1}H (400 MHz) δ = 7.53−7.29 (6 H, m, Ph and CH furanyl), 6.31 (1 H, d, *J* = 11.9, (CH(OH) CH=C*H*), 6.17 (1 H, d, *J* = 9.1, C*H*(OH)), 5.57 (1 H, dd, *J* = 11.9, 9.0, CH(OH)C*H*).

^{13}C (100 MHz) δ = 152.2 (furanyl), 142.6 (Ph), 142.1 (furanyl), 131.2 (CH(OH)*C*H), 128.5 (Ph), 126.4 (Ph), 128.5 (CH(OH)CH=*C*H), 75.1 (CH(OH)).

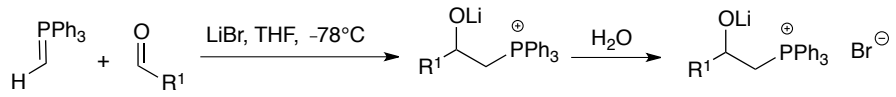
Discernible data for **70**:

^{1}H (400 MHz) δ = 7.53−7.29 (6 H, m, Ph, CH furanyl), 6.71 (1 H, d, *J* = 16.0, PhCH), 6.41 (1 H, dd, *J* = 16.0, 6.6, PhCH=C*H*), 5.40 (1 H, d, *J* = 6.6, C*H*(OH)).

^{13}C (100 MHz) δ = 142.5 (Ph), 142.5 (Ph), 131.2 (PhCH=*C*H), 70.5 (CH(OH)).

4.3 General procedures and data for Chapter 3

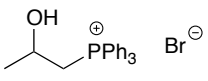
4.3.1 General Procedure C: Synthesis of hydroxyphosphonium bromide salts



A solution of anhydrous LiBr (2 equiv) in THF (7.5 mL/mmol LiBr) was added to anhydrous methyltriphenylphosphonium bromide (1.0 equiv) at room temperature. The mixture was stirred for 10 min before cooling to −78 ºC. *n*-BuLi (1.65M in hexanes, 1.0 equiv) was then added dropwise at −78 ºC. The cooling bath was removed, and the mixture allowed to warm to rt over 15 min during which time a clear-yellow solution formed. After 30 min at rt, the mixture was re-cooled to −78 ºC and a solution of the aldehyde (1.0 equiv) in THF (0.5 mL/mmol aldehyde) was added dropwise. After stirring for 20 min at this temperature, the mixture was quenched with saturated aq. ammonium chloride (20 mL), extracted with Et_2O (3 × 15 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the hydroxyphosphonium bromide salt.

4.3.2 Data for hydroxyphosphonium bromide salts synthesised

(2-hydroxypropyl)-1-triphenylphosphonium bromide (77)



Following **General Procedure C**, methyltriphenylphosphonium bromide (357 mg, 1.0 mmol) was reacted with acetaldehyde (56 μL, 1.0 mmol) to give hydroxyphosphonium bromide salt **77** (381 mg, 95%) as a white wax;

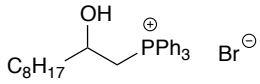
IR (neat) /cm^{-1}: 3244br. w, 2194w, 1438m, 1110m, 908m, 720s, 688s.

^{1}H (400 MHz) δ = 7.79−7.51 (15 H, m, 3 × Ph), 5.63 (1 H, d, *J* = 7.1, OH), 4.20−4.05 (1 H, m, C*H*(OH)), 3.86 (1 H, dt, *J* = 15.4, 10.6, CH_aCH$_b$PPh$_3$), 3.24−3.11 (1 H, m, CH$_a$CH_bPPh$_3$), 1.43 (3 H, dd, *J* = 6.1, 2.5, CH$_3$).

^{13}C (100 MHz) δ = 134.5 (d, $J_{C\text{-}P}$ = 2.4, 3 × CH), 133.7 (d, $J_{C\text{-}P}$ = 10.4, 6 × CH), 123.0 (d, $J_{C\text{-}P}$ = 12.8, 6 × CH), 118.7 (d, $J_{C\text{-}P}$ = 87.1, 3 × C), 62.5 (d, $J_{C\text{-}P}$ = 5.6, CH(OH)), 32.6 (d, $J_{C\text{-}P}$ = 51.1, CH$_2$), 25.1 (d, $J_{C\text{-}P}$ = 15.2, CH$_3$).

LRMS (ESI+): 321.2 (100, M−Br), 322.2 (25); HRMS (ESI+): 321.1403 calculated for $C_{21}H_{22}OP$; found 321.1399.

(2-hydroxydecyl)-1-triphenylphosphonium bromide (81)



Following **General Procedure C**, methyltriphenylphosphonium bromide (357 mg, 1.0 mmol) was reacted with nonanal (142 mg, 1.0 mmol) to give hydroxyphosphonium bromide salt **81** (478 mg, 96%) as a yellow wax;

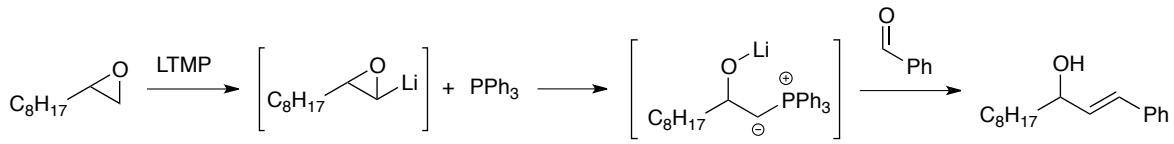
IR (neat) /cm^{-1}: 3218br. w, 2192w, 2360w, 1485m, 1110m, 919m, 720s, 688s, 640m.

^{1}H (400 MHz) δ = 7.75−7.45 (15 H, m, 3 × Ph), 5.16 (1 H, d, *J* = 4.0, OH), 4.05−3.72 (2 H, m, C*H*(OH) and CH_aCH$_b$PPh$_3$), 2.96 (1 H, t, *J* = 13.3, CH$_a$CH_bPPh$_3$), 1.96−1.77 (1 H, m, CH_aCH$_b$CH(OH)), 1.62−1.44 (CH$_a$CH_bCH(OH)), 1.33−0.94 (12 H, m, 6 × CH$_2$), 0.80−0.63 (3 H, m, CH$_3$)

^{13}C (100 MHz) δ = 134.4 (d, $J_{C\text{-}P}$ = 2.4, 3 × CH), 133.5 (d, $J_{C\text{-}P}$ = 10.4, 6 × CH), 129.8 (d, $J_{C\text{-}P}$ = 12.8, 6 × CH), 118.5 (d, $J_{C\text{-}P}$ = 86.3, 3 × C), 66.0 (d, $J_{C\text{-}P}$ = 5.6, CH(OH)), 38.4 (d, $J_{C\text{-}P}$ = 13.6, CH$_2$), 31.3 (d, $J_{C\text{-}P}$ = 4.8, CH$_2$), 29.1 (CH$_2$), 28.9 (CH$_2$), 28.8 (CH$_2$), 25.4 (CH$_2$), 25.1 (CH$_2$), 22.2 (CH$_2$), 13.7 (CH$_3$).

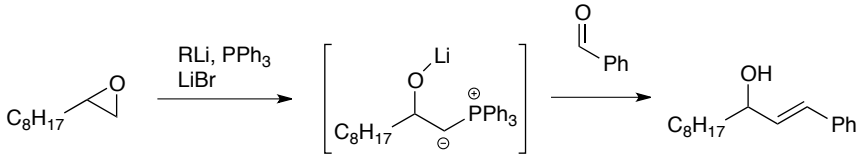
LRMS (ESI+): 399.26 (75), 419.19 (90, M−Br), 420.22 (100), 420.0 (50), 873.43 (100), 919.43 (45)

4.3.3 Synthesis of disubstituted *E*-allylic alcohols via α-lithiated terminal epoxides, using LTMP to lithiate terminal epoxides



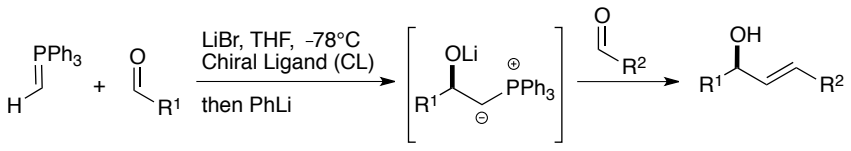
To a solution of 2,2,6,6-tetramethylpiperidine (168 µL, 1.0 mmol, 1.0 equiv) in THF (6 mL/mmol) at 0 °C was added *n*-BuLi (2.5 M in hexanes, 0.4 mL, 1.0 mmol, 1.0 equiv) dropwise with stirring. The mixture was allowed to warm to room temperature over 30 min, during which time a pale yellow solution was formed. This solution was then cooled to 0 °C and a solution of PPh_3 (524 mg, 2.0 mmol, 2 equiv) and anhydrous LiBr (174 mg, 2.0 mmol, 2.0 equiv) in THF (4 mL/mmol PPh_3) was added dropwise followed immediately by a solution of 1,2-epoxydecane (156 mg, 1.0 mmol, 1.0 equiv) in THF (0.5 mL/mmol) slowly dropwise. This solution was then stirred at 0 °C for 24 h during which time a red-orange color developed. This mixture was then cooled to −78 °C and a solution of benzaldehyde (112 mg, 1.05 mmol, 1.05 equiv.) in THF (0.5 mL/mmol) added slowly dropwise. The reaction mixture was stirred at −78 ºC for 2 h, then warmed to rt over 1 h and stirring continued for a further 1 h. The mixture was quenched with saturated aq. ammonium chloride (20 mL), extracted with Et_2O (3 × 15 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by flash chromatography in the solvent system indicated gave allylic alcohol **48** (77 mg, 31%) as a pale yellow oil; R_f 0.41 (30% Et_2O/petrol). Data as p 93.

4.3.4 Synthesis of disubstituted *E*-allylic alcohols via α-lithiated terminal epoxides, using organolithiums to lithiate terminal epoxides



To a solution of 1,2-epoxydecane (156 mg, 1.0 mmol, 1.0 equiv), PPh_3 (262 mg, 1.0 mmol, 1.0 equiv) and anhydrous LiBr (174 mg, 2.0 mmol, 2.0 equiv) in THF (14 mL) at −78 °C was added *s*-BuLi (1.3M in hexanes, 0.77 mL, 1.0 mmol, 1.0 equiv) very slowly, dropwise over ~10 min. The reaction mixture was stirred at −78 °C for 24 h, then a solution of benzaldehyde (112 mg, 1.05 mmol, 1.05 equiv) in THF (0.5 mL/mmol) added slowly dropwise. The reaction mixture was stirred at −78 ºC for 2 h, then warmed to rt over 1 h and stirring continued for a further 1 h. The mixture was quenched with saturated aq. ammonium chloride (20 mL), extracted with Et_2O (3 × 15 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by flash chromatography in the solvent system indicated gave allylic alcohol **48** (45 mg, 18%) as a pale yellow oil; R_f 0.41 (30% Et_2O/petrol). Data as p 93.

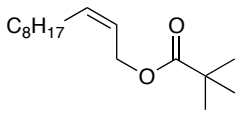
4.3.5 Synthesis of allylic alcohols using chiral, non-racemic diamine additive



A solution of anhydrous LiBr (87 mg, 1.0 mmol, 2.0 equiv) in THF (7.5 mL/mmol LiBr) was added to anhydrous methyltriphenylphosphonium bromide (179 mg, 0.5 mmol, 1.0 equiv) at room temperature. The mixture was stirred for 10 min before cooling to −78 ºC. PhLi (2.0 M in Bu_2O, 0.25 mL, 0.5 mmol, 1.0 equiv) was then added dropwise at −78 ºC.

The cooling bath was removed, and the mixture allowed to warm to rt over 15 min during which time a clear-yellow solution formed. After 30 min at rt, the mixture was re-cooled to −78 ºC and a solution of (−)-sparteine (115 μL, 0.5 mmol, 1.0 equiv) in THF (0.5 mL/mmol diamine) was then added. This mixture was stirred for 10 min at this temperature, after which a solution of nonanal (71 mg, 0.5 mmol, 1.0 equiv) in THF (0.5 mL/mmol aldehyde) was added dropwise. After 20 min, when complete decolourisation had occurred, PhLi (2.0 M in Bu_2O, 0.26 mL, 0.53 mmol, 1.05 equiv) was added dropwise resulting in a cherry-red solution. This solution was stirred for 30 min at −78 ºC, after which time a solution of benzaldehyde (56 mg, 0.53 mmol, 1.05 equiv) in THF (0.5 mL/mmol aldehyde) was added dropwise at −78 ºC. The reaction mixture was stirred at −78 ºC for 2 h. The reaction mixture was then warmed to rt over 1 h and stirring continued for a further 1 h. The mixture was quenched with saturated aq. ammonium chloride (20 mL), extracted with Et_2O (3 × 15 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by flash chromatography (gradient elution 10% Et_2O/petrol to 30% Et_2O/petrol) gave allylic alcohols **48** (25 mg, 20%), **51***E* (7 mg, 13%) and **66***E* (10 mg, 14%) as pale yellow oils and a colourless oil, respectively. Data as p 93, 95−96 and 109−110, respectively. **48**: $[\alpha]_D^{20}$ −4.0 (*c* = 0.72, $CHCl_3$); (*S*)-**48**: $[\alpha]_D^{20}$ +6.6 (*c* = 0.72, $CHCl_3$).[56]

(*Z*)-Undec-2-en-1-yl pivalate (93)



To a solution of 2,2,6,6-tetramethylpiperidine (168 μL, 1.0 mmol, 1.0 equiv) in THF (6 mL/mmol) at 0 °C was added *n*-BuLi (2.5 M in hexanes, 0.4 mL, 1.0 mmol, 1.0 equiv) dropwise with stirring. The mixture was allowed to warm to room temperature over 30 min, during which time a pale yellow solution was formed. This solution was then cooled to 0 °C and a solution of PPh_3 (262 mg, 1.0 mmol, 1.0 equiv) and anhydrous LiBr (87 mg, 1.0 mmol, 1.0 equiv) in THF (4 mL/mmol PPh_3) was added dropwise followed immediately by a solution of 1,2-epoxydecane (156 mg, 1.0 mmol, 1.0 equiv) in THF (0.5 mL/mmol) slowly dropwise. This solution was then stirred at 0 °C for 24 h during which time a red-orange color developed. This mixture was then cooled to −78 °C and a solution of chloromethyl pivalate (158 mg, 1.05 mmol, 1.05 equiv.) in THF (0.5 mL/mmol) added slowly dropwise. The reaction mixture was stirred at −78 ºC for 2 h, then warmed to rt over 1 h and stirring continued for a further 1 h. The mixture was quenched with saturated aq. ammonium chloride (20 mL), extracted with Et_2O (3 × 15 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by flash chromatography gave allylic ester **93**[17b] as a colourless oil (66 mg, 26%); R_f 0.41 (20% CH_2Cl_2/petrol).

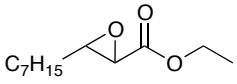
IR (neat) /cm^{-1}: 3066s, 3027s, 2957s, 2854m, 1732m, 1730m, 1151s.

^1H (400 MHz) δ = 5.67−5.59 (1 H, m, C*H*=CHCH$_2$), 5.56−5.48 (1 H, m, =C*H*CH$_2$), 4.60 (2 H, d, *J* = 6.8, CH$_2$Opiv), 2.10 (2 H, q, *J* = 6.9, C*H*$_2$CH=), 1.42−1.23 (m, (12 H, 6 × CH$_2$), 0.88 (3 H, t, *J* = 7, CH$_3$).

^{13}C (100 MHz) δ = 178.5 (C=O), 135.2 (CH_2*C*H=), 123.5 (=*C*HCH_2), 60.3 (CH_2O), 38.7 (C), 31.8 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 27.6 (CH_2), 27.2 (3 × CH_3), 22.6 (CH_2), 14.1 (CH_3).

LRMS (ESI+): 277.20 (75, M+Na), 413.23 (75), 691.36 (70), 803.45 (100); HRMS (ESII+): 277.2138 calculated for $C_{16}H_{30}O_2Na$; found 277.2143.

Ethyl 3-heptyloxirane-2-carboxylate (107)



To a solution of unsaturated ester **106** (2181 mg, 11 mmol) in CH_2Cl_2 (30 mL) was at rt was added m-CPBA (2847 mg, 16.7 mmol). The mixture was refluxed for 12 h then slowly diluted with saturated aq. $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with saturated aq. $NaHCO_3$ (20 mL), brine (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by by chromatography in the solvent system indicated gave epoxide **107** (947 mg, 40%) as a colourless oil; R_f 0.41 (10% Et_2O/petrol).

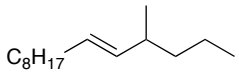
IR (neat) /cm^{-1}:2927m, 2857w, 1751m, 1444w, 1283w, 1193s, 1034m, 902w, 724w.

^{1}H (400 MHz) δ = 4.22 (2 H, dq, *J* = 14.7, 7.3, OCH_2), 3.19 (1 H, s, CH), 3.13 (1 H, td, *J* = 5.8, 1.5, CH), 1.70−1.50 (2 H, m, CH_2), 1.50−1.39 (2 H, m, CH_2), 1.37−1.18 (12 H, m, 4 × CH_2 and CH_3), 0.86 (3 H, t, *J* = 6.6, CH_3).

^{13}C (100 MHz) δ = 169.3 (C=O), 61.4 (OCH_2), 58.4 (CH), 53.0 (CH), 31.6 (CH_2), 31.4 (CH_2), 29.1 ((CH_2), 29.0 (CH_2), 25.6 (CH_2), 22.5 (CH_2), 14.0 (CH_3).

LRMS (ESI+): 237.2 (100); HRMS (ESI+): 237.1461 calculated for $C_{12}H_{22}O_3Na$; found 237.1669.

(*E*)-3-methyltridec-4-ene (109a)[66]

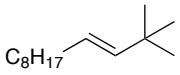


^{1}H (400 MHz) δ = 5.37 (1 H, dt, *J* = 15.2, 6.3, C*H*=CHCH$_2$), 5.27 (1 H, dd, *J* = 15.3, 7.3, CH=C*H*CH$_2$), 2.07−1.92 (2 H, m, C*H*CH$_3$, CH=CHC*H*$_2$), 1.41−1.23 (14 H, m, 7 × CH$_2$), 0.98 (3 H, d, *J* = 6.8, CHC*H*$_3$), 0.94−0.84 (6 H, m, 2 × CH$_3$).

^{13}C (100 MHz) δ = 141.4 (CH), 124.8 (CH), 32.7 (CH$_2$), 32.0 (CH$_2$), 29.8 (3 × CH$_3$), 29.8 (CH$_2$), 29.5 (CH$_2$), 29.4 (CH$_2$), 29.2 (CH$_2$), 14.1 (CH$_3$).

All other data as reported.[66]

(*E*)-2,2-dimethyldodec-3-ene (109b)[67]



^{1}H (400 MHz) δ = 5.45 (1 H, dt, *J* = 15.7, 1.4, C*H*=CHCH$_2$), 5.36-5.27 (1 H, m, CH=C*H*CH$_2$), 1.98 (2 H, q, *J* = 7.2, CH=CHC*H*$_2$), 1.40−1.21 (12 H, m, 6 × CH$_2$), 1.00 (9 H, s, C(CH$_3$)$_3$), 0.90 (3 H, t, *J* = 6.7, CH$_3$).

^{13}C (100 MHz) δ = 141.4 (CH), 124.8 (CH), 32.7 (CH$_2$), 32.0 (CH$_2$), 29.8 (3 × CH$_3$), 29.8 (CH$_2$), 29.5 (CH$_2$), 29.4 (CH$_2$), 29.2 (CH$_2$), 14.1 (CH$_3$).

All other data as reported.[67]

Chapter 5: References

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