SYNTHETIC AND MECHANISTIC INVESTIGATIONS OF SOME NOVEL ORGANOPHOSPHORUS REAGENTS

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Statement of Originality

This work has not previously been submitted for a degree or diploma in any University. To the best of my knowledge and belief, this thesis contains no material previously published or written by another person except where due reference is made in the thesis itself.

Kathryn Fairfull-Smith (née Elson)
BSc (Hons)
Preface

Unless otherwise stated, the results in this thesis are those of the author. Parts of this work have appeared elsewhere. Refereed journal publications are submitted with the dissertation and are presented in Appendix Two.

Refereed Journal Publications

‘The Hendrickson reagent and the Mitsunobu reaction: a mechanistic study’

‘Cyclic analogues of the Hendrickson ‘POP’ reagent’

‘Polymer-supported triphenylphosphine ditriflate: a novel dehydrating reagent’

‘Novel polymer-supported coupling/dehydrating reagents for use in organic synthesis’

Conference Posters

‘Phosphonium Anhydrides as Alternative Mitsunobu Reagents: A Kinetic Study’

‘Towards an Alternative Mitsunobu Protocol – Novel Cyclic Analogues of the Hendrickson ‘POP’ Reagent’

Conference Lectures

‘Mitsunobu Reactions without Azodicarboxylates? Use of the Hendrickson Reagent’
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<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>amu</td>
<td>atomic mass unit</td>
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<tr>
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DMF      dimethylformamide
DMSO     dimethylsulfoxide
dq       doublet of quartets
dqq      doublet of quartet of quartets
dt       doublet of triplets
ESMS (+ve mode)  Electrospray Mass Spectrometry (positive ionisation mode)
ESMS (-ve mode)  Electrospray Mass Spectrometry (negative ionisation mode)
Et       ethyl
eq       equatorial
equiv.   equivalents
$^{19}$F NMR  Fluorine-19 Nuclear Magnetic Resonance Spectroscopy
FTIR     Fourier Transform Infrared Spectroscopy
g       gram
GC/MS     Gas Chromatography/Mass Spectrometry
gCOSY    gradient Correlation Spectroscopy
gHMBC    gradient Heteronuclear Multiple Bond Correlation
gHSQC    gradient Heteronuclear Single Quantum Correlation
HMPA     hexamethylphosphoramide
$^1$H NMR  Proton Nuclear Magnetic Resonance Spectroscopy
HPLC/MS   High Pressure Liquid Chromatography/Mass Spectrometry
$^1$H $^{31}$P NMR  Phosphorus decoupled Proton Nuclear Magnetic Resonance Spectroscopy
HOBT     1-hydroxybenzotriazole
hr       hour
HRMS     High Resolution Mass Spectrometry
Hz       Hertz
- ipso

^{i}Pr  isopropyl

IUPAC  International Union of Pure and Applied Chemistry

Kcal  kilocalorie

kJ  kilojoule

L  litre

LC/MS  Liquid Chromatography/Mass Spectrometry

M  molarity

m  multiplet

m-  meta

mg  milligram

mm  millimetre

MALDI/MS  Matrix Assisted Laser Desorption Ionisation/Mass Spectrometry

MAS NMR  Magic Angle Spinning Nuclear Magnetic Resonance Spectroscopy

Me  methyl

MHz  megahertz

min  minute

mL  millilitre

mmHg  millimetres of mercury

mmol  millimole

mol  mole

Mp  melting point

Nu  nucleophile

o-  ortho

°  degree

°C  degrees Celsius
O/N  overnight
p-  para
PASP  Polymer-Assisted Solution-Phase synthesis
PEG  polyethylene glycol
Ph  phenyl
$^{31}$P NMR  Phosphorus-31 Nuclear Magnetic Resonance Spectroscopy
ppm  parts per million
PS  polymer-supported
q  quartet
RT  room temperature
R$_T$  retention time
s  singlet
sec  second
SPOS  Solid-phase Organic Synthesis
t  triplet
tert-  tertiary
Tf  triflate
THF  tetrahydrofuran
TLC  thin-layer chromatography
UV  ultraviolet
w/v  weight per volume
$\delta$  chemical shift
%  percent
1D  one dimensional
2D  two dimensional
$\mu$L  microlitre
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To produce this thesis, I have had the help of many people. My supervisors Prof. Ian Jenkins and Dr Wendy Loughlin have been inspirational. Thank you both for working so well together as a team, providing me with encouragement, support and guidance. I am going to miss our weekly meetings together, where Ian shares his constant stream of ‘brilliant ideas’ and Wendy cops the brunt of most of Ian’s jokes. I could not ask for a better pair of supervisors.

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A big thank you to Dr Sue Boyd for her assistance with NMR acquisition and interpretation. Sue has always gone out of her way to cater for my obscure experiments and I am extremely grateful to her. To Alan White, thank you for your help with mass spectrometry and for all the floggings you have given me in squash over the past three years. Thanks also must go to Bob Hopkins from the Science store for the great service he has provided throughout my PhD.
Abstract

The alkoxytriphenylphosphonium ion intermediate of the Mitsunobu reaction for the esterification and inversion of configuration of an alcohol can be generated using the Hendrickson reagent, triphenylphosphonium anhydride trifluoromethanesulfonate, 27. While 27 was used in place of the Mitsunobu reagents (triphenylphosphine and a dialkyl azodicarboxylate) for the esterification of primary alcohols, the reaction failed with secondary alcohols such as (−)-menthol giving predominately elimination rather than the desired S_N2 displacement. The difference between the two reactions was shown to be related to the more ‘ionic’ conditions generated when the Hendrickson reagent 27 was employed. An extreme sensitivity of the Mitsunobu reaction to the presence of salts was discussed and may indicate a mechanism involving ion pair clustering.

Five-, six- and seven-membered cyclic analogues of the Hendrickson reagent 90-92 were prepared. A kinetic comparison of the cyclic analogues 90-92 revealed that a considerable increase in the rate of esterification could be achieved when the five-membered ring analogue 90 was used in a non-polar solvent such as toluene. Selected acyclic analogues of the Hendrickson reagent 27 possessing tributyl 118, tricyclohexyl 130 and diphenyl-2-pyridyl 137 functionalities were synthesised. However when 118, 130 and 137 were used for the attempted esterification of (−)-menthol, elimination was the major reaction pathway. Diphenyl-2-pyridylphosphonium anhydride triflate 137 was found to be a useful reagent for the synthesis of acyclic dialkyl ethers from primary alcohols. A polymeric version of the five-membered ring analogue 56, prepared by reaction of the polymer-supported 1,2-bis(diphenylphosphinyl)ethane 57 with triflic anhydride, was used for the preparation of simple esters and amides.
A new dehydrating agent, polymer-supported triphenylphosphine ditriflate 157, was readily prepared from the oxidised form of commercially available polymer-supported triphenylphosphine and triflic anhydride. A wide range of dehydration-type reactions, such as ester, amide, anhydride, peptide, ether and nitrile formation, were performed in high yield using polymer-supported triphenylphosphine ditriflate 157. The reagent 157 was easily recovered and re-used several times without loss of efficiency. The use of 4-dimethylaminopyridine allowed the esterification of secondary alcohols with 157 to proceed without elimination and gave esters in high yield but with retention of configuration. Both reagents 56 and 157 provide an alternative to the Mitsunobu reaction, where the use of azodicarboxylates and chromatography to remove the phosphine oxide by-product can be avoided. However, the Mitsunobu reaction retains its supremacy for the inversion of configuration of a secondary alcohol.

Preliminary investigations on the phosphityation of alcohols via the Hendrickson reagent 27, 1,3-benzodioxole formation using the Mitsunobu reaction and azodicarboxylate alternatives in the Mitsunobu reaction are described.
INTRODUCTION
Preface

The Mitsunobu reaction is one of the most widely used reactions in organic chemistry, particularly for the inversion of configuration of a secondary alcohol. The main drawback of the Mitsunobu reaction is the difficulty of separating the product from the hydrazine and phosphine oxide by-products. In attempting to find an alternative to the Mitsunobu reaction that avoids the use of azodicarboxylates and does not involve the removal of triphenylphosphine oxide, this thesis explores the use of the Hendrickson and related reagents. The Hendrickson reagent results in the formation of the same oxyphosphonium intermediate as the Mitsunobu reaction but has never been used for the inversion of configuration of a secondary alcohol and is almost unknown in mainstream organic chemistry. This thesis also explores this apparent anomaly.

1.0 The Mitsunobu reaction

1.1 General overview

The Mitsunobu reaction has been extensively used in organic synthesis and generally entails the use of the redox couple of triphenylphosphine and a dialkyl azodicarboxylate to bring about inter- or intra-molecular alcohol dehydrations. The overall reaction is generalised in Scheme 1, where the alcohol (ROH) and acidic compound (HX) are condensed to form product (RX). The removal of the elements of water results in the phosphine (phosphorus oxidation level III) accepting oxygen to give the corresponding phosphine oxide (phosphorus oxidation level V) and the azodicarboxylate accepting two hydrogens, generating the corresponding hydrazine derivative.

\[
\begin{align*}
R= & \text{aliphatic} & X = & \text{O-, N-, S-, C-} & R^1 = & \text{Et (DEAD)} & R^1' = & \text{iPr (DIAD)} \\
R\text{OH} + HX \xrightarrow{\text{PPh}_3} & RX + \text{Ph}_3\text{P}=\text{O} + R^1\text{O}_2\text{CNH-NHCO}_2R^1'
\end{align*}
\]

Scheme 1
In 1967 Mitsunobu and Yamada\(^1\) initially reported the esterification of carboxylic acids with primary and secondary alcohols using diethyl azodicarboxylate and triphenylphosphine. Further work by Mitsunobu and Eguchi\(^2\) demonstrated the ability of this reaction to bring about complete inversion of stereochemistry of secondary alcohols during esterification/hydrolysis. Examples of retention of configuration have been reported due to neighbouring group participation,\(^3\) steric congestion at the reaction centre\(^4-6\) or insufficient activation of the stereogenic carbon toward nucleophilic substitution; however in these cases alternative mechanistic pathways are followed.\(^7,8\)

The Mitsunobu reaction has been extended from the use of carboxylic acid nucleophiles to include acidic components such as imides, \(N\)-heterocycles, thiols, sulfonamides, phosphate diesters, sulfonyl, phosphinic and thioacids, phenols, hydrazoic acid, hydrogen cyanide, hydrogen halides and various active methylene compounds. In general, the reaction can be used to construct C-O, C-N, C-S, C-halogen, C-C and S-S bonds. Substantial reviews of the reaction have been provided by Mitsunobu\(^9\) in 1981, Hughes\(^10,11\) in 1992 and 1996, and Jenkins and Mitsunobu\(^12\) in 1995. This introductory section will therefore present only a brief overview of the reaction, its mechanism and some of its applications in the literature.

The mild (0-25\(^\circ\)C) and neutral conditions of the reaction, combined with its high stereospecificity and compatibility with a broad range of functional groups has seen it develop into one of the most versatile reactions in organic chemistry. The widespread use of the reaction in areas such as the synthesis and modification of natural products is verified by more than two thousand citations of the 1981 review. The recent use of the Mitsunobu reaction in the preparation of 1,2 benzoxazoles,\(^13\) alkaloids,\(^14,15\) amino acids\(^16\) and peptide nucleic acid (PNA) monomers,\(^17,18\) nucleosides,\(^19-23\) and
carbohydrates$^{24,25}$ demonstrate its usefulness as part of multistep synthetic protocols. Some examples of the Mitsunobu reaction are displayed in Scheme 2.

Ester formation.$^7$

![Ester formation reaction](image)

Ether formation.$^{26}$

![Ether formation reaction](image)

Epoxide formation.$^{27}$

![Epoxide formation reaction](image)

C-N bond formation.$^{28}$

![C-N bond formation reaction](image)

S-S bond formation.$^{29}$

![S-S bond formation reaction](image)
C-S bond formation.\textsuperscript{30}

\[
\text{Ph-CH(OH)-CH=CH}_2 \overset{\text{PPh}_3, \text{DIAD}}{\underset{\text{THF}}{\xrightarrow{\text{CH}_3\text{COSH}}} \text{Ph-CH(OH)-CH} = \text{CH-S}}
\]

C-C bond formation.\textsuperscript{31}

\[
\text{C}_6\text{H}_{11} \overset{\text{PPh}_3, \text{DEAD}}{\underset{\text{benzene}}{\xrightarrow{} \text{C}_6\text{H}_{11} \text{NO}_2}}
\]

C-halogen bond formation.\textsuperscript{32}

\[
\text{Ph-CH(OH)} \overset{\text{PPh}_3, \text{DIAD}}{\underset{\text{ZnI}_2, \text{THF}}{\xrightarrow{} \text{Ph-CHI}}}\]

\section*{Scheme 2}

\subsection*{1.2 The mechanism of the Mitsunobu reaction}

The mechanism of the Mitsunobu reaction has been generalised in three steps (Scheme 3).\textsuperscript{9} During the first step, the protonated betaine 1 is generated from rapid reaction of the phosphine with the dialkyl azodicarboxylate. This protonated P-N salt adduct activates the alcohol to form an oxyphosphonium salt 2 and reduced hydrazine by-product. The oxyphosphonium salt 2 then undergoes an $S\text{N}_2$ type displacement with the deprotonated nucleophile to generate the inverted product and phosphine oxide.

Finer points of the mechanism of the Mitsunobu reaction have been elucidated.\textsuperscript{10,33} It was shown that the reaction between the phosphine and dialkyl azodicarboxylate results in the formation of a radical cation.\textsuperscript{34} The rate determining step of the reaction has been shown to depend on the basicity of the carboxylate employed.\textsuperscript{35} A less acidic
carboxylate dictates a slow $S_{N}2$ displacement, whereas with a more acidic species, the rates of alcohol activation and $S_{N}2$ reaction are comparable.

\[ \text{PPh}_3 + \text{RO}_2\text{C-N}=\text{N-CO}_2\text{R} \xrightarrow{\text{NuH}} \text{RO}_2\text{C-}\text{N}=\text{N-CO}_2\text{R} + \text{PPh}_3 \]

\[ \text{Nu}^- + \text{RO}_2\text{C-N}=\text{N-CO}_2\text{R} \xrightarrow{\text{PPh}_3} \text{Nu}^- \text{OPPh}_3 + \text{RO}_2\text{CN}=\text{NHC}=\text{O}_2\text{R} \]

\[ \text{Nu}^- \text{OPPh}_3 \xrightarrow{\text{Ph}_3\text{P}=\text{O}} \text{Nu}^- + \text{Ph}_3\text{P}=\text{O} \]

**Scheme 3**

A key intermediate formed during the reaction of alcohol with triphenylphosphine and diethylazodicarboxylate was revealed to be a pentavalent dialkoxyphosphorane 3 by NMR.\textsuperscript{36-38} In the presence of the acidic component, an equilibrium mixture of phosphorane 3 and oxyphosphonium salt 4 exists and thus a revised mechanism for the Mitsunobu reaction was proposed.\textsuperscript{39,40} Scheme 4 illustrates that in the presence of the acidic species HX, the oxyphosphonium intermediate 4 is formed via the protonated betaine 5. The phosphorane 3 is formed in the absence of acid from half of the betaine and quickly forms the oxyphosphonium salt 4 following acid addition. The remaining alcohol is then recycled through the other pathway as acid is now present. Thus, depending on the order of addition and possibly on the pKa of the chosen acid, the Mitsunobu reaction seems to follow a combination of both phosphonium salt and phosphorane pathways or solely the phosphonium salt pathway.
Recently, an enantiomerically pure P-chiral phosphine, (S)-cyclohexylmethyl-(1-naphthyl)phosphine, was used to prove that the participation of the oxyphosphonium salt 4 and phosphorane 3 depends on the order of addition of reactants and on the nature of the alcohol and carboxylic acid used.\textsuperscript{33} Also, previous work from this laboratory has shown the Mitsunobu esterification reaction to be markedly dependant on the solvent polarity (for example, the rate of formation of ethyl benzoate at 0°C is approximately 100 times slower in CH\textsubscript{3}CN than in THF).\textsuperscript{41}

1.3 Modifications and alternative reagents in the Mitsunobu reaction

Much interest has been shown over the years in the modification of the Mitsunobu reaction to improve yields and/or selectivity. Significantly better yields have been reported when 4-nitrobenzoic acid was used for the inversion of sterically hindered
secondary alcohols. It has been suggested that acids of higher pKa give lower yields due to the competitive acid anhydride formation via acyloxyphosphonium salts. In addition, 4-nitrobenzoate esters are often more readily deprotected and easier to purify. Further investigation revealed the Mitsunobu inversion of menthol to be dramatically influenced by the acidic component, with the more acidic species generally affording higher yields of inverted product. Also, the use of chloroacetic acid as the carboxylic acid partner has been effective in cases where the coupling of 4-nitrobenzoic acid with an alcohol moiety, which is flanked by two substituents or possesses large α substituents, is unsuccessful (Scheme 5). Furthermore, picolinic acid has been reported as an excellent coupling partner, wherein the resulting ester can be hydrolysed under essentially neutral conditions using copper acetate promoted methanolysis.

\[
\begin{align*}
\text{OH} & \quad \text{PPh}_3, \text{DEAD} \\
\text{ClCH}_2\text{COOH} & \quad \text{toluene} \\
\end{align*}
\]

Scheme 5

Recently, a vast rate increase in the coupling of sterically hindered alcohols with phenols by the Mitsunobu reaction has been described when the reactions were conducted at high concentration with sonication. The conversion of (S)-sulcatol (or (R)-sulcatol), to its corresponding inverted sulcatyl acetate was achieved by Mitsunobu reaction under microwave conditions (Scheme 6) (the classical Mitsunobu conditions gave poor yields). Various modifications of the Mitsunobu reaction which lead to increased yield and selectivity have been detailed elsewhere.
Novel redox systems have been employed to cater for nucleophiles with pKa’s greater than 11. Replacement of the standard DEAD-triphenylphosphine reagent with tributylphosphine and either 1,1’-(azodicarbonyl)dipiperidine (ADDP) 8, N,N,N’,N’-tetramethylazodicarboxamide (TMAD) 9, N,N,N’,N’-tetraisopropylazodicarboxamide (TIPA) 10, or 4,7-dimethyl-3,5,7-hexahydro-1,2,4,7-tetraazocin-3,8-dione (DHTD) 11, have allowed Mitsunobu couplings to proceed using acid components with high pKa’s (up to 13.5).50-52 Also, the use of cyanomethylene tributylphosphorane (CMBP)52 12, and cyanomethylene trimethylphosphorane (CMMP)53,54 13, have been investigated.

The advantages of these novel redox systems are compared and contrasted in a recent review.55

Despite its widespread use, one problem with the Mitsunobu reaction is the difficulty in separating the desired product from the phosphine oxide and dialkylhydrazino dicarboxylate by-products. Several alternative approaches have been adopted to simplify this purification procedure. The use of phosphines containing a basic group, such as diphenyl(2-pyridyl)phosphine 1456 or (4-dimethylaminophenyl) diphenylphosphine 15,57 (where the corresponding phosphine oxide can be removed by an aqueous acid wash) and phosphines such as 1,2-bis(diphenylphosphino)ethane 1658 (whose oxide is considerably more polar than triphenylphosphine oxide) have simplified product purification. In addition, crown ether tagged triarylphosphines59 have been employed in Mitsunobu reactions to simplify product purification. These crown ether
tags allow selective solid-phase sequestration of the phosphine oxide from the reaction mixture by elution through an ammonium functionalised resin.

![Chemical structures](image)

The problem of separating products from the Mitsunobu reaction by-products has been resolved by using \textbf{14} and di-\textit{tert}-butylazodicarboxylate.\textsuperscript{60} In this case, both reagents and their respective oxidation or reduction products are directly soluble in aqueous acid or are converted to gaseous by-products and water soluble materials upon treatment with acid. In another example, a hydrophobic reaction product \textbf{17}, formed by a Mitsunobu reaction between tetra-\textit{O}-benzyl-\textit{d}-glucopyranose and monoindolylmaleimide, was rapidly purified in high yield using reverse-phase chromatography.\textsuperscript{61}

![Chemical structure](image)

Alternatively, the use of a polymer-supported phosphine has been implemented to eliminate the chromatography, by filtration of the polymer-supported phosphine oxide by-product. A small library of aryl ethers have been prepared using the Mitsunobu reaction with polymer-supported triphenylphosphine (Scheme 7).\textsuperscript{62} However, the
library members still required purification by short-path chromatography to remove the
hydrazine by-product. In other solid-phase work, a polymer-supported triphenylphosphine has been used with di-tert-butylazodicarboxylate to effect a range of alkylolation reactions in parallel.\textsuperscript{63} The hydrazine by-product was decomposed by
treatment with acid and removed following an aqueous wash. In another example, the
use of polymer-supported triphenylphosphine and bis(5-norbornenyl-2-
methyl)azodicarboxylate gave Mitsunobu condensation products without requiring
chromatography for purification as the hydrazine side-product was removed following
ring-opening metathetic polymerization using Grubbs catalyst and filtration.\textsuperscript{64}

\begin{center}
\begin{tabular}{c c c}
\chem{R-OH} & $\rightarrow$ & \chem{R-OH'}
\end{tabular}
\end{center}

$\text{PPh}_2$(DEAD, DCM) $\rightarrow$ \chem{R-O-R'

$\textbf{Scheme 7}$

Complementary to the use of a polymer-supported phosphine, polymer-supported
dialkyl azodicarboxylates\textsuperscript{65} have been utilized in Mitsunobu reactions. The use of
dimethyl azodicarboxylate is advantageous as its corresponding hydrazine is water
soluble.\textsuperscript{66} One problem encountered with polymer-supported reagents is their loss of
reactivity, a result of both their sterically less accessible reaction centre and the biphasic
system which imparts slow reaction kinetics. To circumvent these problems, Mitsunobu
reactions with triphenylphosphine linked to non-cross-linked polystyrene, a soluble
polymeric phosphine, have been used to generate esters of secondary alcohols with
inversion in reasonable yields.\textsuperscript{67} The polymer was recovered by precipitation with
methanol. Moreover, a poly(ethyleneglycol)-arylphosphine conjugate 18 has been
employed to synthesise aryl alkyl ethers.\textsuperscript{68} A high-loading PEG star-triphenylphosphine
conjugate 19 has been used for the Mitsunobu etherification of phenol in high yield. The oxidised reagent was isolated by precipitation from diethyl ether.$^{69}$

An alternative approach to the Mitsunobu reaction is one in which a substrate is attached to a polymer-support, and thus the phosphine oxide and dialkylhydrazino dicarboxylate by-products are washed away from the support. Examples of Mitsunobu reactions using this approach include the synthesis of libraries of aryl ethers with polymer-bound phenols or alcohols,$^{70,71}$ carbon-carbon bond formation by alkylation of a polymer-supported alcohol with active methylene compounds,$^{72}$ and N-benzylation of the iodide salts of polymer-bound secondary aliphatic amines with benzyl alcohols.$^{73}$ Aliphatic amines are usually resistant to N-alkylation under Mitsunobu conditions.$^{74}$ Small peptides have been formed by Mitsunobu esterification of polymer-supported hydroxyl groups$^{75}$ and the conversion of primary alcohols to amines was achieved on solid-phase using a phthalimide-containing resin with hydrazine-induced cleavage.$^{76}$

The use of fluorous chemistry with the Mitsunobu reaction also has been reported. Fluorous compounds are very non-polar and commonly form bilayers with organic solvents, thus facilitating compound isolation. Initially, fluorous azodicarboxylates were employed in the Mitsunobu reaction.$^{77}$ A fully fluorous Mitsunobu reaction$^{78}$ used the fluorous phosphine 20, in combination with a fluorous azodicarboxylate reagent 21, to simplify the work-up and purification procedure. Instead of fluorinating the
phosphine and azodicarboxylate reagents, a fluorinated carboxylic acid\textsuperscript{29} has been utilised in the Mitsunobu reaction with primary and secondary alcohols, resulting in a chromatography-free isolation protocol. Similarly, fluorophilic ethers have been synthesised via a Mitsunobu reaction with fluorinated alcohols.\textsuperscript{80}

\[ \text{HO}_2\text{CH}_2\text{CC}_6\text{F}_{13} \text{C} \]

\[ \text{O} \]

\[ \text{N} \]

\[ \text{N} \]

\[ \text{C} \]

\[ \text{O} \]

\[ \text{C} \]

\[ \text{OCH}_2\text{CH}_2\text{C}_6\text{F}_{13} \]

\[ \text{Ph} \]

\[ \text{P} \]

\[ \text{C}_6\text{H}_4\text{H}_2\text{CH}_2\text{CC}_6\text{F}_{13} \]

\[ \text{C}_6\text{H}_4\text{CH}_2\text{CH}_2\text{C}_6\text{F}_{13} \]

\[ \text{CO}_2\text{t-Bu} \]

\[ \text{t-BuO}_2\text{C} \]

\[ \text{N} \]

\[ \text{N} \]

\[ \text{C} \]

\[ \text{O} \]

\[ \text{N} \]

\[ \text{N} \]

\[ \text{CO}_2\text{t-Bu} \]

\[ \text{t-BuO}_2\text{C} \]

\[ \text{N} \]

\[ \text{N} \]

\[ \text{C} \]

\[ \text{O} \]

\[ \text{N} \]

\[ \text{N} \]

\[ \text{C} \]

\[ \text{O} \]

\[ \text{N} \]

\[ \text{N} \]

\[ \text{C} \]

\[ \text{O} \]

The chemoselective removal of the phosphine oxide and hydrazine by-products from solution has been demonstrated with the use of ‘chemically tagged’ reagents such as bifunctional reagents \textsuperscript{22} and \textsuperscript{23}.\textsuperscript{81} The \textit{t}-butyl ester functionalities of these reagents act as masked carboxylic acid tags, which can be unmasked with trifluoroacetic acid and captured by a base-functionalised ion exchange resin. Similarly, phosphorus based reagents containing trimethylsilyl ethyl esters have been adopted as triphenylphosphine replacements in the Mitsunobu reaction.\textsuperscript{82} The corresponding phosphine oxide can be removed by cleaving with tetrabutylammonium fluoride and the resulting acid removed following washing with aqueous base. An alternative approach using the anthracene-tagged phosphine \textsuperscript{24} in combination with a polymer-supported azodicarboxylate \textsuperscript{25} appears to be a general method for the Mitsunobu reaction (Scheme 8).\textsuperscript{83} The reagents \textsuperscript{24} and \textsuperscript{25}, along with their by-products, are sequestered upon completion of the reaction via a Diels-Alder cyclisation with a maleimide resin \textsuperscript{26}. This method is,
however, limited by final products which would react with the polymer-bound dieneophile 26.

![Scheme 8](image)

With an update of the recent developments in the Mitsunobu reaction completed, consideration of the Hendrickson reaction is explored in the next section.
2.0 The Hendrickson reagent

2.1 General overview

In 1975, the synthesis of a reagent generated from the reaction of two equivalents of triphenylphosphine oxide in DCM at 0°C with one equivalent of trifluoromethanesulfonic (triflic) anhydride was reported (Scheme 9). This reagent, called the Hendrickson reagent and initially formulated as triphenylphosphine ditriflate \([\text{Ph}_3\text{P}-(\text{OTf})_2]\), was revealed to be a general dehydrating agent. The correct structure was subsequently shown to be triphenylphosphonium anhydride trifluoromethanesulfonate \([\mu\text{-oxobis(triphenylphosphonium) bis(trifluoromethanesulfonate)}]\). A recently published X-ray structure of 27 reveals an almost linear (164.5°) P-O-P bond angle.

\[
\begin{align*}
2\text{Ph}_3\text{P}=\text{O} & \quad \text{DMF} \quad 0^\circ\text{C}, \text{15 min} \quad \rightarrow \quad \text{Ph}_3\text{P}=\text{O}^+\text{PPh}_3^- \\
\end{align*}
\]

Scheme 9

The Hendrickson reagent 27 has been used for a variety of substitution and elimination reactions. It allows the conversion of an OH group into an excellent leaving group (an oxyphosphonium salt) which can undergo displacement by nucleophiles (or elimination in the presence of bases). Both steps of the reaction, the formation of the oxyphosphonium salt and subsequent nucleophilic attack, are favoured thermodynamically by the formation of a strong P=O bond (dissociation energy = 536-577 kJ/mol). Addition of a mild base, such as triethylamine, neutralises the triflic acid formed. A summary of the reaction (generating an ester) is presented in Scheme 10. Since the acid may also be activated first with the reagent 27, a rapid equilibrium is established between the acyloxyphosphonium 28 and alkoxypyrophosphonium 4 species. A review of the reagent 27 has appeared and details of its application are described below.
2.2 Uses of the Hendrickson reagent

2.2.1 Reactions with carboxylic acids and O- and N-nucleophiles

The reaction of the Hendrickson reagent 27 with a carboxylic acid forms the activated acyloxyphosphonium triflate. If no other nucleophile is present, substitution by carboxylate yields an anhydride. Thus, the dehydration of two moles of carboxylic acid with 27 in the presence of base gives acid anhydrides such as 29 (Scheme 11).
Initially, carboxylic acids were coupled with primary alcohols to yield simple esters. Generally the alcohol was added first to 27, however due to the equilibrium between the activated acid and alcohol, ester formation may proceed through either intermediate. The use of a tertiary alcohol such as tert-butyl alcohol with 4-toluic acid only gave a modest (40%) yield of ester due to concurrent elimination of the activated alcohol to isobutene (Scheme 12).

![Scheme 12](image)

Amides also have been generated using the Hendrickson reagent 27. A similar equilibrium to that displayed in Scheme 10 appears in amide formation using 27 with an acid and primary or secondary amine. In this case, the aminophosphonium salt exchanges to activate the acid and subsequently yields the amide (Scheme 13).

![Scheme 13](image)

Another use of the Hendrickson reagent 27 with carboxylic acids is in the synthesis of cyclic amidines. The reaction of carboxylic acids with diamines gives 2-arylbenzimidazoles following a double dehydration with two equivalents of 27 (Scheme 14). Similarly, benzoxazoles can be formed from 2-aminophenols and benzothiazoles from 2-aminothiophenols. In addition, the activation of carboxylic acids with the
Hendrickson reagent 27 has lead to the synthesis of azetidinones.\textsuperscript{91} Treatment of the acyloxyphosphonium salt 28 with a \textit{cis}-imine gave the corresponding monocyclic azetidine-2-ones bearing \textit{cis} stereochemistry.

\begin{center}
\textbf{Scheme 14}
\end{center}

2.2.2 Other reactions with carboxylic acids

The Hendrickson reagent 27 has been used as a coupling agent in the formation of internucleoside sulfonate and sulfonamide linkages.\textsuperscript{92} The conversion of sulfonic acids to their esters and amides was achieved in modest (30-36\%) yields using 27. Internal cyclisation of phenylalkanoic acids occurs with the Hendrickson reagent 27 in the absence of base to yield cyclic ketones.\textsuperscript{89} The expelled triflic acid acts as a strong acid for catalysis of the intra-molecular Friedel-Crafts reaction. Indanones, tetralones and benzosuberones were afforded and in addition, an acid-catalysed Claisen condensation was observed with phenylacetic acid (Scheme 15).

\begin{center}
\textbf{Scheme 15}
\end{center}

2.2.3 Other substitutions

Epoxides, cyclic ethers and amines have been synthesised from the corresponding diols and amino alcohols.\textsuperscript{93} These cyclodehydration reactions using the Hendrickson reagent
27 have yielded three-, five- and six-membered rings, such as 30 and 31, with epoxide formation being the fastest. The four-membered ring did not form, presumably due to ring strain. It has been postulated that an alternate mechanistic pathway, 1,3-diol cleavage, may block the four-membered ring formation.\textsuperscript{93} In the cyclodehydration of amino alcohols, the formation of cyclic amines (in the presence of two nucleophilic centres) implies a preference for the phosphonium group on oxygen, a result of the very stable phosphine oxide leaving group. The amide of a primary amine also can be activated with the Hendrickson reagent 27 to generate a phosphonium imino ether, which can subsequently be displaced by an amine to form an amidine such as 32.\textsuperscript{89} In addition, thiazolines have been formed using 27 by dehydrocyclisation of \(N\)-acylated cysteine substrates.\textsuperscript{86}

Phosphonium salts, such as the Hendrickson reagent 27, have been used in catalytic amounts to activate carbonyl compounds towards attack by silyl nucleophiles.\textsuperscript{94} Aldehydes react with silyl enol ethers or ketene silyl acetals in the presence of the diphosphonium salt 27, to afford the corresponding aldol products such as 33. Similarly, acetals and ortho esters form aldol products with silyl nucleophiles such as allyltrimethylsilane and trimethylsilyl cyanide. Furthermore, the reaction of \(\alpha,\beta\)-unsaturated ketones or acetals with silyl or alkyl enol ethers gave Michael adducts such as 34 in the presence of a catalytic amount of diphosphonium salt 27.
Recently, the regioselective 4-O-alkylation of tetronic acids\textsuperscript{95} was reported with 27. As an alternative to the Mitsunobu reaction, which failed with hindered alcohols such as tert-butyl alcohol, the Hendrickson reagent 27 was successfully employed to produce a set of 4-alkoxy-5\textit{H}-furan-2-ones from tetronic acids and primary and secondary alcohols (Scheme 16). The reaction of 27 with tert-butyl alcohol gave small amounts (7\%) of the respective alkylation product.

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme16.png}
\end{center}
\textbf{Scheme 16}

The Hendrickson reagent 27 can be used in the glycosylation of sugars. 1,2-\textit{Cis}-ribofuranosides have been synthesised directly from readily available sugars and alcohols using the Hendrickson reagent 27 (Scheme 17).\textsuperscript{96,97} The glycosylated sugars were stereoselectively synthesised, a result reflecting the apparent difference in reactivities of the \textit{α}- and \textit{β}-anomer phosphonium intermediates. The \textit{β}-anomer reacts faster with the alcohol to yield predominately 1,2-cis-ribofuranosides.

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme17.png}
\end{center}
\textbf{Scheme 17}

Triphenylphosphinimine has been synthesised by bubbling ammonia through a solution of the Hendrickson reagent 27.\textsuperscript{98} Reactions with 27 usually yield phosphine oxide by-
products but in this case, the resulting phosphine oxide was re-treated with triflic anhydride and ammonia and after eight cycles an 82% yield of triphenylphosphinimine was obtained (Scheme 18).

\[
\text{Ph}_3P\overset{+}{\rightarrow}O\overset{+}{\rightarrow}\text{Ph}_3 + \text{NH}_3 \rightarrow \text{Ph}_3P\overset{+}{=NH}_2 + \text{NH}_4^+ + \text{Ph}_3P\overset{+}{=}O
\]

\[\frac{1}{2}(\text{CF}_3\text{SO}_2\text{O})\]

Scheme 18

2.2.4 Eliminations

Initially, the Hendrickson reagent 27 was used to yield alkenes by means of alcohol elimination.\textsuperscript{84} The reaction of secondary alcohols, such as (–)-menthol, with 27 immediately formed the corresponding alkoxyphosphonium salt 35 which cleanly eliminated upon heating to yield both 2- and 3-menthene 36 and 37 (Scheme 19). While the regiochemistry was not detailed, \textit{cis} elimination has been suggested\textsuperscript{88} to account for the mixture of menthene obtained.

\[
\text{Ph}_3P\overset{+}{\rightarrow}O\overset{+}{\rightarrow}\text{Ph}_3 + \text{DCM} \rightarrow \text{Ph}_3P\overset{\text{CF}_3\text{SO}_2\text{O}^-}{\text{K}_2\text{CO}_3} \Delta \rightarrow \text{Ph}_3P\overset{+}{=}O
\]

Scheme 19

Amides also were dehydrated to their corresponding nitriles, such as 38, after stirring with the Hendrickson reagent 27 at room temperature overnight.\textsuperscript{84,90} Similarly, oximes rapidly dehydrate to nitriles, such as 39, when activated with 27.\textsuperscript{90} The formation of ketenes from carboxylic acids is possible with the Hendrickson reagent 27, although the \(\alpha\)-hydrogen of the carboxylic acid must be sufficiently acidic.\textsuperscript{89} For example,
diphenylacetic acid and 27 immediately generates diphenylketene 40 in the presence of triethylamine through the elimination of water.

In addition, alkynes have been obtained by dehydration of ketones activated by the Hendrickson reagent 27. As with ketene formation from carboxylic acids, the α-hydrogen of the ketone must be sufficiently acidic to be removed by base and hence form the alkyne. For example, in Scheme 20, if enolate formation is activated by a carbonyl at $R^1$, the reaction between the ketone and 27 requires an hour or less. However, when the ketone is unactivated ($R^1 = H$ or alkyl), no reaction occurs.

![Scheme 20](image)

Finally, dienes have been constructed using the Hendrickson reagent 27 by a double elimination of epoxides with base. Preliminary $^3$P NMR studies indicate a mechanism which may involve a diol bis-phosphonium ether.

### 2.2.5 Reductions

Another interesting application of the reagent 27 is reduction of alcohols to alkanes, a reaction which does not occur under Mitsunobu conditions. With primary and acyclic secondary alcohols, reduction with sodium borohydride occurs to give the
corresponding alkane. The reaction does not occur with cyclic secondary alcohols, presumably due to steric hindrance in the $S_N2$ reaction.

### 2.3 Variations of the Hendrickson reagent

The phenyl groups of the Hendrickson reagent 27 have been varied to the related tributyl derivative\(^{96}\) to make 1,2-\textit{cis}\textendash{}furanoside ethers\(^{97}\) and as catalysts in the aldol and Michael reactions of silyl enol ethers.\(^{94}\) Other groups on phosphorus, such as napthyl-, cyclohexyl- and CH\(_3\)(CH\(_2\))\(_{15}\)-, have been trialled but the best yields were obtained with the bis-tributyl analogue of 27.\(^{97}\)

The reaction generates two moles of phosphine oxide per mole of reagent 27 and thus, to aid work-up and purification of products, a variant of the reagent has been prepared from Ph\(_2\)PO-N(CH\(_2\)CH\(_2\))\(_2\)NMe,\(^{89}\) which can be removed by aqueous extraction. Also, the reaction of HMPA with triflic anhydride has been reported to generate a diphosphonium salt 41, which is much more stable to hydrolysis than the Hendrickson reagent 27. However, 41 also is much less reactive than 27. Interestingly, an X-ray crystallographic study of 41 revealed that the nitrogen atoms are completely sp\(^2\) hybridised and that the P-O-P angle is 180°. Alternatively, the counter-ion of the Hendrickson reagent 27 can be varied. Meerwein’s salt (triethyloxonium tetrafluoroborate) has been used in the place of triflic anhydride to generate triphenylphosphonium anhydride tetrafluoroborate [µ-oxobis(triphenylphosphonium) bis(tetrafluoroborate)] 42.\(^{102}\) In addition, fluorosulfonic anhydride/triphenylphosphine oxide has been employed for simple conversions such as anhydride, ester and amidine formation.\(^{103}\)

\[
\begin{align*}
\text{Ph}_3\text{P}^-\text{O}^-\text{P}^-\text{Ph}_3 & \quad 2\text{BF}_4^- \\
2\text{CF}_3\text{SO}_2\text{O}^- & \quad 41 \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph}_3\text{P}^-\text{O}^-\text{P}^-\text{Ph}_3 & \quad 42 \\
\end{align*}
\]
The alkoxytriphenylphosphonium ions, regarded as intermediates in both the Mitsunobu and Hendrickson reactions, can be prepared electrochemically by anodic oxidation of triphenylphosphine in the presence of an alcohol. These ions have been used to alkylate imidazole, thiophenol and carboxylic acid functionalities. In the presence of base, amides and ureas have been dehydrated to their respective nitriles and carbodiimides. Alkoxytriphenylphosphonium ions prepared from β- and α-cholestanol were reacted with a variety of nucleophiles, such as Bu₄N⁺ · X⁻ (X = Br, Cl, F, N₃, SCN), PhSH and PhOH, with soft nucleophiles giving S₉2 reaction products in good yield. In addition, electrochemically generated alkoxytriphenylphosphonium tetrafluoroborates can be used to transform alcohols into their corresponding fluorides following thermal decomposition. Acyloxytriphenylphosphonium ions have similarly been prepared from triphenylphosphine and carboxylic acids and used to generate esters and amides.

The above discussion on the Mitsunobu and Hendrickson reagents serves to highlight the utility of these reactions. Notably absent from Hendrickson-type chemistry is the use of solid-phase or polymer-supported reagents. A brief account of important aspects of solid-phase chemistry will be presented now.

3.0 Solid-phase chemistry

3.1 General overview

With an ever increasing demand on the synthetic chemist to produce new compounds that will become pharmaceuticals, perfumes, cosmetics, pesticides, preservatives, paints, pigments and plastics, there exists a demand for new methods to simplify and automate organic synthesis, making it more efficient and allowing greater structural variation.
One popular strategy for producing large numbers of compounds in a multi-parallel fashion is to use solid-phase organic synthesis (SPOS). Solid-phase organic synthesis has evolved rapidly in the last fifteen years with the introduction of combinatorial synthesis. It is in this area that SPOS has had major impact. Primarily, solid-phase organic synthesis has accelerated the numbers of compounds available for high-throughput screening of compound libraries in medicinal chemistry programs.

Recently, applications beyond medicinal chemistry are emerging in the area of materials science, such as new catalysts and devices. The use of the solid-phase in organic synthesis will be discussed within this context.

3.2 Solid-phase organic synthesis (SPOS)

The first major influence in solid-phase chemistry was the Merrifield synthesis of a tetrapeptide on a solid resin particle in an automated fashion, in an attempt to simplify the standard lengthy procedure. Although the impact of Merrifield’s idea was only used by peptide chemists for many years, today organic synthesis by solid-phase methods has emerged as a powerful tool for the clean generation of organic molecules.

Classical solid-phase organic synthesis involves the tethering of a substrate to an insoluble polymer matrix for subsequent elaboration. The essential goal in using SPOS is to be able to separate one substance from another. The key strength in forming molecules immobilised on a polymeric support is the ease of reaction work-up and product isolation. Each reaction which follows can then be driven to completion by the addition of excess reagents and coupling components. Excess reagents and those by-products which are not attached to the polymeric resin can be eliminated by simply washing and filtering the polymeric resin. At the end of the synthetic process, the assembled molecule is cleaved from the solid support and isolated following a simple
filtration. Another advantage of this biphasic methodology is that the simplification of all handling steps renders a synthetic method feasible for automation. This general process has become the backbone of modern combinatorial chemistry and is now a widely used technique for the synthesis of libraries of pure compounds.

Despite the success and benefits of SPOS, there are limitations associated with its use. Additional steps are required to attach the substrate and cleave the final product from the polymeric support. It is also necessary to design and develop a suitable linking functionality, however not all desired templates offer viable linking units for tethering to a polymer support. The linker group may dictate the type of chemistry achievable during a particular solid-phase reaction. As large libraries based on a common template are not always desired, time is required to develop robust and versatile chemistry for multistep synthesis on solid supports. Reactions on solid-phase can be limited to certain solvents and reagents, depending on which solvents are capable of swelling the polymeric resin. Large scale preparations are often difficult due to the moderate loading capacities of the polymer support. A severe disadvantage of SPOS is the inability to monitor the reaction progress by conventional analytical techniques, such as TLC, NMR, GC/MS and LC/MS. There are difficulties optimising reactions and identifying compounds attached to a solid support. Analytical methods such as FTIR, MALDI/MS and gelphase and MAS NMR are being developed to overcome these difficulties. In addition, reactions may be slower than in solution-phase and some reactions, for example heterogeneous catalysis, cannot be performed on solid-phase. Consequently, it is an ongoing challenge to convert reactions in solution to insoluble polymer-supported methodology.
To overcome the limitations of solid-phase organic synthesis, there is a considerable effort focusing on the development of new technologies which assist in rapid purification of solution-phase reactions. These efforts have spurred a renewed interest in the use of solid-supported reagents in solution-phase chemistry.

3.3 Polymer-assisted solution-phase synthesis (PASP)

Solid-supported reagents have been in use since 1946 but only recently has the level of interest in them increased, as their specific application as reagents capable of generating large numbers of compounds in a clean and efficient manner has been realised. An historical account of the emergence of solid-phase reagents has been detailed elsewhere. The use of polymer supports in solution-phase organic synthesis to immobilise reactants, reagents or catalysts is termed polymer-assisted solution-phase synthesis (PASP). The definition of ‘polymer assisted solution-phase synthesis’ first used polymers to sequester products or by-products from reaction mixtures. PASP can involve the use of polymeric reagents, catalysts, scavengers, sequestering agents or recognition elements. Figure 1 illustrates the various uses of polymer supports in organic synthesis.

Unlike solid-phase synthesis where the desired compound is built on a solid-support during a multistep synthetic sequence, PASP entails the promotion of a chemical transformation of a substrate present in solution by a polymer-bound reagent or catalyst. PASP combines the advantages of product isolation and purification of SPOS with the benefits of traditional solution-phase methods.
PASP also allows reactions that do not proceed to completion to be purified. As a result, the use of polymer-supported reagents and scavengers has greatly improved the efficiency of classical solution-phase chemistry. Given that this purification strategy avoids liquid-phase extraction and chromatography, there is a reduction in waste solvents. In addition, the supported species can often be re-used after regeneration. Molecular diversity within chemical libraries is not compromised by an obligatory linking functionality as library members do not require attachment to a support. As no linker functionality is required, the pre-library validation time is subsequently shorter. The use of polymeric supports in solution-phase allows the use of conventional analytical tools for assessing reaction progress and chemical purities. With PASP, a whole repertoire of previously known organic reactions are available and convergent, linear and batch splitting synthetic strategies can be accommodated (Figure 2). Also, attaching species to solid supports reduces their toxicity and odour, improving their

Figure 1. Various uses of polymer supports in organic synthesis.137
general acceptability and making them easier and safer to handle. Another attractive aspect is that the combination of two or more solid supports with incompatible functionality can be used in a single reaction vessel without compromising the overall reaction sequence because of the site isolation of the reagents by immobilisation.

**Figure 2.** The opportunities for solid-supported reagents in synthesis.\(^{138}\)

Recently, a number of excellent reviews on PASP and its application in combinatorial chemistry have appeared.\(^{137-141}\) Hence, due to the sudden increase in the number of scientific papers describing novel reagents, catalysts and methods of purification in PASP, the following sections will only give a broad overview of the supported species used in PASP and highlight specific examples from the literature.

### 3.3.1 Polymeric reagents

There are two main types of polymer-supported reagents: those in which there is a covalent bond between the active molecule and the polymer backbone and those in which there is an ionic interaction between the active molecule and the polymer backbone. Polymeric reagents have been substantially reviewed in the literature.\(^{137,139,142-147}\) Their use for oxidations, reductions, halogenations, C-C coupling
reactions, nucleophilic substitution reactions, protection and deprotection, and dehydration reactions is well documented. Some selected examples of chemical transformations relevant to the work encompassed in this thesis are provided below.

3.3.1.1 Nucleophilic substitution reactions with anionic resins

Resins loaded with various inorganic and organic anions are ideally suited for promoting substitution reactions. For example, the conversion of alkyl halides and tosylic esters into thioacetates can be achieved using a thioacetate ion supported on an Amberlyst resin (Scheme 21). Due to the ease of work-up, this reaction presents a convenient method for the introduction of sulfur into organic molecules. Phenoxides can be supported on an Amberlite resin, serving as a method for performing O-alkylations when reacted with alkyl halides. Azide ion, supported on Amberlite, can be employed to synthesise azides from activated and non-activated alkyl halides. Also, epoxides of polycyclic aromatic hydrocarbons can be opened using this reagent to give azidohydrins.

![Scheme 21](image)

3.3.1.2 Dehydration reactions

Various functionalised polymers derived from triphenylphosphine are strongly dehydrating. The reagent system comprising of polymer-supported triphenylphosphine and carbon tetrachloride has numerous applications in organic synthesis, such as halogenation, P-N linking reactions and dehydration. With this reagent, primary carboxamides and oximes can be converted into nitriles and secondary amides into imidoyl chlorides. Polymer-supported triphenylphosphine dibromide has been used...
to prepare unstable carbodiimides from ureas and thioureas (Scheme 22) and convert secondary amides into imidoylbromides.$^{155}$

![Scheme 22](image)

Furthermore, polymer-supported triphenylphosphine diiodide can promote the conversion of primary or secondary alcohols into their corresponding formate esters in the presence of DMF.$^{156}$ Carboxylic acids can be esterified by polymer-supported triphenylphosphine diiodide with a variety of alcohols, such as 5α-cholestan-3β-ol.$^{157}$ Dehydration reactions also can occur in the presence of a polymer-supported activating agent. For example, the use of polymer-supported 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (PS-EDC)$^{43}$ provided a convenient synthesis of both thiol$^{158}$ and hapten$^{159}$ active esters. In addition, N-hydroxysuccinimide esters have been prepared using polymer-bound 1-hydroxybenzotriazole (PS-HOBT)$^{44}$.$^{160}$

![Image of compounds 43 and 44](image)

**3.3.1.3 Amide bond formation**

Amide bonds are present in a large number of pharmacologically active compounds and numerous methods for their formation have been developed using polymer-supported reagents. Polymer-supported triphenylphosphine dihalides are useful reagents for amide bond formation. N-protected amino acids can be coupled with amines in the presence of polymer-supported triphenylphosphine and carbon tetrachloride.$^{161}$ Similar results have
been achieved with the polymer-supported triphenylphosphine diiodide complex and no racemisation of the synthesised peptide was observed.\textsuperscript{162}

The carbodiimide coupling method is popular and versatile and has been used on polymeric support since the 1970s.\textsuperscript{163} A side-product of these reactions is the leaving group of the activated esters and hence, immobilisation of these activators on solid-support removes the most dominant side-product from the reaction mixture. For example, the utilisation of PS-EDC \textsuperscript{43} has coupled amines with carboxylic acids efficiently and cleanly\textsuperscript{164} (Scheme 23). An acylsulfonamide library has been prepared with PS-EDC \textsuperscript{43} in good yield and purity.\textsuperscript{165}

\begin{center}
\textbf{Scheme 23}
\end{center}

Amide synthesis can be achieved using PS-HOBT \textsuperscript{44}\textsuperscript{160} as well as an analogue of PS-HOBT, polymer-supported \(N\)-benzyl-1-hydroxybenzotriazole-6-sulfonamide \textsuperscript{45}.\textsuperscript{166} The advantage of \textsuperscript{45} over PS-HOBT \textsuperscript{44} lies in its electron-withdrawing sulfonamide group, which makes the corresponding active ester more susceptible toward nucleophilic attack. The reagent \textsuperscript{45} is particularly suitable for the high throughput parallel synthesis of amide libraries.\textsuperscript{166} Polystyrene is a commonly used solid support, however its use can limit the choice of reaction solvent to one which will swell the resin. Therefore, HOBT immobilised on macroporous support has been synthesised and used in a variety of solvents to generate amides in good yield.\textsuperscript{160}
A polymer-bound 4-hydroxy-3-nitrobenzophenone 46 was used to synthesise a library of eight thousand amides and esters. The polymer-supported phenol 46 was treated with a range of acid chlorides to generate active esters which were then attacked by amine or alcohol nucleophiles in the presence of triethylamine (Scheme 24). Many other polymer-supported activating agents have been used in the formation of amide bonds.

Scheme 24

The solution-phase synthesis of amides can be achieved with Amberlite IRA-68, a weakly basic ion-exchange resin. Treatment of the resin with an acid chloride and an amine gives amides cleanly following filtration. The excess acid chloride is hydrolysed with water and the resulting carboxylic acid and hydrochloric acid absorbed into the resin. In peptide synthesis, HOBT-derived phosphonium salts are well established coupling reagents because of their efficiency and low degree of racemisation. Polymer-supported version of these reagents, such as polymer-bound 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (PS-TBTU) 47 are being developed and show promise as solid-supported peptide coupling reagents.
3.3.2 Polymeric catalysts

Catalysts are often required to increase the reactivity of one or more reaction partners in organic reactions. In many cases these catalysts complicate reaction work-up, making product purification and catalyst recycling difficult and tedious. Functionalised polymers therefore have an obvious application in catalysis. Resin-bound catalyst systems with transition metals are particularly beneficial in reducing metallic contamination in the final products. For example, carbon-carbon bonds have been formed via a Suzuki cross-coupling reaction employing a polymer-bound palladium catalyst. The palladium (0) catalyst coupled organoboranes with 1-alkenyl bromides, aryl halides and aryl or alkenyl triflates (Scheme 25). Reviews on immobilised catalysts and on solid-supported reagents which include sections on polymeric catalysts have been written.

\[
\text{OTf} + \text{Me} \quad \text{Polymer-bound palladium} \quad \text{K}_3\text{PO}_4, \text{dioxane} \\
\text{Me} \quad 5\text{ hr, } 85^\circ\text{C} \\
\]

Scheme 25

3.3.3 Polymer-supported scavengers, quenching agents and recognition elements

The shift in combinatorial synthesis towards defined chemical libraries has seen considerable effort devoted towards the search for alternative strategies which will assist in the rapid purification of solution-phase reactions. The results have cumulated in the use of complementary functionalised polymer-supported reagents, known as scavengers, quenching agents or recognition elements to purify traditional solution-phase chemical synthesis. A series of reviews detailing these modern separation techniques have been published, including sections in the broader reviews. The first use of polymer-supported scavengers was where excess starting materials or impurities were selectively removed from a solution-phase reaction by
covalent (electrophilic and nucleophilic) or ionic (acidic and basic) interactions between the impurity and the solid-phase (Scheme 26). Some examples of polymeric scavengers that are electrophilic (48, 49), nucleophilic (50, 51), acidic (52, 53) and basic in functionality (54, 55) are shown below.

![Scheme 26]

Nucleophilic and electrophilic polymer-supported reagents have been used as scavengers in synthesis (a nucleophilic polymer is an electrophilic scavenger and vice versa). For example, during the coupling of primary amines with isocyanates to generate ureas, aminomethylpolystyrene was utilised as a scavenger to sequester the excess isocyanate used during the reaction. The basis of this technique relied on the fact that the chemoselectivity of the electrophilic acylating agent (the isocyanate) was much different to that of the corresponding nucleophilic amine or the amide product. Another form of reactant sequestration employs functionalised resins to perform reaction-quenching operations. An example involves the use of a polymer-supported carboxylic acid to quench any unreacted alkyl-lithium or alkyl-magnesium reagents and their alkoxide derivatives (via a proton transfer) that are formed during the reaction of organometallic reactants with aldehydes (Scheme 27).
Ion-exchange resins, polystyrene-based macroporous resins functionalised with sulfonates or quarternised amines, also can be used as scavengers. For example, a cationic ion-exchange resin can be used to scavenge amines or ammonium salts. Another purification strategy can be employed in which soluble reagents are ‘tagged’ with a functional group which will not alter the desired outcome of the reaction but will be present in both the reagent and reagent by-product upon completion of the reaction. These chemical tags allow both the reagents and its by-products to be trapped onto a complementary functionalised resin, leaving the desired compound in solution. A chloroacetyl group tag has been reported to aid in the purification of oligosaccharides (Scheme 28). A thiol containing resin can effectively capture saccharides tagged with the chloroacetyl group and the desired products can be released following treatment with 4-(aminoethyl)piperidine. An alternative process, termed capture and release, can be used to selectively trap the desired product of a solution-phase reaction onto a functionalised support. Following filtration and washing to remove the solution-phase contaminants, the compound may then be released from the support in pure form.
3.3.4 Multistep organic synthesis

The potential for the application of more than one polymer-bound species to either effect reaction or product clean-up in multistep organic sequences has been realised for the generation of both small molecule libraries and more complex architectures such as natural products. The use of polymeric reagents in combination avoids the need to isolate intermediates and illustrates that by immobilisation on a polymer, mutually incompatible reagents can be present in the same reaction vessel, as the majority of their reactive groups do not come into contact with each other.

A simple example to demonstrate the usefulness of multistep polymer-assisted solution-phase synthesis is seen in a three step synthesis using three different polymeric reagents simultaneously in the one reaction vessel (Scheme 29).\textsuperscript{135} A 48\% yield of the substituted phenylethanone was obtained upon filtration, compared with only 42\% when the reaction was performed in a sequential fashion. The advantages of multistep sequences using the polymeric reagents can be appreciated, given that no product would
result if the same synthesis was undertaken using the soluble equivalents in a homogenous solution.

![Chemical structures](image)

**Scheme 29.** (a) Poly(4-vinylpyridinium dichromate), (b) Perbromide on Amberlyst A26, (c) Amberlite IRA-900 (4-chloro-1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-ol).

Much of the work on the development of supported reagents for multistep solution-phase organic synthesis has been reported only recently.\(^{140,187-189}\) Many libraries of compounds relevant to medicinal chemistry have been synthesised via multistep sequences employing polymeric species, including a bicyclo[2.2.2]octane library using a tandem Michael addition of enolates of 2-cyclohexenones with a range of substituted acrylates.\(^{190}\) In addition, the synthesis of natural products, such as (±)-epimaritidine,\(^{191}\) (±)-epibatidine\(^{192}\) and (±)-carpanone,\(^{193}\) have been achieved via multistep processes using a combination of supported reagents and scavengers. More recently, the first fully automated multistep polymer-assisted solution-phase synthesis of an array of histone deacetylase inhibitors has been reported, which revealed the utility of polymer-assisted strategies to bring about full automation of a solution-phase synthesis.\(^{194}\)

### 3.4 Choice of polymer support

There are two main approaches for the preparation of functionalised polymers: monomers which carry the desired functionality can be polymerised or preformed
polymers can be chemically modified. The later is mainly exploited today, particularly because the polymerisation of monomers demands a profound knowledge of polymers and polymerisation. In addition, many functionalised polymers are now becoming commercially available, making their use quicker, simpler and more practical.

While much effort in the field of solid-phase organic synthesis has been directed towards improving linker groups for substrate and reagent attachment, little has been done on the development of polymeric supports. For the successful design of new polymer-supported reagents, it is important to consider the physical properties and role of the polymeric support. The macromolecule employed can affect the course of a reaction as a result of steric, electrostatic and diffusion effects. In the case of polymeric resins, one also must consider the diffusion of reagents to the reactive sites on bound molecules and thus, choose an appropriate solvent with good swelling ability.

Commonly used supports in solid-phase organic synthesis are derived from lightly (1-2%) cross-linked polystyrene, polyethylene glycol (PEG) grafted polystyrene and macroporous polystyrene. The original divinylbenzene cross-linked polystyrenes continue to be the most widely used supports because of their stability, reasonably high loading capacity and good swelling characteristics. PEG-grafted polystyrene supports, such as TentaGel, are useful because of compatibility of the resin with polar aprotic solvents and the ability to monitor reactions on single beads by NMR. Macroporous polystyrene resins have an internal pore structure through which reagents are transported. As the functionality is largely confined to the pore surface when high cross-linking levels are employed, solvents which do not swell lightly cross-linked polystyrene very well can be used. Furthermore, non-cross-linked polystyrene copolymer supports and soluble PEG resins have been introduced to overcome restricted access to active sites.
Along with organic polymers, potential supports have been developed from other materials such as Kieselguhr (or diatomaceous earth),\textsuperscript{213} cellulose paper disks\textsuperscript{214} and surface-functionalised colloids, nanoparticles or hollow spheres.\textsuperscript{215-218} Thus, the potential for use of other sorts of polymers as supports in synthesis is gradually being recognised. Lightly cross-linked polystyrene resins continue to be the most commonly used for synthesis, however there is renewed interest in providing interesting and useful alternatives with the expansion of the field of solid-phase organic synthesis.

4.0 Aims and scope of thesis

The Mitsunobu reaction has been established as a versatile and useful reaction in organic synthesis for converting a primary or secondary alcohol into an excellent leaving group (an oxyphosphonium salt) which can subsequently be displaced inter- or intra-molecularly by a wide range of nucleophiles. Despite its widespread use, there is a significant drawback associated with the Mitsunobu reaction: the difficulty in removal of the phosphine oxide and dialkyl azodicarboxylate by-products, particularly on a commercial scale where product purification by chromatography is not feasible. Another disadvantage with large-scale applications is the explosive nature and/or cost of most dialkyl azodicarboxylate reagents.

Several alternative approaches mentioned previously can be adopted to overcome the drawbacks of the Mitsunobu reaction, however the standard solution-phase phosphine/alkyl azodicarboxylate combination is still used by most chemists and another synthetic method sought if scale-up is required. An alternative protocol for the Mitsunobu reaction may lie in a modification of the Hendrickson reagent \textsuperscript{27}. This reagent \textsuperscript{27} seems to effect dehydrations (ester, amide formation etc) in a similar fashion to the Mitsunobu reaction. Undoubtedly, the analogous key intermediate (an oxyphosphonium salt) is present in both reactions. The similarity between the two
reactions has for the most part been overlooked, although it has been mentioned in other\textsuperscript{219} and more recent publications.\textsuperscript{88,101} Compared with the Mitsunobu reaction, the use of the Hendrickson reagent \textsuperscript{27} has been sporadic and thus far not reported for inverting the configuration of an alcohol.

The first aim of this project was to prepare a polymer-supported P-O-P reagent, based on a 1,2-bis-phosphine oxide. It was proposed that a reagent such as \textsuperscript{56} would allow Mitsunobu conversions to be carried out without the use of the azodicarboxylate reagent, would avoid the use of chromatography for the removal of the phosphine oxide and should be amenable to large-scale use (reactions could possibly be carried out in flow reactors). The reagent \textsuperscript{56} would be such that after reaction, both phosphine oxide moieties remain attached to the polymer support. The removal of the phosphine oxide would be achieved simply by filtration of the polymer beads, which could subsequently be recycled for further reactions. In addition, competing Mitsunobu-type side reactions such as alkylation of the hydrazinedicarboxylate should be eliminated with this method. Treatment of \textsuperscript{57} with triflic anhydride should generate the desired polymer-supported reagent \textsuperscript{56} (Scheme 30).

\begin{center}
\includegraphics[width=\textwidth]{scheme30.png}
\end{center}

\textbf{Scheme 30}

The proposed synthesis of the polymer-supported 1,2-bis-phosphine oxide \textsuperscript{57} is based on literature precedent\textsuperscript{87,220,221} and outlined in Scheme 31. Reaction of the phosphorus anion \textsuperscript{58} with brominated poly(styrene-co-divinylbenzene) \textsuperscript{59} should yield polymer-supported 1,2-bis(diphenylphosphino)ethane \textsuperscript{60}, which can then be oxidised to the desired phosphine oxide \textsuperscript{57}. The basis for selecting a 1,2-bis-phosphine oxide is
because it is a simple way of ensuring that both phosphine oxide moieties remain attached to the polymer support after the reaction.

**Scheme 31**

Once the polymer-supported 1,2-bis-phosphine oxide \( \text{57} \) and corresponding phosphonium anhydride analogue \( \text{56} \) have been prepared, it will be necessary to explore the generality and scope of the reagent \( \text{56} \) in Mitsunobu-type conversions. This will involve, in particular, investigations into the conversion of a chiral alcohol into its inverted 4-nitrobenzoate ester in high yield and under mild conditions. This will be carried out using (–)-menthol as has been done previously in the Mitsunobu reaction.\(^{44,49}\) Also, exploration of the polymer-supported P-O-P derivative \( \text{56} \) as a dehydrating agent would be interesting as the alkylation of hydrazinedicarboxylate is often a competitive process in the Mitsunobu reaction. Following these investigations, it was anticipated that the polymer-supported phosphonium anhydride reagent \( \text{56} \) could be shown to be a more user-friendly reagent than the standard Mitsunobu combination of triphenylphosphine and diethylazodicarboxylate.
CHAPTER ONE

USE OF THE HENDRICKSON REAGENT IN AN ALTERNATIVE MITSUNOBU PROTOCOL
In seeking an alternative protocol for the Mitsunobu reaction, that would allow conversions to be undertaken without the use of azodicarboxylates, would avoid the use of chromatography for the removal of the phosphine oxide and eliminate competing Mitsunobu-type side reactions such as alkylation of the hydrazinedicarboxylate, a novel polymer-supported analogue 56 of the Hendrickson reagent 27 was designed. In contrast to the Mitsunobu reaction that is widely used, the Hendrickson reagent 27 has only been used occasionally and has not been previously examined as a means for inverting the configuration of an alcohol (a common use for the Mitsunobu reaction). In order for the proposed modified Hendrickson reagent 56 to offer a comprehensive and alternative protocol for the Mitsunobu reaction, inversion of stereochemistry of optically active alcohols following esterification/hydrolysis must be demonstrated. Thus, prior to the synthesis and evaluation of 56 as a Mitsunobu alternative, the Hendrickson reagent 27, its reaction with primary alcohols and its use for the inversion of secondary alcohols was investigated.

1.0 Reactions of the Hendrickson reagent 27 with primary alcohols

Initially, the Hendrickson reagent 27 was examined for the simple esterification of a primary alcohol. Simple esters have been formed by Hendrickson\textsuperscript{84,89} previously and a similar procedure was followed. Addition of triflic anhydride to an ice-cooled solution of triphenylphosphine oxide in DCM formed the reagent 27 as a white precipitate. 4-Nitrobenzyl alcohol, 4-nitrobenzoic acid and diisopropylethylamine were added and after stirring for two hours at room temperature, work-up and chromatography, 4-nitrobenzyl 4-nitrobenzoate 61 was obtained in high yield (95%) (Scheme 32) (Table 1, entry 1). To ensure that all of the triflic anhydride was consumed, a slight excess of triphenylphosphine oxide was employed. Excess triflic anhydride could react with the alcohol to form the triflate ester or the carboxylic acid to form the corresponding anhydride.
An increase in the yield of 4-nitrobenzyl 4-nitrobenzoate 61 (from 86% to 97.5% conversion by comparison via $^1$H NMR integration of the benzyl CH$_2$ groups of starting alcohol and product ester 61) was observed when the triflic anhydride reagent was freshly distilled from phosphorus pentoxide (P$_2$O$_5$). During optimisation of the reaction, it was found that the best conversion (by $^1$H NMR integration) of 4-nitrobenzyl alcohol to 4-nitrobenzyl 4-nitrobenzoate 61 was achieved when only one equivalent of the Hendrickson reagent 27 was used. Excess reagent 27 led to reduced yields of the ester 4-nitrobenzyl 4-nitrobenzoate 61, as shown in Figure 3, possibly because a more polar reaction environment is generated when excess reagent is employed, thereby slowing the reaction.

**Figure 3.** The effect of equivalents of Hendrickson reagent 27 on yield (by $^1$H NMR spectroscopy) of 4-nitrobenzyl 4-nitrobenzoate 61.
As the use of the Hendrickson reagent 27 regenerates triphenylphosphine oxide, it was considered that the reaction might take place using only a catalytic amount of triphenylphosphine oxide. Also, the use of a reduced amount of triphenylphosphine oxide should simplify chromatographic separations. Treatment of a chilled solution of triphenylphosphine oxide (0.12 equiv.), 4-nitrobenzyl alcohol and 4-nitrobenzoic acid in DCM, with triflic anhydride and diisopropylethylamine, followed by stirring at room temperature overnight gave complete conversion to the ester 4-nitrobenzyl 4-nitrobenzoate 61 as determined by $^1$H NMR analysis of the crude product. However, in the presence of excess triflic anhydride, the reaction could proceed through the 4-nitrobenzyl triflate 62 or 4-nitrobenzoyl triflate 63 to give the desired ester 61. Therefore, a control reaction was performed in the absence of triphenylphosphine oxide and the ester 61 was again obtained quantitatively after stirring at room temperature overnight, following analysis of the crude product by $^1$H NMR spectroscopy. Hence, it was not possible to show that a catalytic amount of triphenylphosphine oxide can be used to continually form the Hendrickson reagent 27, due to competing esterification brought about by the triflic anhydride.

The use of the Hendrickson reagent 27 for substitution of primary alcohols with several other nucleophiles was investigated (Table 1). Treatment of 27 with 4-chlorobenzyl alcohol, thiolacetic acid, and diisopropylethylamine in DCM at room temperature overnight gave a 97% yield of 4-chlorobenzyl thioacetate 64. This is the first example of carbon-sulfur bond formation using the Hendrickson reagent 27. Similarly, treatment of 27 with 4-chlorobenzyl alcohol, sodium azide, and diisopropylethylamine in 3:1 DCM/DMF at room temperature overnight gave a 93% yield of 4-chlorobenzyl azide 65. The DMF was required to partially solubilise the sodium azide. Interestingly,
treatment of 4-chlorobenzyl alcohol under Mitsunobu conditions (triphenylphosphine and DIAD) with sodium azide in 3 : 1 DCM/DMF at room temperature overnight gave no reaction, the alcohol being recovered unchanged. However, this result could be a function of solubility as azides can be formed under Mitsunobu conditions using the organic soluble zinc azide/bis pyridine complex (Zn(N$_3$)$_2$.2Py).$^{28}$

Table 1. Reactions of the Hendrickson reagent 27 with primary alcohols.

<table>
<thead>
<tr>
<th>Entry$^{a,b}$</th>
<th>Alcohol</th>
<th>Nucleophile</th>
<th>Product</th>
<th>Yield (%)$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-NO$_2$-C$_6$H$_4$-CH$_2$-OH</td>
<td>4-NO$_2$-C$_6$H$_4$-COOH</td>
<td>4-Nitrobenyl 4-nitrobenzoate 61</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>4-Cl-C$_6$H$_4$-CH$_2$-OH</td>
<td>CH$_3$-C(O)-SH</td>
<td>4-Chlorobenzyl thioacetate 64</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>4-Cl-C$_6$H$_4$-CH$_2$-OH</td>
<td>NaN$_3$</td>
<td>4-Chlorobenzyl azide 65</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>4-NO$_2$-C$_6$H$_4$-CH$_2$-OH</td>
<td>4-OMe-C$_6$H$_4$-OH</td>
<td>O-(4-Nitrobenzyl)-4-methoxyphenol 66</td>
<td>84</td>
</tr>
</tbody>
</table>

$^a$All reactions were carried out with the Hendrickson reagent 27 (1.0 equiv.), alcohol (1.0 equiv.), nucleophile (1.0 equiv.), diisopropylethylamine (2.2 equiv.) in DCM (10 mL). $^b$Reaction conditions: entry 1 (room temperature for 2 hours), entries 2-4 (room temperature overnight). $^c$Yields calculated following chromatography. $^d$Added as a suspension in DMF (3 mL).

The use of the Hendrickson reagent 27 for etherification of phenols also was examined. Consecutive addition of 4-nitrobenzyl alcohol, 4-methoxyphenol and diisopropylethylamine to 27 gave O-(4-nitrobenzyl)-4-methoxyphenol 66 in good (84%) yield after stirring at room temperature overnight. It is clear from these examples and the work of Hendrickson$^{89}$ that the reagent 27 provides a mild and useful procedure for the esterification of primary alcohols, the synthesis of primary azides and the formation of ethers from phenols.

2.0 Reactions of the Hendrickson reagent 27 with secondary alcohols

Following the successful esterification of a primary alcohol, the use of the Hendrickson reagent 27 for esterification of optically active alcohols with inversion of configuration was investigated. (−)-Menthol was chosen for this study as it has been used previously
by Dodge\textsuperscript{44,222} to investigate the stereochemistry of esterification under Mitsunobu conditions. Treatment of the Hendrickson reagent 27 with (–)-menthol, 4-nitrobenzoic acid and diisopropylethylamine in DCM at room temperature overnight gave unreacted (–)-menthol. The reaction was repeated at 40°C for 24 hours, then quenched and an aliquot of the organic phase analysed by GC/MS. Surprisingly, the major products formed were the products of elimination, 2- and 3-menthene 36 and 37 (97%), along with small amounts of (–)-menthol (1%) and the inverted ester, neomenthyl 4-nitrobenzoate 67 (2%) (Scheme 33). Attempts to separate the menthene isomers by gas chromatography proved difficult and mixtures of 36 and 37 were obtained. Thus, an authentic sample of 2- and 3-menthene 36 and 37, was prepared by thermolysis of menthyl diphenylphosphate.\textsuperscript{223} The characteristic second order olefinic \textsuperscript{1}H NMR multiplets (3-menthene 37: δ 5.35–5.38 ppm and 2-menthene 36: δ 5.50–5.57 ppm) attributable to the menthenes 36 and 37 were identified in the \textsuperscript{1}H NMR spectrum of the crude reaction mixture following the reaction between the Hendrickson reagent 27, (–)-menthol and 4-nitrobenzoic acid. Analysis of the product mixture by \textsuperscript{1}H NMR spectroscopy also revealed the major product to be 3-menthene 37 (ratio 3-menthene 37 : 2-menthene 36 = 2:1).

\[
\begin{align*}
\text{OH} & \quad \text{Ph$_3$P} \quad \text{O} \quad \text{Ph$_3$} \\
27 & \quad 2\text{CF}_3\text{SO}_2\text{O} \\
\text{4-NO$_2$-C$_6$H$_4$-COOH} & \quad \text{4-NO$_2$-C$_6$H$_4$-COOH} \\
\text{1Pr$_2$NEt, DCM} & \quad \text{1Pr$_2$NEt, DCM} \\
24 \text{ hr, 40°C} & \quad 24 \text{ hr, 40°C} \\
\end{align*}
\]

\[
\begin{align*}
\text{36} & \quad \text{37} \quad \text{67} \\
1 : 2 & \quad 97\% + 2\% \\
\end{align*}
\]

\textbf{Scheme 33}

In an effort to decrease the amount of elimination occurring, the reaction was examined under a range of conditions, and with different solvents and different nucleophiles. Due to the volatile nature of the menthenes 36 and 37, the reaction products were analysed
primarily by GC/MS, as analysis by $^1$H NMR spectroscopy generally required solvent evaporation prior to NMR sample preparation, which resulted in partial loss of the menthens 36 and 37. $^1$H NMR analysis was, however, used to determine the ratio of 2-menthene 36 to 3-menthene 37 by integration. Table 2 displays the reactions of (−)-menthol with the Hendrickson reagent 27 and various nucleophiles in different solvents.

### Table 2. Reaction of (−)-menthol with the Hendrickson reagent 27 and nucleophiles.

<table>
<thead>
<tr>
<th>Entry$^{a,b}$</th>
<th>Solvent</th>
<th>Nucleophile</th>
<th>Products</th>
<th>Product ratios$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DCM</td>
<td>4-NO$_2$-C$_6$H$_4$-COOH</td>
<td>36$^+$/37$^-$ : (−)-menthol : 67</td>
<td>97 : 1 : 2</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>4-NO$_2$-C$_6$H$_4$-COOH</td>
<td>36$^+$/37$^-$ : (−)-menthol : 67</td>
<td>84 : 12 : 4</td>
</tr>
<tr>
<td>3</td>
<td>Toluene</td>
<td>4-NO$_2$-C$_6$H$_4$-COOH</td>
<td>36$^+$/37$^-$ : (−)-menthol : 67</td>
<td>68 : 10 : 22</td>
</tr>
<tr>
<td>4</td>
<td>Toluene$^d$</td>
<td>4-NO$_2$-C$_6$H$_4$-COOH</td>
<td>36$^+$/37$^-$ : (−)-menthol : 67</td>
<td>58 : 48 : 0</td>
</tr>
<tr>
<td>5</td>
<td>Toluene</td>
<td>4-NO$_2$-C$_6$H$_4$-COOH$^e$</td>
<td>36$^+$/37$^-$ : (−)-menthol : 67$'$</td>
<td>27 : 0 : 72$'$</td>
</tr>
<tr>
<td>6</td>
<td>DCM</td>
<td>4-NO$_2$-C$_6$H$_4$-COOH$^e$</td>
<td>36$^+$/37$^-$ : (−)-menthol : 67</td>
<td>86 : 1 : 13</td>
</tr>
<tr>
<td>7</td>
<td>Toluene</td>
<td>CH$_3$C(O)-SH</td>
<td>36$^+$/37$^-$ : (−)-menthol : 70</td>
<td>38 : 24 : 38</td>
</tr>
<tr>
<td>8</td>
<td>DCM</td>
<td>CH$_3$C(O)-SH</td>
<td>36$^+$/37$^-$ : (−)-menthol : 70</td>
<td>70 : 20 : 10</td>
</tr>
<tr>
<td>9</td>
<td>Toluene</td>
<td>4-MeO-C$_6$H$_4$-COOH</td>
<td>36$^+$/37$^-$ : (−)-menthol : 68</td>
<td>54 : 35 : 11</td>
</tr>
<tr>
<td>10</td>
<td>DCM/DMF (2:1)</td>
<td>NaN$_3$</td>
<td>36$^+$/37$^-$ : (−)-menthol : 71</td>
<td>20 : 54 : 26</td>
</tr>
<tr>
<td>11</td>
<td>Toluene</td>
<td>Zn(N$_3$)$_2$·2Py</td>
<td>36$^+$/37$^-$ : (−)-menthol : 71</td>
<td>92 : 2 : 6</td>
</tr>
<tr>
<td>12</td>
<td>DCM$^g$</td>
<td>4-NO$_2$-C$_6$H$_4$-COOH</td>
<td>36$^+$/37$^-$ : (−)-menthol : 67</td>
<td>93 : 0 : 7</td>
</tr>
</tbody>
</table>

$^a$All reactions were carried out with Hendrickson reagent 27 (1.0 equiv.), (−)-menthol (1.0 equiv.), nucleophile (1.0 equiv.) and diisopropylethylamine (2.2 equiv.) in 10 mL solvent. $^b$Reaction conditions were 40°C for 24 hours. For entry 12, reaction was sonicated for 6 hours and then stirred at room temperature overnight. $^c$Product ratios determined by GC/MS analysis. $^d$100mL solvent. $^e$4-Nitrobenzoic acid (4.5 equiv.) and diisopropylethylamine (5.5 equiv.). $^f$Ester displays retention and inversion of configuration in the ratio of 88:12 by $^1$H NMR. $^g$3 mL solvent.

It can be seen from Table 2 that in the majority of cases, the major product observed was that of elimination. Comparing entries 1, 2 and 3, which were carried out under identical conditions with a change of solvent (DCM, THF and toluene respectively), the highest relative yield of inverted ester 67 (and less elimination) was 22% when toluene
was used, indicating that the ratio of elimination to substitution is clearly solvent dependant. The use of an excess of 4-nitrobenzoic acid (entry 6, with excess diisopropylethylamine to assist with its solubility) in DCM only improved the yield of inverted product 67 from 2% to 13%. Use of the more nucleophilic acid, 4-methoxybenzoic acid, in toluene led to a decrease in the yield of inverted ester 68 relative to elimination (entry 9). The only reaction where esterification was the major product was when a large excess of 4-nitrobenzoic acid was used (entry 5). However, under these conditions the ester obtained was mainly the product of retention not inversion (analysis by $^1$H NMR spectroscopy showed an 88 : 12 ratio of retention to inversion by comparison of the respective H1 signals at δ 4.98 ppm (ddd, O-(4-nitrobenzoyl)-(–)-menthol 69) and δ 5.51 ppm (br s, neomenthyl 4-nitrobenzoate 67). Presumably with excess acid, carbonyl group activation or anhydride formation become kinetically competitive leading to (–)-menthol acylation with retention. The conversion of carboxylic acids to their corresponding anhydrides can occur with both the Hendrickson and Mitsunobu reagents. Attempting the reaction under dilute conditions (entry 4, ten-fold increase in volume of solvent) led to a slower reaction which gave none of the desired ester 67 but a large amount of elimination product (52%). Lepore has found that a vast rate increase in the Mitsunobu reaction of sterically hindered alcohols and phenols can be accomplished by the combined use of sonication with high concentration. However, when a reaction using the Hendrickson reagent 27 was attempted under these conditions, analysis by GC/MS revealed 2- and 3-menthene 36 and 37, to be the major products (entry 12).
Use of the much more nucleophilic thiolacetic acid instead of 4-nitrobenzoic acid in DCM only gave a 10% yield of inverted thioacetate 70 relative to elimination (entry 8), however when the least polar solvent, toluene, was employed (entry 9), an increase in the SN2 substitution product 70 to 38% was observed. Nonetheless, in both these cases elimination was still a significant pathway. The use of sodium azide as a nucleophile (entry 10, in DCM/DMF 2:1) gave a considerably slower reaction with 54% of (–)-menthol remaining unreacted, however 26% of the expected neomenthyl azide 67 also was obtained. The use of the much more organic soluble zinc azide/bis pyridine complex gave a higher overall conversion but lower yield of the azide 71 (6%), with elimination to form the menthenes 36 and 37 (92%) again being the dominant pathway (entry 11). Possibly the presence of pyridine led to increased elimination. Analogous alkoxytriphenylphosphonium ions have been generated electrochemically from secondary alcohols such as α-cholestanol and their SN2 displacement was reported to occur by bromide or chloride ions but not by azide (Bu4NN3 was used).225 The sulfonation of a secondary alcohol with clean inversion can be achieved in high yield under Mitsunobu conditions with sulfonic acids.226 Therefore, the use of tosic acid as a hard nucleophile in the reaction between the Hendrickson reagent 27 and (–)-menthol was attempted. After heating a DCM solution of 27, (–)-menthol, tosic acid and diisopropylethylamine at reflux for 24 hours, analysis of the crude reaction mixture by 1H NMR spectroscopy revealed the presence of 2-menthene 36 (4%), 3-menthene 37 (9%), (–)-menthol (8%), neomenthyl tosylate 72 (6%) and (–)-menthylxytriphenylphosphonium triflate 35 (73%). Thus, the use of a tosic acid nucleophile did not appear to increase the rate of the reaction nor give exclusively SN2 products. Clearly, the use of the reagent 27 with hindered secondary alcohols such as (–)-menthol leads predominately to elimination, regardless of the nucleophilic species present.
It is interesting to note from a mechanistic point of view, that the elimination products of 2- and 3-menthene 36 and 37, were always formed in a ratio of 1 : 2 respectively. Thus, the elimination mechanism cannot be anti (E2), as this would imply formation of 2-menthene 36 exclusively. *Cis* elimination has been suggested by Hendrickson and Schwartzman, who found that the Hendrickson reagent 27 reacts with (−)-menthol in the presence of potassium carbonate to give a mixture of menthens 36 and 37. An E1 mechanism would be consistent with the formation of both menthens 36 and 37, however with strong nucleophiles such as thioacetate and azide present, this pathway seems less feasible as intermediate carbocations could be competitively trapped, generating a mixture of products displaying inversion and retention, which were not observed. Interestingly, a similar ratio of 2- and 3-menthene 36 and 37 was formed by thermolysis of menthyldiphenylphosphate 73. Hence by analogy, a *cis* elimination mechanism has been suggested for the formation of 2- and 3-menthene 36 and 37 (Scheme 34).

\[
\begin{align*}
\text{Hendrickson reagent 27} & \quad -\text{CF}_3\text{SO}_2\text{OH} \\
\text{2CF}_3\text{SO}_2\text{O}^- & \quad \text{Ph}_3\text{PO}^- \\
\text{74} & \quad \text{Ph}_3\text{PO} \\
\text{37} & \quad (+ 2\text{-menthene 36}) \\
\text{73} & \quad \text{X} = \text{4-nitrobenzoate} \\
\text{68} & \quad \text{X} = \text{4-methoxybenzoate} \\
\text{70} & \quad \text{X} = \text{SC(O)CH}_3 \\
\text{71} & \quad \text{X} = \text{N}_3 \\
\text{35} & \quad \text{H} \quad \text{CF}_3\text{SO}_2\text{O}^- \\
\text{67} & \quad \text{(slow)} \\
\end{align*}
\]

**Scheme 34**

It is anticipated that reaction of (−)-menthol with the Hendrickson reagent 27 would result in the formation of a mixed phosphorane/phosphonium salt 74. This could then
undergo electrocyclic fragmentation to give the two products of elimination, 2- and 3-menthene 36 and 37. Alternatively, 74 could eliminate triphenylphosphine oxide to yield the standard Mitsunobu oxyphosphonium salt intermediate 35, which could undergo $S_N2$ displacement by a nucleophile $X^-$ to give the neomethyl products 67, 68, 70 and 71. As the products of elimination, 2- and 3-menthene 36 and 37, were the major products in most of the reactions between the Hendrickson reagent 27 and (−)-menthol, the substitution reaction is understood to be kinetically slow relative to elimination. Attempts to find evidence for the presence of the mixed phosphorane/phosphonium salt 74 proved unsuccessful. The mixing of (−)-menthol with 27 in an NMR tube at room temperature showed the immediate formation of the (−)-menthylxytriphenylphosphonium triflate 35 by both $^{31}P$ NMR ($\delta$ 59.5 ppm) and $^1H$ NMR spectroscopy ($\delta$ 4.25 ppm, dddd which collapsed to a ddd upon phosphorus decoupling) (Figure 4).

Figure 4. (−)-Menthylxytriphenylphosphonium triflate 35, formed by reaction of the Hendrickson reagent 27 with (−)-menthol in CD$_2$Cl$_2$. (a) $^1H$ NMR spectrum (400 MHz) of signal due to H1 in 35. (b) $^1H$/$^{31}P$ NMR spectrum (400 MHz) of signal due to H1 in 35.
The substitution of (–)-menthol for the less hindered secondary alcohol cyclohexanol also was examined. The Hendrickson reagent 27 was treated with cyclohexanol, 4-nitrobenzoic acid and diisopropylethylamine in DCM at 40°C for 24 hours. Analysis by GC/MS revealed the presence of cyclohexene 75 (66%), O-(4-nitrobenzoyl)-cyclohexanol 76 (28%) and cyclohexanol (6%) (Scheme 35). The use of 4-methoxyphenol as a nucleophile in the place of 4-nitrobenzoic acid did not improve the ratio of elimination to substitution. Addition of cyclohexanol, 4-methoxyphenol and diisopropylethylamine to 27, following by stirring at room temperature overnight, gave cyclohexene 75 (52%), 4-methoxyphenol (40%) and cyclohexanol (8%). The noticeable difference in the amounts of 4-methoxyphenol and cyclohexanol obtained by GC/MS was clarified following analysis by ¹H NMR spectroscopy. The presence of cyclohexyloxytriphenylphosphonium triflate 77 was detected as evidenced by both the ³¹P NMR (δ 59.7 ppm) and ¹H NMR (δ 4.5 – 4.6 ppm, H1) spectra. Thus, the difference in reactivity between primary and secondary alcohols for the Hendrickson reagent 27 mediated esterifications is clearly dependant on steric factors, with the greater extent of steric congestion resulting in competing elimination. Based on NMR evidence, the reaction between the Hendrickson reagent 27 and (–)-menthol generates an oxyphosphonium salt intermediate 35. Although the same intermediate is formed under Mitsunobu conditions, high yields of inverted esters have been reported⁴⁴,²²² and elimination has not been previously observed in the Mitsunobu reaction of (–)-menthol with 4-nitrobenzoic acid. It was initially puzzling why the outcome was different in both the Mitsunobu and Hendrickson reactions, yet both reactions proceeded through the same (–)-menthoxytriphenylphosphonium salt intermediate.
Scheme 35

The main difference between the two reactions is the presence of salts (diisopropylethylammonium triflate) in reactions involving the Hendrickson reagent 27. The rate of the Mitsunobu esterification has been reported to be markedly dependant on solvent polarity. For example, the rate of formation of ethyl benzoate at 0°C is approximately 100 times slower in acetonitrile than in THF. It was hypothesised that reactions involving the Hendrickson reagent 27 would possess a more polar reaction environment which was favouring elimination over substitution.

3.0 Removal of the triflate salts from reactions using the Hendrickson reagent 27

In an attempt to remove the triflate salts from reactions involving the Hendrickson reagent 27, which may then tip the balance in favour of substitution over elimination, various alternatives to diisopropylethylamine were considered. These alternatives were initially trialled during the formation of 4-nitrobenzyl 4-nitrobenzoate 61 with the Hendrickson reagent 27 and the results are displayed in Table 3. It was anticipated that by replacing diisopropylethylamine with sodium hydride, the by-products in the reaction would be hydrogen gas and sodium triflate. The sodium triflate should only have limited solubility in the organic phase and thus decrease the polarity of the reaction environment in solution. Treatment of a DCM solution of the Hendrickson reagent 27 with 4-nitrobenzyl alcohol, 4-nitrobenzoic acid and sodium hydride (2.2 equiv.) formed
a cloudy white solution. A small quantity of DMSO was added in an effort to partially solubilise the sodium hydride. After stirring for 48 hours at room temperature, analysis by $^1$H NMR spectroscopy following work-up, revealed only 6% conversion to the desired ester 61. The reaction was repeated using four equivalents of sodium hydride in a mixture of DCM/THF (1 : 3). An improvement in the yield of 61 to 23% was obtained after stirring at room temperature for 48 hours. The use of a large excess of potassium fluoride in DCM/THF or potassium carbonate in DCM for 24 hours at room temperature gave none of the desired ester 61. However, an 80% conversion to 4-nitrobenzyl 4-nitrobenzoate 61 was obtained when polymer-supported diisopropylethylamine was employed as the base. It was predicted that the use of a polymer-supported base would sequester the triflate salts from the reaction taking place in solution.

**Table 3.** Base alternatives in the formation of 4-nitrobenzyl 4-nitrobenzoate 61 with the Hendrickson reagent 27.

<table>
<thead>
<tr>
<th>Entry$^{a,b}$</th>
<th>Base</th>
<th>Equivalents</th>
<th>Solvent</th>
<th>Conversion (%)$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sodium hydride</td>
<td>2.2</td>
<td>DCM/DMSO (10:1)</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>Sodium hydride</td>
<td>4.0</td>
<td>DCM/THF (1:3)</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>Potassium fluoride</td>
<td>8.0</td>
<td>DCM/THF (1:1)</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Potassium carbonate</td>
<td>4.5</td>
<td>DCM</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>PS-diisopropylethylamine</td>
<td>2.0</td>
<td>DCM</td>
<td>80</td>
</tr>
</tbody>
</table>

$^a$All reactions were carried out with Hendrickson reagent 27 (1.0 equiv.), 4-nitrobenzyl alcohol (1.0 equiv.) and 4-nitrobenzoic acid (1.0 equiv.). $^b$Reaction conditions were room temperature for 48 hours (entries 1 and 2); room temperature for 24 hours (entries 3-5). $^c$Conversion ratio of 4-nitrobenzyl alcohol to 4-nitrobenzyl 4-nitrobenzoate 61 determined by $^1$H NMR integration.

Hence, the reaction between the Hendrickson reagent 27, (−)-menthol and 4-nitrobenzoic acid was repeated using polymer-supported diisopropylethylamine. After heating at 40°C overnight, analysis by GC/MS revealed complete conversion to 2- and
3-methene 36 and 37. Analysis by $^1$H NMR spectroscopy however, showed the presence of (−)-menthloxytriphenylphosphonium triflate 35 (45%) in addition to 2- and 3-methene 36 and 37 (55%, ratio 1 : 2) (Scheme 36). Although the reaction was significantly slower than the analogous reaction employing the non-polymeric base, it disappointingly still gave the menthene elimination products 36 and 37 rather than the desired inverted ester 67.

$$\begin{array}{c}
\begin{array}{c}
\text{Ph}_3\text{P}^+\text{O}^--\text{PPh}_3^-
\end{array}
\quad + \\
\text{2CF}_3\text{SO}_2\text{O}^-
\end{array}$$

DCM, 24 hr, 40°C

\[ \text{OH} \]

\[ \text{Ph}_3\text{PO} \]

\[ \text{PPh}_3 \]

\[ \text{2CF}_3\text{SO}_2\text{O}^- \]

\[ \text{4-NO}_2\text{-C}_6\text{H}_4\text{-COOH} \]

\[ \text{35} \]

45%

\[ \text{36} \]

\[ \text{37} \]

\[ \text{1} : \text{2} \]

55%

Scheme 36

The attempts to remove the triflate salts from reactions involving the Hendrickson reagent 27 were ineffective. The hypothesis that reactions involving the Hendrickson reagent 27 would possess a more polar reaction environment which is favouring elimination over substitution, was investigated further by examining the Mitsunobu esterification of (−)-menthol with 4-nitrobenzoic acid in the presence of diisopropylethylammonium triflate.

4.0 Addition of diisopropylethylammonium and tetrabutylammonium triflates to the standard Mitsunobu reaction

Prior to the addition of diisopropylethylammonium triflate to the standard Mitsunobu esterification of (−)-menthol, several control esterification reactions were carried out in the absence of added salt. The standard Mitsunobu reaction detailed in Organic Syntheses by Dodge$^{222}$ was repeated. DIAD was added to a cooled THF solution containing triphenylphosphine, (−)-menthol and 4-nitrobenzoic acid and the resulting solution stirred at room temperature for 24 hours. Analysis of the mixture by GC/MS
showed the formation of neomethyl 4-nitrobenzoate \(67\) (88%) and 2-menthene \(36\) (12%). Following work-up and chromatography, the ester \(67\) was isolated in 82% yield (Lit.\(^{222}\) yield, 85%). Although alkene formation has previously been observed in the Mitsunobu reaction during the total synthesis of doliculide\(^{227}\) and with sterically hindered alcohols such as homopropargylic alcohol \(78^{,228}\) cyanoalcohol \(79^{,229}\) and lactone \(80^{,230}\), the formation of 2-menthene \(36\) from \((-\)\)-menthol under Mitsunobu conditions has not been reported, and surprisingly, was not reported in the procedure detailed in Organic Syntheses.\(^{222}\) As it is quite volatile, it is presumably lost during normal reaction work-up and solvent evaporation.

The reaction was then repeated in DCM as this is the preferred solvent for reactions employing the Hendrickson reagent.\(^{88}\) The reaction was carried out in an NMR tube so it could be monitored by both NMR spectroscopy and GC/MS. After standing a solution of CD\(_2\)Cl\(_2\) containing \((-\)\)-menthol, 4-nitrobenzoic acid, triphenylphosphine and DIAD at room temperature for 24 hours, the \(^{31}\)P NMR spectrum showed two main signals (ratio ~ 9 : 1) corresponding\(^{40}\) to triphenylphosphine oxide (\(\delta\) 29.1 ppm) and the oxyphosphonium salt \(81\) (\(\delta\) 59.5 ppm). Analysis by GC/MS indicated the presence of neomethyl 4-nitrobenzoate \(67\) (76%) along with small amounts of \((-\)\)-menthol (10%) and 2-menthene \(36\) (14%) (Scheme 37).
The reaction was repeated in the presence of one equivalent of diisopropylethylammonium triflate, which was prepared from triflic acid and diisopropylethylamine. Analysis by $^{31}$P NMR spectroscopy showed slow formation of the oxyphosphonium salt 81 ($\delta$ 59.5 ppm) from the protonated betaine 82 ($\delta$ 52.6 ppm)\(^{40}\) (Scheme 38). After 24 hours at room temperature, the ratio of 81 : 82 was approximately 4 : 1 (Figure 5).

![Scheme 38](image)

**Figure 5.** Mitsunobu reaction (PPh$_3$, DIAD, (–)-menthol and 4-nitrobenzoic acid in CD$_2$Cl$_2$) in the presence of diisopropylethylammonium triflate (1.0 equiv.). (a) $^{31}$P NMR spectrum (162 MHz) at 25°C following DIAD addition. (b) $^{31}$P NMR spectrum (162 MHz) at 25°C after standing at room temperature for 24 hours.
As there was very little increase (<5%) in the triphenylphosphine oxide peak over this
 time, the presence of the diisopropylethylammonium triflate was effectively blocking
 the Mitsunobu reaction. The diisopropylethylammonium triflate was presumably
 protonating the betaine 83, leaving no base to form alkoxide ion, which has been
 shown by Hughes35 to be required for oxyphosphonium salt 81 formation. This was
 confirmed by performing the reaction in the presence of an extra two equivalents of
diisopropylethylamine, which resulted in an increase in the proportion of
 oxyphosphonium salt 81 (ratio 81 : 82 = 7 : 8) (Figure 6).

Figure 6. Mitsunobu reaction (PPh3, DIAD, (−)-menthol and 4-nitrobenzoic acid in
 CD2Cl2) in the presence of diisopropylethylammonium triflate and
diisopropylethylamine (2 equiv.). (a) 31P NMR spectrum (162 MHz) at 25°C following
 DIAD addition. (b) 31P NMR spectrum (162 MHz) at 25°C after standing at room
temperature for 24 hours.
The SN2 step of the Mitsunobu reaction is known\textsuperscript{35} to be slowed by the presence of proton sources, which can hydrogen bond with the carboxylate anion. Thus, in the presence of diisopropylethylamine, it is not surprising that the reaction does not progress beyond the oxyphosphonium intermediate stage. In order to avoid the complications brought about by the effects of protonation and hydrogen bonding, the diisopropylethylammonium triflate was substituted with tetrabutylammonium triflate (n-Bu\textsubscript{4}N OTf).

A solution of triphenylphosphine, (–)-menthol and 4-nitrobenzoic acid was prepared in dry CD\textsubscript{2}Cl\textsubscript{2} in an NMR tube and one equivalent of n-Bu\textsubscript{4}N OTf in CD\textsubscript{2}Cl\textsubscript{2} was added, followed by the slow addition of DIAD to the tube cooled on ice. Initially, the \textsuperscript{31}P NMR spectrum showed the immediate formation of both the oxyphosphonium salt \textsuperscript{81} (δ 59.5 ppm) and betaine \textsuperscript{83} (δ 44.2 ppm\textsuperscript{36}), in the presence of triphenylphosphine oxide (ratio ~ 1 : 3 : 1). After standing for 24 hours at room temperature, the ratio of oxyphosphonium salt \textsuperscript{81} to protonated betaine \textsuperscript{82} to triphenylphosphine oxide changed to approximately 1 : 1 : 5, indicating that the major product observed by \textsuperscript{31}P NMR spectroscopy was the triphenylphosphine oxide (Figure 7), presumably due to competing acylation of the hydrazine.\textsuperscript{36,224} Also, a sample of the reaction mixture was analysed by GC/MS, which revealed that the normal Mitsunobu esterification reaction was dramatically slowed (4% yield of ester \textsuperscript{67}, 18% yield of 2-menthene \textsuperscript{36}, 78% recovered (–)-menthol) and that elimination had become the major reaction pathway. The combined data from \textsuperscript{31}P NMR spectroscopy and GC/MS suggests that the betaine \textsuperscript{83} is formed but the oxyphosphonium salt \textsuperscript{81} is only slowly generated in the presence of one equivalent of n-Bu\textsubscript{4}N OTf and undergoes slow elimination to give 2-menthene \textsuperscript{36} and a minor amount of SN\textsubscript{2} displacement to form ester \textsuperscript{67}. 
The much faster rate of reaction of (–)-menthol with the Hendrickson reagent 27 is not surprising as the phosphonium centre in 27 would be expected to be more electrophilic than the phosphonium centre in the betaine 81 or protonated betaine 83, and triphenylphosphine oxide is a much better leaving group than the hydrazide anion. These results contrast with previous work,\textsuperscript{39} where it was reported that the addition of sodium benzoate dramatically accelerated the formation of trifluoroacetate esters. A catalytic amount of dissolved benzoate can, however, act as a base and increase the rate of the alcohol activation step.\textsuperscript{35} This is not possible with $n$-Bu$_4$NOTf as it is not basic.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure7.png}
\caption{Mitsunobu reaction (PPh$_3$, DIAD, (–)-menthol and 4-nitrobenzoic acid in CD$_2$Cl$_2$) in the presence of $n$-Bu$_4$NOTf (1.0 equiv.). (a) $^{31}$P NMR spectrum (162 MHz) at 25°C following DIAD addition. (b) $^{31}$P NMR spectrum (162 MHz) at 25°C after standing at room temperature for 24 hours.}
\end{figure}
The Mitsunobu esterification of (–)-menthol was studied at a range of concentrations of 
\( n\text{-Bu}_4\text{NOTf} \) and the results showing the effect on the outcome of the Mitsunobu reaction 
are shown in Figure 8. Table 4 displays the ratio of elimination to substitution as the 
number of equivalents of \( n\text{-Bu}_4\text{NOTf} \) is increased. Intriguingly, the reaction is sensitive 
to even trace amounts of \( n\text{-Bu}_4\text{NOTf} \) salt. A change in the elimination to substitution 
ratio from 0.2 to 1.4 was observed in going from no salt to just 0.01 molar equivalents 
(0.036 mmol salt, 3.6 mmol triphenylphosphine/DIAD). At higher quantities of salt, the 
ratio of elimination to substitution rose gradually to reach 10.4 at 2.0 molar equivalents 
of \( n\text{-Bu}_4\text{NOTf} \). However, at this level of salt, greater than 80% of the (–)-menthol was 
recovered unreacted after 24 hours at room temperature.

![Figure 8](image)

**Figure 8.** The effect of added \( n\text{-Bu}_4\text{NOTf} \) on the outcome of the Mitsunobu reaction 
between (–)-menthol and 4-nitrobenzoic acid. Menthenes 36 and 37 (□), (–)-menthol 
(●), neomenthyl 4-nitrobenzoate 67 (○). Conditions: PPh$_3$ (1.0 equiv.), DIAD (1.0 
equiv.), (–)-menthol (0.85 equiv.), 4-nitrobenzoic acid (0.85 equiv.), \( n\text{-Bu}_4\text{NOTf} \) 
(Figure 8(a) 0.0-2.0 equiv.; Figure 8(b) 0.0-0.2 equiv.) and DCM (8 mL); 24 hours at 
room temperature.
When both the E2 and S\textsubscript{N}2 processes are sufficiently slow, side reactions such as acylation of the hydrazine can become competitive,\textsuperscript{36,224} such that most of the (–)-menthol is recovered at the end of the reaction.

**Table 4.** The effect of added \textit{n}-Bu\textsubscript{4}NOTf on the outcome of the Mitsunobu reaction between (–)-menthol and 4-nitrobenzoic acid.

<table>
<thead>
<tr>
<th>Entry\textsuperscript{a}</th>
<th>\textit{n}-Bu\textsubscript{4}NOTf (equiv.)</th>
<th>GC analysis (%)</th>
<th>Elimination/Substitution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>\textit{\textit{n}}-Menthol</td>
<td>Menthenes \textsuperscript{36+37}</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>9.7</td>
<td>14.3</td>
</tr>
<tr>
<td>2</td>
<td>0.01</td>
<td>10.2</td>
<td>51.9</td>
</tr>
<tr>
<td>3</td>
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<td>15.3</td>
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<tr>
<td>4</td>
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<tr>
<td>5</td>
<td>0.1</td>
<td>49.2</td>
<td>31.1</td>
</tr>
<tr>
<td>6</td>
<td>0.2</td>
<td>57.7</td>
<td>26.8</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>77.9</td>
<td>18.5</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>81.8</td>
<td>16.6</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction conditions: PPh\textsubscript{3} (1.0 equiv.), DIAD (1.0 equiv.), (–)-menthol (0.85 equiv.), 4-nitrobenzoic acid (0.85 equiv.), \textit{n}-Bu\textsubscript{4}NOTf (0.01-2.0 equiv.) and DCM (8 mL); room temperature for 24 hours.

It is clear from these results that the addition of salts to the Mitsunobu reaction had a profound effect on both its rate and outcome. Elimination, rather than S\textsubscript{N}2 substitution, became the major reaction pathway after addition of just traces of \textit{n}-Bu\textsubscript{4}NOTf. Previous work\textsuperscript{35} has shown that the S\textsubscript{N}2 substitution rate is decreased ten-fold by addition of a large amount of a salt (0.5 M Bu\textsubscript{4}NBF\textsubscript{4}). In addition, the rate of the Mitsunobu esterification reaction has been reported to be much slower in polar solvents.\textsuperscript{41} Both of these effects can be understood in terms of a late transition state (TS) for the S\textsubscript{N}2 substitution reaction, where the reactants are oppositely charged and the products are neutral (Scheme 39). A non-polar reaction environment would favour the formation of
such as TS in accordance with the Hughes-Ingold rules.\textsuperscript{231} By the Hammond Postulate\textsuperscript{232} the TS would resemble the products.

![Scheme 39](image)

Increasing the concentration of $n$-Bu$_4$NOTf causes a decrease in both the rate of formation of ester 67 ($S_N2$ product) and in the rate of formation of 2-menthene 36 (E2 product), but the effect on the $S_N2$ process is much greater. This suggests that the TS for the E2 process 84 is earlier (less product like) than for the corresponding $S_N2$ process 85. Steric factors would be more important with a late TS, so it is conceivable that small changes in the reaction environment might tip the balance in favour of the elimination pathway in the case of (−)-menthol, where the $S_N2$ transition state 85 is quite crowded. Although the trends observed can be explained in terms of a later TS for the $S_N2$ process than the E2 process, it is still difficult to rationalise how traces of $n$-Bu$_4$NOTf can cause such a remarkable turnaround in reaction pathway from substitution to elimination.

One possible explanation is that the mechanism of the Mitsunobu esterification reaction involves the formation of ion pair aggregates.\textsuperscript{39,219,233-237} To form the $S_N2$ TS 85 required for back-side attack in the normal $S_N2$ process, the alkoxyphosphonium and
carboxylate ions must be separated. Such charge separation can be avoided by ion pair clustering wherein a positive phosphorus ion in one ion pair is in part electrically neutralised by the negative carboxylate moiety in another ion pair (Scheme 40).\textsuperscript{235} Traces of salts (or polar solvents) could certainly hinder the formation of such ion pair clusters, thereby preventing the S\textsubscript{N}2 process. As any Lewis base present in the reaction medium could bring about the corresponding E2 process\textsuperscript{84}, not just the carboxylate ion shown, the E2 elimination process does not require ion pair clustering.

![Scheme 40](image)

Another intriguing difference between the Mitsunobu and Hendrickson induced elimination reactions with (–)-menthol is that the Mitsunobu reaction resulted in stereospecific \textit{anti} elimination to give only 2-menthene 36, whereas the Hendrickson reagent 27 resulted in the formation of both 2- and 3-menthene 36 and 37 in a ratio of 1:2 (Figure 9). To confirm the formation of both menthenes 36 and 37 and not simply the isomerisation of 2-menthene 36 to 3-menthene 37 under Hendrickson conditions, a sample of 2-menthene 36 (prepared by stirring a THF solution of triphenylphosphine, DIAD and (–)-menthol overnight at room temperature) was treated with triflic acid and diisopropylethylamine and stirred at room temperature overnight. Analysis of the mixture by \textsuperscript{1}H NMR spectroscopy revealed only 5% conversion of the 2-menthene 36 to 3-menthene 37.
Figure 9. $^1$H NMR spectra (400 MHz) of menthene 36 and 37 formed by (a) thermolysis of menthol diphenylphosphate ester$^{20}$; (b) Mitsunobu reagents (Organic Syntheses conditions)$^{16}$; (c) Hendrickson reagent 27 (Table 2, entry 3) and (d) Hendrickson reagent 27 (Table 2, entry 8).
It is difficult to understand such a difference in elimination products as both the Mitsunobu and Hendrickson reactions take place via a common oxyphosphonium salt. However, *cis* elimination is feasible if the Hendrickson reagent 27 results in the initial formation of the mixed phosphorane/phosphonium salt intermediate 74. Attempts to convert the Mitsunobu intermediate 35 into an intermediate analogous to 74, by performing a Mitsunobu reaction in the presence of a five-fold excess of triphenylphosphine oxide relative to triphenylphosphine, DIAD and (−)-menthol (no 4-nitrobenzoic acid was added in this experiment) still only gave 2-menthene 36.

5.0 Investigation of the influence of the menthyl leaving group on the reaction outcome – elimination versus substitution

In the reaction between the Hendrickson reagent 27, (−)-menthol, a nucleophile and base, elimination was the predominant pathway. It has been postulated that this observation may be independent of the leaving group employed. In the case of the Hendrickson reagent 27, the oxyphosphonium triflate intermediate 35 forms triphenylphosphine oxide as the leaving group when attacked by a nucleophile. The potential influence of the choice of leaving group was investigated in the reactions between (−)-menthyl triflate 86 and (−)-menthyl tosylate 87 with 4-nitrobenzoic acid and diisopropylethylamine respectively.

Consecutive addition of triflic anhydride and diisopropylethylamine to a solution of (−)-menthol and 4-nitrobenzoic acid in DCM formed, after stirring at room temperature overnight, 2- and 3-menthene 36 and 37 (91%, 1 : 2 ratio by $^1$H NMR spectroscopy), $O$-
(4-nitrobenzoyl)-(–)-menthol 69 and neomenthyl 4-nitrobenzoate 67 (9%, ratio 1 : 3 by
$^1$H NMR spectroscopy) as determined by GC/MS analysis (Scheme 41). Compared to the analogous reaction employing 27, the use of a triflate leaving group gave a significantly faster reaction, however the stereoselectivity was poor, presumably due to the reduced bulk of the leaving group. Furthermore, the triflate leaving group did not change the outcome of the reaction, with the major products formed being the products of elimination.

\[
\begin{align*}
\text{OH} & \quad \text{O}_2\text{N} \\
\text{CF}_3\text{SO}_2\text{O} & \quad \text{Pr}_2\text{NEt}, \text{DCM} \\
\text{RT, O/N} & \quad \text{O}_2\text{N} \quad \text{O} \\
\text{Scheme 41} & \quad \text{O}_2\text{N} \quad \text{OH}
\end{align*}
\]

(–)-Menthyl tosylate 87 was prepared from the reaction of (–)-menthol with tosyl chloride in pyridine. A solution of (–)-menthyl tosylate 87 and 4-nitrobenzoic acid in DCM was then treated with diisopropylethylamine and left to stir overnight at room temperature. Analysis by both GC/MS and $^1$H NMR revealed unreacted (–)-menthyl tosylate 87. This result was not surprising as tosylates are about five hundred times less reactive than triflates.\(^{238}\) The reaction was repeated at reflux overnight in DCM, however analysis by both GC/MS and $^1$H NMR spectroscopy still showed unreacted (–)-menthyl tosylate 87. A final attempt at the reaction was made using the sodium salt of 4-nitrobenzoic acid, which is a more reactive nucleophile than the acid alone. (–)-Menthyl tosylate 87 was added to a slurry of 4-nitrobenzoic acid sodium salt (generated from 4-nitrobenzoic acid and sodium hydride) in DCM. After stirring at room temperature overnight, analysis by GC/MS revealed the formation of 2- and 3-menthene 36 and 37 (5%) and (–)-menthyl tosylate 87 (95%). Analysis by $^1$H NMR spectroscopy
showed unreacted (–)-menthyl tosylate 87. Due to the poor leaving ability of the
tosylate group, no substantial reaction between (–)-menthyl tosylate 87 and 4-
nitrobenzoic acid occurred. However, the oxyphosphonium triflate 35 and (–)-menthyl
triflate intermediates 86 or 87 both gave 2- and 3-menthene 36 and 37 as major reaction
products. Based on these preliminary results, it can be proposed that the leaving group
on (–)-menthol does not effect the reaction pathway (i.e. elimination or substitution)
between (–)-menthol and a nucleophile.

6.0 Esterification of secondary alcohols with retention using the Hendrickson
reagent 27 and an activating agent

The Hendrickson reagent 27 primarily gives elimination rather than S\textsubscript{N}2 products when
reacted with secondary alcohols, such as (–)-menthol or cyclohexanol, and a
nucleophile in the presence of base. The substitution of secondary alcohols may,
however, be possible in the presence of an activating agent. In order to avoid
competing elimination, the order of addition was altered and DMAP was employed as
an activating agent. Addition of 4-nitrobenzoic acid to a solution of the Hendrickson
reagent 27 in DCM presumably formed the corresponding acyloxyphosphonium salt 88.
Subsequent treatment of 88 with DMAP gave the active ester 89, which underwent
nucleophilic displacement after the addition of cyclohexanol and diisopropylethylamine.
O-(4-Nitrobenzoyl)-cyclohexanol 76 was obtained after stirring at room temperature for
15 minutes in 96% yield, following chromatography to remove the phosphine oxide.
In a similar fashion, treatment of the acyloxyphosphonium salt 88 with (−)-menthol and diisopropylethylamine formed O-(4-nitrobenzoyl)-(−)-menthol 69 in good yield (92%) after stirring in DCM for 15 minutes (Scheme 42). A significantly faster reaction was observed when a slight excess (1.2 equiv.) of both 4-nitrobenzoic acid and DMAP were employed. With 1.0 equivalents of both 4-nitrobenzoic acid and DMAP, 38% unreacted (−)-menthol, relative to O-(4-nitrobenzoyl)-(−)-menthol 69 by $^1$H NMR, remained after stirring at room temperature overnight. It should be noted that retention of configuration was observed when (−)-menthol was used as a nucleophile (the $^1$H NMR shift of H1 of O-(4-nitrobenzoyl)-(−)-menthol 69 at δ 4.98 ppm was in agreement with the literature). Importantly, very little (<5%) or no elimination was observed by GC/MS or $^1$H NMR spectroscopy in the reactions involving both cyclohexanol and (−)-menthol. The change in order of addition and use of DMAP ensured that formation of the mixed phosphorane/phosphonium salt of the alcohol 74, an intermediate required for elimination, did not occur.

![Scheme 42](image)

### 7.0 General conclusions

The Hendrickson reagent 27 has been shown to be a useful method for the esterification of primary alcohols, the synthesis of primary azides and the formation of ethers from phenols. Evidence from $^{31}$P NMR spectroscopy suggests that when reacted with (−)-menthol, the Hendrickson and Mitsunobu reagents generate the same menthylxylophosphonium salt intermediate. Under Mitsunobu conditions, the major reaction pathway is inverted ester formation with a minor amount of competing
elimination. When the Hendrickson reagent 27 is used for the esterification of (−)-menthol, however, the major reaction pathway is syn elimination, giving a mixture of 2- and 3-menhene 36 and 37, in a ratio of 1 : 2, respectively. An increase in the ratio of \( \text{S}_{\text{N}}2 \) product to elimination product can be achieved by use of the Hendrickson reagent 27 in a non-polar solvent such as toluene.

The difference in reaction outcome between the Hendrickson and Mitsunobu reagents appears to be a consequence of the more ionic conditions generated by the Hendrickson reagent 27. Addition of salts to the standard Mitsunobu reaction resulted in elimination becoming the dominant pathway. Attempts to remove the salts from reactions involving the Hendrickson reagent 27 by employing alternative bases were not successful. Elimination was still a dominant pathway when polymer-supported diisopropylethylamine was used. A change in the order of addition of reactants and the use of an activating agent allowed elimination to be avoided and gave esters from secondary alcohols with retention in high yield. Thus, as a general rule, the Hendrickson reagent 27 can only be used as an alternative to the Mitsunobu reagents for the replacement of a primary hydroxyl group by various nucleophiles and the substitution of secondary alcohols with retention of configuration. The ionic nature of 27 also brings about reactions with some nucleophiles (such as sodium azide) where the Mitsunobu reaction fails.

Concurrent to the work presented in this chapter was the investigation of novel cyclic analogues 90-92 of the Hendrickson reagent 27. Their synthesis and use are described in the next chapter.
CHAPTER TWO

CYCLIC ANALOGUES OF THE HENDRICKSON REAGENT
Although the reaction of the Hendrickson reagent 27 with secondary alcohols such as (−)-menthol was revealed in Chapter One to result primarily in dehydration rather than the expected SN2 displacement, the reagent 27 was shown to be useful for simple condensations such as the conversion of primary alcohols to esters, azides and ethers. Concurrent to the work in the previous chapter, the synthesis of the novel polymer-supported analogue 56 of the Hendrickson reagent 27 was examined. Prior to polymer attachment, the synthesis, characterisation and use of novel solution-phase cyclic analogues 90-92 of the Hendrickson reagent 27 was carried out and is detailed in this chapter.

1.0 Synthesis and characterisation of five-, six- and seven-membered cyclic analogues 90-92

It was anticipated that the cyclic analogues 90-92 could be prepared by addition of triflic anhydride to the corresponding bis-phosphine oxide 93-95 in DCM. As the desired bis-phosphine oxides 93-95 were not commercially available, they were obtained by oxidation of the corresponding bis-phosphines.

\[
\text{Ph}_2\text{P} = \text{O} = \text{Ph}_2\quad 2\text{CF}_3\text{SO}_2\text{O}^-
\]

1.1 Synthesis of bis-phosphine oxides 93-95 by oxidation of bis-phosphines

Phosphines possess a great reactivity towards practically every sort of oxidising agent. Hydrogen peroxide and peroxide derivatives are, however, commonly employed for oxidation. Treatment of 1,2-bis(diphenylphosphino)ethane with an excess of hydrogen peroxide in DCM gave the desired 1,2-bis(diphenylphosphinyl)ethane 93 in five minutes. Following work-up and recrystallisation, the identification and purity of 93
was verified by $^{31}$P NMR spectroscopy ($\delta$ 33.0 ppm) and by comparison of the melting point with the literature value. 1,3-Bis(diphenylphosphino)propane 94 ($\delta$ 32.8 ppm) and 1,4-bis(diphenylphosphino)butane 95 ($\delta$ 34.1 ppm) were obtained in a similar fashion by oxidation of 1,3-bis(diphenylphosphinyl)propane and 1,4-bis(diphenylphosphinyl)butane with hydrogen peroxide in DCM respectively (Scheme 43).

A mechanism for the oxidation of 1,2-bis(diphenylphosphino)ethane with hydrogen peroxide is suggested in Scheme 44.\textsuperscript{239} The phosphorus attacks the O-O bond, which is broken to yield a protonated mono-phosphine oxide species 96 and a hydroxide ion. Removal of a proton from 96 by the hydroxide ion gives the mono-oxidised species 97 and water. Oxidation of the other phosphorus atom occurs in an analogous manner to give 1,2-bis(diphenylphosphinyl)ethane 93. With the bis-oxides in hand, the cyclic analogues 90-92 could now be prepared.
1.2 $^{31}$P NMR spectroscopy study of the formation of the five-membered cyclic analogue 90 and its subsequent reaction with alcohols

The mechanism of formation of the five-membered cyclic analogue 90 and its subsequent reaction with alcohols was initially investigated by $^{31}$P NMR spectroscopy. Addition of one equivalent of triflic anhydride to an ice-cooled NMR tube containing 1,2-bis(diphenylphosphinyl)ethane 93 and CD$_2$Cl$_2$ showed immediate formation of a broad singlet at $\delta$ 60 ppm following analysis by $^{31}$P NMR spectroscopy at room temperature. As the reaction was clearly too fast to observe intermediates at room temperature, it was repeated by addition of triflic anhydride portion-wise to the bis-oxide 93 at -80°C (Figure 10).

Addition of 0.2 equivalents of triflic anhydride to the solution of 1,2-bis(diphenylphosphinyl)ethane 93 in CD$_2$Cl$_2$ at -80°C generated a broad peak at $\delta$ 38 ppm in the $^{31}$P NMR spectrum, initially thought to correspond to the protonated phosphine oxide 96. Any trace of water in the sample would generate triflic acid, which would readily protonate the phosphine oxide 93 and form the protonated phosphine oxide 96 (Scheme 45). The peak at $\delta$ 38 ppm was attributable to an equilibrium peak from the two species 93 and 96. This assignment was confirmed when a drier sample (distillation of the triflic anhydride from P$_2$O$_5$ and drying of the phosphine oxide 93 with P$_2$O$_5$ under high vacuum on a Kugelrohr apparatus) was used. The small amount of water present was consumed at a lower equivalence of triflic anhydride and at 0.8 equivalents, two broad peaks at $\delta$ 52.1 ppm and $\delta$ 59.3 ppm were observed for 98 and 90 respectively (Figure 10). Further evidence was provided by the titration of triflic acid to a solution of 1,2-bis(diphenylphosphinyl)ethane 93 in CD$_2$Cl$_2$ at -70°C (a 10°C increase in temperature was used to make NMR shimming easier). As the amount of triflic acid was gradually increased from none to 1.0 equivalents, a shift in the oxide 93 peak from $\delta$ 33.4 ppm to $\delta$ 39.8 ppm was observed.
Scheme 45

The second intermediate at $\delta$ 51.7 ppm was formed in the presence of the protonated phosphine oxide 96 after addition of 0.4 equivalents of triflic anhydride at -80$^\circ$C (Figure 10). The intermediate at $\delta$ 51.7 ppm was thought to be the dimeric species 98 generated by coupling of two bis(diphenylphosphinyl)ethane 93 molecules. The broadening was possibly due to exchange processes and/or protonation. Intermolecular nucleophilic attack of the excess phosphine oxide on the triflated phosphine oxide molecule 99, which was too short-lived to be detect by $^{31}$P NMR spectroscopy, would generate this linear P-O-P species 98. Alternatively, the triflated phosphine oxide 99 could cyclise intramolecularly to afford the five-membered cyclic reagent 90, which could immediately be ring-opened in the presence of excess phosphine oxide to produce the linear P-O-P species 98.
Figure 10. $^{31}$P NMR stack spectra (162 MHz) showing the addition of triflic anhydride to a solution of 1,2-bis(diphenylphosphinyl)ethane 93 in CD$_2$Cl$_2$ at -80°C.
Addition of excess phosphine oxide 93 (0.5 equiv.) to a pre-formed sample of the five-membered cyclic reagent 90 generated a similar peak in the $^{31}$P NMR spectrum at $\delta$ 52.2 ppm, providing evidence for the existence of linear P-O-P species 98. As the addition of triflic anhydride continued, the phosphine oxide 93 was no longer in excess and the linear P-O-P species 98 was content to cyclise and generate the desired five-membered cyclic species 90 after standing at low temperature overnight.

In addition, the reaction between the five-membered cyclic analogue 90 and an alcohol was studied by $^{31}$P NMR spectroscopy at low temperature. The cyclic reagent 90 was pre-formed in an NMR tube in CD$_2$Cl$_2$ and $^{31}$P and $^1$H NMR spectra acquired at -80°C following the addition of 4-chlorophenol (0.5 equiv.). In addition to the cyclic P-O-P species 90 (singlet at $\delta$ 60.3 ppm) in the $^{31}$P NMR spectrum, two doublets also were present at $\delta$ 59.9 ppm and $\delta$ 76.8 ppm respectively (ratio 2 : 1 : 1) (Figure 11). These doublets represent the oxyphosphonium intermediate 100, as the phosphorus atoms are now non-equivalent and couple to each other. The experiment was repeated using the secondary alcohol cyclohexanol (0.5 equiv.) and the oxyphosphonium salt 101 obtained immediately, as evidenced by doublets at $\delta$ 60.7 ppm and $\delta$ 68.9 ppm in the $^{31}$P NMR spectrum.
Following the $^{31}$P NMR study, further characterisation of the cyclic analogues 90-92 was carried out. The cyclic phosphonium anhydrides 90-92 were easily prepared from the corresponding phosphine oxides 93-95 by treatment with triflic anhydride in DCM (Scheme 46). The P=O bond of the bis-phosphine oxide readily attacks triflic anhydride to generate the corresponding triflate intermediates 99, 102 and 103. This can then cyclise following attack on the positively charged phosphorus by the neighbouring phosphoryl oxygen, to give the cyclic phosphonium anhydrides 90-92. Each cyclic analogue 90-92 precipitated out of solution as a white solid immediately after mixing the corresponding oxide with triflic anhydride. The extreme sensitivity of these species 90-92 to moisture made characterisation difficult. In a standard reaction, the analogues 90-92 are formed \textit{in situ} and used immediately. Formation of each of the
analogues 90-92 in an NMR tube under an inert atmosphere allowed the analogues 90-92 to be characterised by $^1$H, $^{13}$C and $^{31}$P NMR spectroscopy.

Scheme 46

The reagents 90-92 were allowed to stand in a freezer at -18°C for 24 hours before collection of NMR spectra. It was found that the $^{31}$P NMR resonances were considerably sharper if the sample was allowed to stand for 24 hours before recording the spectrum (e.g. see Figure 10). This might possibly be due to the initial formation of some polymeric phosphonium anhydrides in equilibrium with the cyclic form. However, broad peaks were still observed in the $^1$H NMR spectra of the cyclic phosphonium anhydrides 90-92. Of note was the characteristic downfield shift in the methylene protons on formation of the cyclic analogues 90-92. The five-, six- and seven-membered cyclic analogues 90-92 all gave $^{31}$P NMR spectra with clean singlets, with resonances at $\delta$ 58.6 ppm, $\delta$ 85.7 ppm and $\delta$ 91.5 ppm respectively. The observed downfield shift in the $^{31}$P NMR spectra of the analogues 90-92 from their corresponding phosphine oxides 93-95 is consistent with the more positive (deshielded) nature of the phosphorus atom in the oxyphosphonium salts 90-92. The large difference in chemical shift observed between the five-membered analogue 90 and the six- and seven-membered analogues 91 and 92 can be possibly be explained by presuming that each analogue is in equilibrium with phosphoranes 104 and 105 (illustrated in Scheme 47 for analogue 90) and that the $^{31}$P NMR chemical shift
observed for each cyclic analogue 90-92 is a time averaged signal. As phosphoranes possessing a five-membered ring are well known to be more stable than the corresponding six or seven-membered ring phosphoranes,\textsuperscript{240-242} (see Chapter two, section 3.2), the equilibrium between 90, 104 and 105 would be shifted further towards the phosphorane structures than would be the case for 91 and 92, resulting in a chemical shift for 90 that is further upfield. ¹³C NMR spectra were recorded with selective phosphorus decoupling to simplify the second order spin systems which arose due to the presence of multiple phosphorus coupling pathways.

During the synthesis of the five-, six- and seven-membered cyclic analogues 90-92, the formation of the four-membered cyclic species 106 also was investigated briefly by ³¹P NMR spectroscopy. Oxidation of bis(diphenylphosphino)methane with hydrogen peroxide in DCM (see Chapter Two, section 1.1) gave the corresponding phosphate oxide, bis(diphenylphosphinyl)methane 107. Subsequent addition of 1.0 equivalent of triflic anhydride to a solution of the phosphate oxide 107 in CD₂Cl₂ gave a mixture of products following analysis by ³¹P NMR spectroscopy. In the ³¹P NMR spectrum, four broad singlets were observed at δ 48.8, 56.4, 61.1 and 71.2 ppm in a ratio of 41 : 9 : 25 : 25 respectively. Intriguingly, similar mixtures of products were obtained when the oxide 107 was treated with excess triflic anhydride. Addition of excess triflic anhydride should promote the formation of 106. With 1.2 equivalents of triflic anhydride, broad singlets were observed at δ 48.8, 61.0 and 71.1 ppm in the ³¹P NMR
spectrum in a ratio of 60 : 19 : 21. With 2.0 equivalents of triflic anhydride, broad singlets were observed at δ 48.8, 61.2 and 71.3 ppm in the $^{31}$P NMR spectrum in a ratio of 52 : 25 : 23. Such a complex mixture of products may arise from the triflated species 108 or 109, or by the ring closure of dimeric species such as 110 to give larger rings like 111. Indeed, the desired four membered cyclic species 106 may also be present. Attempts to form the ester 4-nitrobenzyl 4-nitrobenzoate 61 by addition of 4-nitrobenzyl alcohol, 4-nitrobenzoic acid and diisopropylethylamine to a solution containing the oxide 107 and 1.0 equivalent of triflic anhydride gave a complex mixture of products following immediate analysis by $^{31}$P NMR and $^1$H NMR spectroscopy. In the $^{31}$P NMR spectrum, peaks at δ 25.1, 39.7, 65.8 and 69.1 ppm were observed in a ratio of 30 : 33 : 1 : 36 respectively. The peak at δ 25.1 ppm is likely to be the phosphine oxide 107. Individual species could not be identified in the $^1$H NMR spectrum, however it was clear that there was little or no formation of ester 61. Although a range of structures could be proposed for the formation of a number of distinct species in the $^{31}$P NMR spectrum, formation of the four-membered cyclic analogue 106 is clearly more complicated than the analogous five-, six- and seven-membered species 90-92 and thus requires further investigation. As little or no ester was formed in the case of the putative four-membered cyclic analogue 106, this reaction was not further pursued.
During the formation of amides using the Hendrickson reagent 27, it was found that consecutive treatment of 27 with benzylamine, 4-nitrobenzoic acid and diisopropylethylamine (Hendrickson procedure), affored not the expected amide 112, but benzylaminotriphenylphosphonium trifluoromethanesulfonate 113 (Scheme 48). Hendrickson has previously described a rapid equilibrium between the intermediates Ph₃P⁺NR₂ and RCOOP⁺Ph₃. However in this case, this equilibrium appears to be dependant on the nucleophilicity of the carboxylate anion employed. Hendrickson’s acid of choice was 4-toluic acid, which is more nucleophilic than 4-nitrobenzoic acid. Thus, which intermediate forms first depends on the relative nucleophilicities and concentrations under the reaction conditions.

![Scheme 48](image)

The reaction protocol was therefore modified to ensure initial reaction of the carboxylate anion with 27. Stirring a 1:1 mixture of 27 and 4-nitrobenzoic acid for fifteen minutes in DCM gave the acyloxyphosphonium salt 88 as evidenced by 31P NMR spectroscopy (δ 65.3 ppm). Subsequent treatment with benzylamine and diisopropylethylamine for two hours at room temperature resulted in the formation of N-benzyl-4-nitrobenzamide 112 in 90% yield (Scheme 48). The finding that primary amines react with phosphonium anhydrides to yield air stable aminophosphonium salts such as 113 provided another method for further characterisation of the cyclic analogues 90-92. The reaction of 90-92 with benzylamine in the presence of diisopropylethylamine gave the corresponding aminophosphonium salts 114-116 after stirring at room temperature for two hours (Scheme 49).
Scheme 49

Analysis of the aminophosphonium salts 114-116 by $^1$H NMR spectroscopy showed a characteristic doublet of doublets at around $\delta$ 4.0 ppm for the benzyl protons, resulting from coupling to both the NH and P atoms. After selective phosphorus decoupling, the signal at $\delta$ 4.0 ppm collapsed to a doublet. The $^{31}$P NMR spectra showed two doublets at around $\delta$ 33 ppm and $\delta$ 45 ppm due to phosphorus coupling of the non-equivalent phosphorus atoms. As a result of the ionic nature of these species 114-116, excellent electrospray mass spectrometry signals were obtained showing the molecular weight of the respective cationic and anionic species of each compound 114-116. Analysis by FTIR gave medium strength absorbances in the region between 630-740 cm$^{-1}$ and at 1030 cm$^{-1}$, corresponding to vibrations of the P-N-C bonds. At 1250-1280 cm$^{-1}$, a strong absorbance was observed for the P=O bond. Good microanalytical data on these compounds 114-116 was difficult to obtain, possibly due to the ability of the phosphine oxide to strongly hydrogen bond with water. Attempts to remove the water either by drying over P$_2$O$_5$ under vacuum for extended periods or by azeotropic distillation with toluene were not successful. Analysis by high resolution mass spectrometry did, however, show the aminophosphonium cation of each species 114-116.

2.0 Use of the cyclic analogues 90-92 for ester and amide formation

The key advantage of the synthesised cyclic analogues 90-92 over the established Hendrickson reagent 27 lies in the ease of the removal of the phosphine oxide by-product. Bis-phosphine oxides are significantly more polar than mono-oxides and
hence, generally facilitate chromatographic separations. For example, in a solvent mix of diethyl ether/ethyl acetate (1:1), the Rf values for 1,2-bis(diphenylphosphinyl)ethane 93 and triphenylphosphine oxide were 0.05 and 0.46 respectively.

The use of the cyclic analogues 90-92 was examined for a range of simple dehydrations. The esterification of primary alcohols and generation of amides from primary amines were achieved using all three analogues 90-92 in good yield after chromatography (Table 5). For ester formation, treatment of a prepared solution of 90, 91 or 92 with 4-nitrobenzyl alcohol, 4-nitrobenzoic acid and diisopropylethylamine formed 4-nitrobenzyl 4-nitrobenzoate 61 after stirring at room temperature for 2 hours. Similarly, N-phenyl-4-toluamide 117 was obtained following addition of 4-toluic acid, aniline and diisopropylethylamine to 90, 91 or 92 in DCM (entries 4-6, Table 5) (Scheme 50). A small excess of the bis-phosphine oxide was employed in all cases as excess triflic anhydride could react with the alcohol, the amide or the carboxylic acid. It was also important to use only one equivalent of the cyclic reagent 90-92. The use of the Hendrickson reagent 27 in excess has previously been shown to lead to reduced yields (see Chapter One, section 1.1).
Table 5. Esters and amides formed using cyclic reagents 90-92.

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;ab&lt;/sup&gt;</th>
<th>Reagent</th>
<th>Acid</th>
<th>Alcohol/amine</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>90</td>
<td>4-NO₂-C₆H₄-COOH</td>
<td>4-NO₂-C₆H₄-CH₂-OH</td>
<td>4-Nitrobenzyl 4-nitrobenzoate 61</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>91</td>
<td>4-NO₂-C₆H₄-COOH</td>
<td>4-NO₂-C₆H₄-CH₂-OH</td>
<td>4-Nitrobenzyl 4-nitrobenzoate 61</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>92</td>
<td>4-NO₂-C₆H₄-COOH</td>
<td>4-NO₂-C₆H₄-CH₂-OH</td>
<td>4-Nitrobenzyl 4-nitrobenzoate 61</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>90</td>
<td>4-CH₃-C₆H₄-COOH</td>
<td>C₆H₅-NH₂</td>
<td>N-phenyl-4-toluamide 117</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>91</td>
<td>4-CH₃-C₆H₄-COOH</td>
<td>C₆H₅-NH₂</td>
<td>N-phenyl-4-toluamide 117</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>92</td>
<td>4-CH₃-C₆H₄-COOH</td>
<td>C₆H₅-NH₂</td>
<td>N-phenyl-4-toluamide 117</td>
<td>85</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reaction conditions: reagent (formed from Ph₂PO(CH₂)nPOPh₂, 1.2 equiv. and triflic anhydride, 1.0 equiv.), acid (1.0 equiv.), alcohol/amine (1.0 equiv.), diisopropylethylamine (2.2 equiv.), DCM (10mL).

<sup>b</sup>Reaction times were 2 hours at room temperature.

<sup>c</sup>Yields calculated following chromatography.

3.0 Kinetic studies

With the cyclic analogues 90-92 prepared and their use in simple condensation reactions demonstrated, their rates of reaction relative to the Hendrickson reagent 27 were examined to determine the optimal analogue for polymer attachment.

3.1 The influence of solvent polarity on the rate of formation of 4-nitrobenzyl 4-nitrobenzoate 61 using the Hendrickson reagent 27

The rate of formation of 4-nitrobenzyl 4-nitrobenzoate 61 using the Hendrickson reagent 27 was examined in several solvents by ¹H NMR spectroscopy. A dilute solution of triphenylphosphine oxide in DCM, DCM/toluene 1 : 1 or DCM/acetonitrile 1 : 1 at 0°C was treated with triflic anhydride to generate the Hendrickson reagent 27 as a pale yellow solution. Chlorinated solvents were used in all cases to assist with the solubility of the triflic anhydride. Reaction conditions involving a large volume of
solvent (0.013 M in 27), held at 0°C for the entire reaction, were found to be necessary to give a reaction of sufficient speed to allow monitoring by $^1$H NMR spectroscopy. 4-Nitrobenzyl alcohol, 4-nitrobenzoic acid (in large excess to achieve pseudo-first-order kinetics) and diisopropylethylamine (in a large excess to dissolve the 4-nitrobenzoic acid) were added in succession to the solution of 27 at 0°C. Aliquots of the reaction mixture were removed periodically and quenched immediately with aqueous sodium bicarbonate. The aliquots were examined by $^1$H NMR spectroscopy, using the signals due to the CH$_2$ groups of 4-nitrobenzyl alcohol (δ 4.8 ppm) or 4-nitrobenzyl 4-nitrobenzoate 61 (δ 5.5 ppm), to determine the ratio of 4-nitrobenzyl alcohol to desired ester 61. Figure 12 shows the rate of ester 61 formation over time using the Hendrickson reagent 27 in the three solvent systems.

**Figure 12.** The effect of solvent polarity on the rate of 4-nitrobenzyl 4-nitrobenzoate 61 formation using the Hendrickson reagent 27. DCM/toluene 1:1 (□), DCM (●), DCM/CH$_3$CN 1:1 (○). Reaction conditions: Hendrickson reagent 27 (1.0 equiv.), 4-nitrobenzyl alcohol (1.0 equiv.), 4-nitrobenzoic acid (5.0 equiv.), diisopropylethylamine (5.0 equiv.), solutions 0.013 M in 27, 0°C.
To test that the reactions followed first-order kinetics, plots of \( \ln \left( \frac{[4\text{-nitrobenzyl alcohol}]}{[\text{initial 4-nitrobenzyl alcohol}]} \right) \) versus time were constructed (see Appendix One). A straight line was obtained in each case, allowing pseudo-first-order rate constants to be calculated from the gradient. Pseudo-first-order rate constants (Table 6) of \( 5.61 \times 10^{-3} \text{ sec}^{-1} \) (entry 1), \( 1.74 \times 10^{-3} \text{ sec}^{-1} \) (entry 2), and \( 4.68 \times 10^{-4} \text{ sec}^{-1} \) (entry 3) were obtained for the respective esterification reactions in DCM/toluene 1:1, DCM and DCM/CH$_3$CN 1:1. Thus, using a non-polar solvent increased the rate of esterification of 4-nitrobenzyl alcohol with 4-nitrobenzoic acid by the Hendrickson reagent 27 considerably.

**Table 6.** Kinetic data for 4-nitrobenzyl 4-nitrobenzoate 61 formation using the Hendrickson reagent 27 and cyclic reagents 90-92.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Rate constant (sec$^{-1}$)$^a$</th>
<th>$T_{1/2}$ (sec)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27</td>
<td>DCM/toluene 1:1</td>
<td>( 5.61 \times 10^{-3} )</td>
<td>123.6</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>DCM</td>
<td>( 1.74 \times 10^{-3} )</td>
<td>398.4</td>
</tr>
<tr>
<td>3</td>
<td>27</td>
<td>DCM/CH$_3$CN 1:1</td>
<td>( 4.68 \times 10^{-4} )</td>
<td>1481.1</td>
</tr>
<tr>
<td>4</td>
<td>90</td>
<td>DCM</td>
<td>( 3.25 \times 10^{-3} )</td>
<td>213.3</td>
</tr>
<tr>
<td>5</td>
<td>91</td>
<td>DCM</td>
<td>( 2.41 \times 10^{-4} )</td>
<td>2876.1</td>
</tr>
<tr>
<td>6</td>
<td>92</td>
<td>DCM</td>
<td>( 2.10 \times 10^{-4} )</td>
<td>3300.7</td>
</tr>
</tbody>
</table>

$^a$Percentage conversion to ester obtained via $^1$H NMR integration. Rate constants (at 0°C) based on gradients from pseudo-first-order plots \((k = -m)\). $^b$\(T_{1/2}\) values obtained using \(t_{1/2} = \ln \ 2/k\).

Similar observations have previously been reported under Mitsunobu conditions, where the rate of ethyl benzoate formation was found to be much faster in non-polar solvents.$^{41}$ A decrease in solvent polarity is known to result in an increase in the rate of reactions in which the charge density of the transition state is lower than that in the initial reactants (i.e., if the reactants are oppositely charged and formation of the transition state involves a decrease in charge separation, then the reaction will be...
favoured by a non-polar solvent).\textsuperscript{231} For this reaction, the rate-determining step involves either attack of the alkoxide on the Hendrickson reagent \textsuperscript{27} to form a phosphorane intermediate, or attack by carboxylate on the alkoxyphosphonium salt, i.e. a transition state which is less charged than the reactants. The presence of ionic salts or polar solvents also can inhibit ion pair clustering and therefore, the formation of ion pair clusters may also be important.\textsuperscript{39,40,219,234-236}

3.2 The rates of formation of 4-nitrobenzyl 4-nitrobenzoate 61 using cyclic phosphonium anhydries 90-92

In order to establish the best analogue for subsequent polymer attachment, the rate of formation of 4-nitrobenzyl 4-nitrobenzoate 61 using the cyclic analogues 90-92 was investigated in DCM. The reactions were performed in a similar fashion to the above study using the Hendrickson reagent \textsuperscript{27}. Successive addition of 4-nitrobenzyl alcohol, excess 4-nitrobenzoic acid and diisopropylethylamine to a dilute DCM solution of the cyclic analogue 90, 91 or 92 was carried out at 0\degree C. Again aliquots were removed regularly, quenched and analysed \textsuperscript{1}H NMR spectroscopy. From this data, the rate of formation of 4-nitrobenzyl 4-nitrobenzoate 61 was determined (Figure 13).

Interestingly, the five-membered cyclic analogue 90 produced a pseudo-first-order rate constant (k = 3.25 x 10\textsuperscript{-3} sec\textsuperscript{-1}, entry 4, Table 6) almost double that obtained for the Hendrickson reagent \textsuperscript{27} (k = 1.74 x 10\textsuperscript{-3} sec\textsuperscript{-1}, entry 2, Table 6). The rates of reaction for the six- and seven-membered ring compounds 91 and 92 were comparable, k = 2.41 x 10\textsuperscript{-4} sec\textsuperscript{-1} for 91 and k = 2.1 x 10\textsuperscript{-4} sec\textsuperscript{-1} for 92, yet notably slower than for the Hendrickson reagent \textsuperscript{27} (k = 1.74 x 10\textsuperscript{-3} sec\textsuperscript{-1}) in the same solvent. A mechanism for the esterification reaction induced by these cyclic reagents is suggested for compound 90 in Scheme 51.
**Figure 13.** A comparison of 4-nitrobenzyl 4-nitrobenzoate 61 formation over time using reagents 27, 90-92 in DCM. Five-membered cyclic analogue 90 (○), Hendrickson reagent 27 (■), seven-membered cyclic analogue 92 (●), six-membered cyclic analogue 91 (□). Reaction conditions: reagents 27, 90-92 (1.0 equiv.), 4-nitrobenzyl alcohol (1.0 equiv.), 4-nitrobenzoic acid (5.0 equiv.), diisopropylethylamine (5.0 equiv.), solutions 0.013 M in reagent 27, 90, 91 or 92, 0°C.

![Scheme 51](image-url)
As an order of magnitude difference in the rate constant was observed when the alkyl side chain was changed from \( \text{CH}_2\text{CH}_2\text{P(O)Ph}_2 \) to \( \text{CH}_2\text{CH}_2\text{CH}_2\text{P(O)Ph}_2 \) (i.e. five-versus six-membered ring), it appears unlikely that step three is rate-determining. Similarly, step two is also unlikely to be rate-determining as it is anticipated that a rapid ring-opening would occur to form 119. Additionally, the six-membered ring should open faster than the five-membered ring, as the six-membered ring phosphorane would be less stable. In the case of primary alcohols, it has been deduced that step one is rate-determining.

The observation that 90 leads to an esterification reaction much faster than that of 91 or 92 can be explained by the relative ease of formation of the phosphorane intermediate 118. Phosphoranes possessing a five-membered ring are well known to be more stable than the corresponding six- or seven-membered ring phosphoranes,\(^ {240-242} \) so it is anticipated that the formation of the phosphorane intermediate 118 would be facilitated in the case of the five-membered ring compound 90. The difference in rate constants between the Hendrickson reagent 27 and the six- and seven-membered ring compounds 91 and 92 respectively, can be explained by the higher positive charge on the phosphorus atoms of the Hendrickson reagent 27. The alkyl group attached to the positively charged phosphorus atom in 91 and 92 is more electron donating than the extra phenyl group present in the Hendrickson reagent 27. The slightly slower rate observed for the seven-membered ring compound 92, is consistent with this explanation as \( \text{CH}_2\text{CH}_2\text{CH}_2 \) should be slightly more electron donating than \( \text{CH}_2\text{CH}_3 \).

4.0 General conclusions

Novel cyclic analogues 90-92 of the Hendrickson reagent 27 have been synthesised by reaction of the corresponding bis-phosphine oxides 93-95 with triflic anhydride. The
The mechanism of formation of the five-membered ring compound 90 was investigated by $^{31}$P NMR spectroscopy and it was found that the dimeric species 98 is formed as an intermediate. Oxyphosphonium salts 100 and 101 also were identified by $^{31}$P NMR spectroscopy following the addition of alcohols to the five-membered ring compound 90. The cyclic analogues 90-92 were characterised as their more stable aminophosphonium salts 114-116 after it was found that treatment of the Hendrickson reagent 27 with benzylamine gave benzylaminotriphenylphosphonium triflate 113. The cyclic species 90-92 were useful for the synthesis of simple esters and amides and have the advantage over the Hendrickson reagent 27 that the bis-phosphine oxide by-product is more easily removed by chromatography. Investigations of reaction rates revealed the esterification of a primary alcohol using the Hendrickson reagent 27 to be faster in non-polar solvents. The fastest rate of esterification was obtained using the five-membered ring compound 90, due to the ease of formation of the putative phosphorane intermediate 118. Thus, at present, the best reagent for solid-phase attachment would appear to be the five-membered cyclic analogue 90.

During the preparation of the cyclic analogues 90-92, acyclic analogues of the Hendrickson reagent 27 also were examined. The synthesis and reaction of analogues substituted at phosphorus with butyl, cyclohexyl and 2-pyridyl functionalities are investigated in the next chapter.
CHAPTER THREE

ACYCLIC ANALOGUES OF THE HENDRICKSON REAGENT
In addition to the cyclic analogues 90-92 prepared in Chapter Two, selected acyclic analogues of the Hendrickson reagent 27 were investigated concurrently (this Chapter). At the time of this work, the reactions involving the addition of salts such as tetrabutylammonium triflate to the Mitsunobu reaction detailed in Chapter One had not been performed. It was anticipated that a phosphonium anhydride reagent, which would bring about the inversion of secondary alcohols in high yield, could be identified prior to polymer attachment. This chapter will examine the synthesis and use of analogues of the Hendrickson reagent 27 possessing butyl and cyclohexyl functionalities. These analogues were originally considered to examine the effect of changing the groups attached to phosphorus on the reaction between the phosphonium anhydride reagent, (−)-menthol, a nucleophile and a base. The butyl and cyclohexyl group were considered representatives of a range of other possible analogues, that explore a simple n-alkyl and a more sterically bulky case. In addition, the preparation and use of an analogue of the Hendrickson reagent 27 containing a 2-pyridyl group (an internal base) will be described.

1.0 Tributylphosphonium anhydride triflate 120 [µ-oxobis(tributylphosphonium) bis(trifluoromethanesulfonate)]

1.1 Synthesis and characterisation of tributylphosphonium anhydride triflate 120

Tributylphosphonium anhydride triflate 120 was formed by treatment of two equivalents of commercially available tributylphosphine oxide 121 with triflic anhydride in CD₂Cl₂ (Scheme 52). Due to its hygroscopic nature and sensitivity to moisture, tributylphosphonium anhydride triflate 120 was characterised by NMR spectroscopy in a sealed tube under an inert atmosphere.
Analysis of 120 by $^{31}$P NMR spectroscopy gave a spectrum with a singlet at $\delta$ 119.2 ppm. The synthesis of tributylphosphonium anhydride triflate 120 has been described previously, however a different $^{31}$P NMR shift for 120 at $\delta$ 84.74 ppm was reported. Initial attempts to prepare 120 for analysis by $^{31}$P NMR spectroscopy gave a $^{31}$P NMR spectrum with peaks at $\delta$ 119.2 ppm and $\delta$ 85.7 ppm in a ratio of 9 : 1 respectively. However, following drying of the tributylphosphine oxide 121 by azeotropic distillation with toluene, the experiment was repeated and only a singlet at $\delta$ 119.2 ppm obtained in the $^{31}$P NMR spectrum. The singlets at $\sim$ $\delta$ 85 ppm are likely to correspond to protonated tributylphosphine oxide. Further evidence for the protonated tributylphosphine oxide was obtained when addition of one equivalent of triflic acid to a CD$_2$Cl$_2$ solution of tributylphosphine oxide 121 showed a downfield shift in the signal in the $^{31}$P NMR spectrum from $\delta$ 47.8 ppm to $\delta$ 85.2 ppm. Analysis of tributylphosphonium anhydride triflate 120 by $^1$H NMR spectroscopy gave multiplets between $\delta$ 1.5-1.7 ppm and $\delta$ 2.78-2.88 ppm and a triplet at $\delta$ 0.99 ppm, corresponding to the six methyl groups of 120. Four signals were observed in the $^{13}$C NMR spectrum of 120, with the signal due to the carbons $\alpha$ and $\beta$ to phosphorus being present as doublets. Due to the slight broadening of signals in the $^{13}$C NMR spectrum, potential small phosphorus couplings in the $\gamma$ and $\delta$ carbons were not observed. In a similar fashion to the cyclic analogues 90-92, tributylphosphonium anhydride triflate 120 was characterised as its more stable aminophosphonium triflate. Treatment of 120 (generated in situ in DCM) with benzylamine and diisopropylethylamine gave benzylaminotributylphosphonium triflate 122 after stirring at room temperature overnight (Scheme 53).
Analysis of 122 by $^1$H NMR spectroscopy showed a characteristic doublet of doublets at $\delta$ 4.12 ppm corresponding to the two benzyl protons, which collapsed to a doublet upon phosphorus decoupling (Figure 14). Additional coupling was observed in the amine proton at $\delta$ 5.76 ppm, which was present as a quartet (doublet of triplets) and collapsed to a triplet upon phosphorus decoupling (Figure 14).

**Figure 14.** $^1$H NMR spectrum (400 MHz) of benzylaminotributylphosphonium triflate 122. (a) benzyl CH$_2$ at $\delta$ 4.12 ppm (c) benzyl CH$_2$ at $\delta$ 4.12 ppm with phosphorus decoupling (b) NH at $\delta$ 5.76 ppm (d) NH at $\delta$ 5.76 ppm with phosphorus decoupling.

The $^{31}$P NMR spectrum of benzylaminotributylphosphonium triflate 122 revealed a singlet at $\delta$ 59.4 ppm, with the $^{13}$C NMR spectrum displaying phosphorus coupling in the butyl chain, benzyl CH$_2$ carbon and ipso carbon of the phenyl ring. In the FTIR spectrum, medium absorbances at 640 cm$^{-1}$ and 1031 cm$^{-1}$ were attributable to the
respective stretches of the carbon-phosphorus and carbon-nitrogen bonds. Mass spectrometry showed both the benzylaminotributylphosphonium cation and triflate anions in positive and negative modes respectively. The microanalysis result for 122 was consistent with the molecular formula of C_{20}H_{35}F_{3}NO_{3}PS.

1.2 Reactions using tributylphosphonium anhydride triflate 120

1.2.1 Primary alcohols

Initially, the use of tributylphosphonium anhydride triflate 120 was examined for the simple esterification of a primary alcohol. Addition of triflic anhydride to a solution of tributylphosphine oxide 121 in DCM at 0°C formed the reagent 120 as a clear solution. A slight excess of tributylphosphine oxide 121 was used to avoid unwanted side reactions (see Chapter One, section 1.0). 4-Nitrobenzyl alcohol, 4-nitrobenzoic acid and diisopropylethylamine were added and after stirring for two hours at room temperature, work-up and chromatography, 4-nitrobenzyl 4-nitrobenzoate 61 was obtained in high yield (90%) (Scheme 54).

\[ \text{Bu}_3\text{P}^\dagger - \text{O} - \text{PBu}_3^\dagger \]
\[ 2\text{CF}_3\text{SO}_2\text{O}^- \rightarrow \]
\[ 4\text{-NO}_2\text{C}_6\text{H}_4\text{-CH}_2\text{-OH} \]
\[ 4\text{-NO}_2\text{C}_6\text{H}_4\text{-COOH} \]
\[ \text{iPr}_2\text{NEt, DCM} \]
\[ 2 \text{hr, RT} \]

Scheme 54

1.2.2 Secondary alcohols

Following the successful esterification of a primary alcohol, the use of the reagent 120 for esterification of optically active alcohols with inversion of configuration was examined. It has been previously detailed (Chapter One, section 2.0) that reaction of the Hendrickson reagent 27 with (−)-menthol, 4-nitrobenzoic acid and diisopropylethylamine in DCM at 40°C overnight gave predominantly 2- and 3-menthene 36 and 37. At the time of this work, the reason for this difference in
reactivity between the Hendrickson and Mitsunobu reagents, which proceed through the same menthylxyphosphonium salt intermediate, was unclear. Thus, sterically less demanding reagents such as tributylphosphonium anhydride triflate 120 were pursued in the search for an understanding of these apparent differences. The reaction of 120 with (-)-menthol, 4-nitrobenzoic acid and diisopropylethylamine in DCM at room temperature overnight gave 2- and 3-menthene 36 and 37, and (-)-menthol (ratio 1 : 9) following analysis by GC/MS. Analysis of the reaction mixture by ¹H NMR spectroscopy revealed unreacted (-)-menthol. The reaction was repeated with heating at 40°C overnight and analysis by GC/MS indicated the presence of 2- and 3-menthene 36 and 37, and neomenthyl 4-nitrobenzoate 67 (ratio 9 : 1). Following work-up, analysis by ¹H NMR spectroscopy showed the presence of 2- and 3-menthene 36 and 37 (ratio 1 : 2), alongside an unknown species exhibiting a doublet of doublets at δ 4.35 ppm. The unknown species was isolated by column chromatography and shown, following analysis by 1D and 2D (gCOSY, gHSQC, gHMBC) NMR techniques, to be the oxyphosphonium salt intermediate (-)-menthylxytributylphosphonium trflate 123.

In the ¹H NMR spectrum of 123, the characteristic signal from the proton attached to the carbon bearing the O-P group (H1) was a dddd at δ 4.35 ppm, which collapsed to a ddd upon phosphorus decoupling. The ³¹P NMR spectrum of (-)-menthylxytributylphosphonium trflate 123 revealed a singlet at δ 95.2 ppm, with the ¹³C NMR spectrum displaying phosphorus coupling in the butyl chain and C1 and C2 of the (-)-menthyl ring (Figure 15). A strong absorbance at 1269 cm⁻¹ in the FTIR spectrum was attributable to the stretch of the phosphorus-oxygen bond. Mass spectrometry showed both the (-)-menthylxytributylphosphonium cation and trflate anions in positive and negative modes respectively. The microanalysis result for 123 was consistent with the molecular formula of C_{23}H_{46}F_{3}O_{4}PS.
Figure 15. (a) $^{13}$C NMR spectrum (100 MHz, $\delta$ 20.7-25.7 ppm) of (–)-menthyl oxytributylphosphonium triflate 123. (b) $^{13}$C{$_{31}$P, $^1$H} NMR spectrum (100 MHz, $\delta$ 20.7-25.7 ppm) of (–)-menthyl oxytributylphosphonium triflate 123.

Scheme 55
It was difficult to obtain a precise ratio of the products formed in the reaction between tributylphosphonium anhydride trflate 120, (−)-menthol, 4-nitrobenzoic acid and diisopropylethylamine at 40°C overnight as the oxyphosphonium salt 123 was not observed in the GC/MS trace and a large portion of the menthene 36 and 37, were lost during solvent evaporation prior to analysis by NMR spectroscopy. However, as only a small amount of 123 was obtained (19.5% yield after chromatography), the major products were 2- and 3-menthene 36 and 37. Thus, in the same way as reactions involving the Hendrickson reagent 27, tributylphosphonium anhydride trflate 120 appears to react smoothly with (−)-menthol to give (−)-menthyloxytributylphosphonium trflate 123, which can then eliminate to yield 2- and 3-menthene 36 and 37 or undergo SN2 displacement to give the desired neomenthyl 4-nitrobenzoate 67 (Scheme 55). Therefore, replacing the phenyl groups of the Hendrickson reagent 27 with butyl groups did not dramatically alter the reaction outcome since elimination was still the dominant pathway.

1.2.3 The stability of (−)-menthyloxytributylphosphonium trflate 123

It was initially surprising that (−)-menthyloxytributylphosphonium trflate 123 was stable to aqueous work-up given that the analogous Mitsunobu intermediate (where the trflate counter-ion is replaced with a carboxylate anion) is not. To determine the stability of (−)-menthyloxytributylphosphonium trflate 123 two simple tests were carried out. A solution containing 123, water and THF (1:1) was stirred at room temperature overnight. The THF was required to aid solubility and was also chosen as it is miscible with water. After work-up, analysis by ³¹P and ¹H NMR spectroscopy revealed quantitative recovery (92%) of (−)-menthyloxytributylphosphonium trflate 123. However, when the same reaction was conducted using saturated aqueous sodium hydrogen carbonate, THF and 123, analysis by ³¹P and ¹H NMR spectroscopy revealed
the presence of (–)-menthol and tributylphosphine oxide 121. These experiments indicate that (–)-menthyloxytributylphosphonium triflate 123 was stable in aqueous conditions (pH 6) but not in solutions which were basic. The difference between the relative stabilities of the respective Hendrickson and Mitsunobu intermediates may to be a function of the ability of the triflate counter-ion to form a tight ion pair.

1.2.4 Reactions with (–)-menthyloxytributylphosphonium triflate 123

After establishing the relative stability of (–)-menthyloxytributylphosphonium triflate 123, attempts were made to exchange the triflate counter-ion for a carboxylate anion. This may possibly yield the standard Mitsunobu intermediate and subsequently give the desired S_N_2 reaction. Initially, (–)-menthyloxytributylphosphonium triflate 123 was added to a solution of sodium benzoate 124 in toluene and the solution stirred at room temperature overnight. Following work-up, analysis of the crude reaction mixture by ^{31}P and ^{1}H NMR spectroscopy showed unreacted (–)-menthyloxytributylphosphonium triflate 123. The reaction was repeated in DMF, however unreacted (–)-menthyloxytributylphosphonium triflate 123 again was obtained.

![Chemical structures](image1.png)

Alternative counter-ions such as lithium and zinc also were examined. Addition of (–)-menthyloxytributylphosphonium triflate 123 to a toluene solution containing lithium 4-nitrobenzoate 125 (prepared from 4-nitrobenzoic acid and n-butyllithium) gave unreacted (–)-menthyloxytributylphosphonium triflate 123 following analysis of the reaction mixture by ^{31}P and ^{1}H NMR spectroscopy. Treatment of (–)-menthyloxytributylphosphonium triflate 123 with zinc benzoate 126 (prepared from benzoic acid and zinc carbonate) in DMF at room temperature overnight also gave
unreacted (–)-menthloxytributylphosphonium triflate 123. In addition, the more organic soluble tetrabutylammonium 4-nitrobenzoate 127 (prepared from 4-nitrobenzoic acid and tetrabutylammonium hydroxide) failed to give a reaction when stirred overnight at room temperature with (–)-menthloxytributylphosphonium triflate 123. The use of sodium iodide in acetone did, however, afford (–)-menthloxytributylphosphonium iodide 128 after stirring at room temperature for two days (Scheme 56). The sodium triflate by-product was removed by precipitation with diethyl ether. The absence of the triflate counter-ion (present as a quartet at δ 120 ppm in the $^{13}$C NMR spectrum) was confirmed by $^{13}$C NMR spectroscopy. The presence the iodide ion was confirmed by electrospray mass spectrometry with a molecular mass observed in the negative mode at 127 amu. An attempt to generate the desired neomenthyl iodide 129 by heating a solution of 128 in DCM at reflux overnight was not successful. Analysis of the crude reaction mixture by $^{31}$P and $^1$H NMR spectroscopy indicated the presence of (–)-menthloxytributylphosphonium iodide 128.

![Scheme 56](image)

Thus, attempts to replace the triflate counter-ion of (–)-menthloxytributylphosphonium triflate 123 and bring about an S$_{N}$2 displacement reaction were not successful. This phosphonium salt was much more stable than the corresponding triphenylphosphonium salt. At this stage, the use of a butyl functionality was not pursued/considered further and attention was directed towards the cyclohexyl analogue of the Hendrickson reagent 27. The cyclohexyl group was chosen as a more sterically bulky analogue of a phenyl...
group, and it was hoped that this additional steric bulk might result in steric acceleration of the S_N2 displacement step.

2.0 Tricyclohexylphosphonium anhydride triflate 130 [µ-oxobis(tricyclohexylphosphonium) bis(trifluoromethanesulfonate)]

2.1 Synthesis and characterisation of tricyclohexylphosphonium anhydride triflate 130

Tricyclohexylphosphonium anhydride triflate 130 was formed by treatment of two equivalents of tricyclohexylphosphine oxide 131 (obtained by oxidation of tricyclohexylphosphine with hydrogen peroxide – see Chapter Two, section 1.1) with triflic anhydride in CD_2Cl_2 (Scheme 57). Due to its hygroscopic nature and sensitivity to moisture, tricyclohexylphosphonium anhydride triflate 130 was characterised by NMR spectroscopy.

\[
\begin{align*}
&\text{2.} \quad \text{2} \left( \text{PhCH}_2\text{NH}_2 \right) \quad \left( \text{CF}_3\text{SO}_2\right)_2\text{O} \\
&\text{CD}_2\text{Cl}_2 \\
&\text{O}^\circ \text{C, 30 min} \\
&\text{131} \\
&\text{130} \\
&\text{132}
\end{align*}
\]

Scheme 57

In the ^1H NMR spectrum, a downfield shift in the cyclohexyl protons was noted on the formation of 130. Phosphorus coupling was observed in the carbons α and β to phosphorus in the ^13C NMR spectrum of 130 and analysis by ^31P NMR spectroscopy gave a singlet at δ 118.8 ppm. Tricyclohexylphosphonium anhydride triflate 130 also
was characterised as its more stable aminophosphonium salt 132 following reaction with benzylamine and diisopropylethylamine overnight at room temperature (Scheme 57). Analysis of benzylaminotricyclohexylphosphonium triflate 132 by $^1$H NMR spectroscopy revealed a signal that was a characteristic doublet of doublets at $\delta$ 4.17 ppm, attributable to the two benzyl protons, which collapsed to a doublet upon phosphorus decoupling. In the $^{13}$C NMR spectrum, phosphorus coupling was observed throughout the cyclohexyl ring and in the ipso carbon of the phenyl ring. Analysis of 132 by $^{31}$P NMR gave a signal that was a singlet at $\delta$ 57.2 ppm. Medium absorbances in the FTIR spectrum at 636 cm$^{-1}$ and 1028 cm$^{-1}$ were attributable to the respective stretches of the carbon-phosphorus and carbon-nitrogen bonds. Mass spectrometry showed both the benzylaminotricyclohexylphosphonium cation and triflate anions in positive and negative modes respectively. Elemental analysis of 132 gave results consistent with the molecular formula of C$_{26}$H$_{41}$F$_3$NO$_3$PS.

2.2 Reactions using tricyclohexylphosphonium anhydride triflate 130

2.2.1 Primary alcohols – ester formation

Addition of 4-nitrobenzyl alcohol, 4-nitrobenzoic acid and diisopropylethylamine to a preformed solution of 130 in DCM afforded 4-nitrobenzyl 4-nitrobenzoate 61 in good yield (95%) after stirring at room temperature for two hours. The rate of formation of 4-nitrobenzyl 4-nitrobenzoate 61 with tricyclohexylphosphonium anhydride triflate 130 was examined in DCM under identical conditions to those described in Chapter Two, section 3.2. However, under these conditions, 84% conversion to 4-nitrobenzyl 4-nitrobenzoate 61 was observed after only one minute using analysis by $^1$H NMR spectroscopy. Thus, under these conditions no accurate rate data could be obtained for
comparison with analogues such as the cyclic species 90-92. The reaction was more efficient than the Hendrickson reagent 27 under these conditions.

2.2.2 Reaction with secondary alcohols

The use of tricyclohexylphosphonium anhydride triflate 130 for esterification of optically active alcohols with inversion of configuration was examined next. (–)-Menthol, 4-nitrobenzoic acid and diisopropylethylamine were added to a solution containing 130 in DCM and stirred at room temperature overnight. Analysis of the reaction mixture by GC/MS indicated the formation of 2- and 3-menthene 36 and 37, and unreacted (–)-menthol (ratio 1 : 19). Analysis of the reaction mixture by 1H NMR spectroscopy revealed unreacted (–)-menthol. The reaction was repeated with heating at 40°C overnight and analysis by GC/MS showed the presence of 2- and 3-menthene 36 and 37, neomenthyl 4-nitrobenzoate 67 and (–)-menthol (ratio 22 : 2 : 1). Following work-up, analysis by 1H NMR spectroscopy showed the presence of 2- and 3-menthene 36 and 37 (ratio 1 : 2), (–)-menthol and an oxyphosphonium salt intermediate. (–)-Menthyloxytricyclohexylphosphonium triflate 133 was isolated in 16% yield and characterised using 1D and 2D NMR techniques, mass spectrometry, FTIR and elemental analysis. Thus, like the corresponding tributylphosphonium anhydride 123, when tricyclohexylphosphonium anhydride triflate 130 is reacted with secondary alcohols in the presence of a nucleophile and base, it gives predominately the products of elimination, 2-and 3-menthene 36 and 37, rather than the desired S_N2 substitution product, neomenthyl 4-nitrobenzoate 67.
3.0 Triphenylphosphonium anhydride tetrafluoroborate 42 [µ-oxobis-(triphenylphosphonium) bis(tetrafluoroborate)]

As replacing the phenyl rings of the Hendrickson reagent 27 with butyl or cyclohexyl groups did not substantially increase the ratio of substitution to elimination in the reaction between 27, (−)-menthol, a nucleophile and a base, the effect of altering the counter-ion was examined next. Triphenylphosphonium anhydride tetrafluoroborate 42 has been previously synthesized by the addition of triethyloxonium tetrafluoroborate (Meerwein’s salt) to a DCM solution containing triphenylphosphine oxide at 0°C (Scheme 58). Like the Hendrickson reagent 27, triphenylphosphonium anhydride tetrafluoroborate 42 precipitates out of the cold DCM immediately as a white solid. As 42 has been previously characterised, it was synthesised in situ and used immediately.

\[
\begin{align*}
2 \text{Ph}_3\text{P}^\ominus \text{O}^- & \text{Et}_3\text{O}^+ \text{BF}_4^- \\
\text{DCM, 0°C} & \rightarrow \\
\text{Ph}_3\text{P}^\ominus \text{O}^- \text{Et}^- & 2\text{BF}_4^- \\
136 & \\
\text{Ph}_3\text{P}^\ominus \text{O}^- & \text{Ph}_3\text{P}^\ominus \text{O}^- \text{Ph}_3^- \\
2\text{BF}_4^- & 42
\end{align*}
\]

Scheme 58

3.1 Esterification of primary alcohols

The use of triphenylphosphonium anhydride tetrafluoroborate 42 was initially trialled on the formation of the simple ester, 4-nitrobenzyl 4-nitrobenzoate 61. Triphenylphosphonium anhydride tetrafluoroborate 42 was prepared in situ from triethyloxonium tetrafluoroborate and triphenylphosphine oxide. Addition of 4-nitrobenzyl alcohol, 4-nitrobenzoic acid and diisopropylethylamine, after stirring at room temperature overnight, produced a mixture of products, 4-nitrobenzyl 4-nitrobenzoate 61, ethyl 4-nitrobenzoate 134 and 4-nitrobenzyl ethyl ether 135 in the ratio of 1 : 2 : 2 (by integration of crude \(^1\)H NMR spectrum)(Scheme 59). The products 61, 134 and 135 also were isolated by chromatography.
It would appear that alkylation of both 4-nitrobenzyl alcohol and 4-nitrobenzoic acid has occurred by competitive reaction with either ethoxytriphenylphosphonium tetrafluoroborate 136 or Meerwein’s salt. Ethoxytriphenylphosphonium tetrafluoroborate 136 is also formed when triphenylphosphine oxide is treated with Meerwein’s salt. To avoid the unwanted alkylation side products, the reaction was repeated using a sample of triphenylphosphonium anhydride tetrafluoroborate 42 which had been washed three times with dry DCM under Schlenk conditions, dried and re-suspended in fresh DCM. This approach was adopted in an effort to remove any excess triethyloxonium tetrafluoroborate. However, subsequent addition of 4-nitrobenzyl alcohol, 4-nitrobenzoic acid and diisopropylethylamine to the suspension of 42 gave 4-nitrobenzyl ethyl ether 135 and 4-nitrobenzyl alcohol after stirring at room temperature overnight. A ratio of 3 : 2 was obtained following analysis of the crude reaction mixture by $^1$H NMR spectroscopy. This result suggested that the unwanted alkylation was due to ethoxytriphenylphosphonium tetrafluoroborate 136. It was decided that due to the apparent difficulty of generating pure triphenylphosphonium anhydride tetrafluoroborate 42, and the ensuing complication of competing alkylation reactions, the use of 42 would not be examined further.

Scheme 59
4.0 Diphenyl-2-pyridylphosphonium anhydride triflate 137 \([\mu\text{-oxobis(diphenyl-2-pyridylphosphonium)} \text{ bis(trifluoromethanesulfonate)}]\)

Following the work presented in Chapter One, an analogue of the Hendrickson reagent 27 was designed such that it could act as an internal base, thereby removing the need for chromatography as the aminophosphine oxide, returned as its triflate salt, would extract completely into an aqueous phase after the reaction. In Chapter One, the reaction of the Hendrickson reagent 27 with secondary alcohols such as (−)-menthol was shown to result primarily in dehydration instead of the expected S\text{N}2 displacement because of the more ionic conditions generated by the Hendrickson reagent 27. The use of diphenyl-2-pyridylphosphonium anhydride triflate 137 could therefore potentially tip the balance of the reaction in favour of substitution over elimination, as the leaving group would be a charged moiety and this could influence the reaction mechanism.

4.1 Synthesis and characterisation of diphenyl-2-pyridylphosphonium anhydride triflate 137

Treatment of a solution of diphenyl-2-pyridylphosphine oxide 137 (formed by oxidation of the corresponding phosphine, see Chapter Two, section 1.1) with triflic anhydride in \(\text{CD}_2\text{Cl}_2\) at 0°C for 30 minutes gave diphenyl-2-pyridylphosphonium anhydride triflate 137 (Scheme 60). The pyridyl species 137 was characterised by NMR spectroscopy, as a result of its hygroscopic nature and sensitivity to moisture. Analysis of 137 by \(^{31}\text{P}\) NMR spectroscopy displayed a singlet at \(\delta\) 64.7 ppm. Interestingly, all resonances in the \(^1\text{H}\) NMR, \(^{13}\text{C}\) NMR and \(^{31}\text{P}\) NMR spectra exhibited slight line broadening.
The line broadening could arise because of a potential coordination between the pyridyl nitrogen and positively charged phosphorus atom, forming five-membered ring species such as 139 and 140, which are averaged on the NMR timescale (Scheme 61). Such broadening was not observed in the NMR spectra of diphenyl-2-pyridylphosphine oxide 138 or benzylaminodiphenyl-2-pyridylphosphonium triflate 141.

Additional characterisation of diphenyl-2-pyridylphosphonium anhydride triflate 137 was achieved following the reaction of 137 with benzylamine and diisopropylethylamine in DCM at room temperature overnight to form the corresponding aminophosphonium salt 141 (Scheme 60). Isolation of benzylaminodiphenyl-2-pyridylphosphonium triflate 141 from diphenyl-2-pyridylphosphine oxide 138 by standard chromatographic procedures proved difficult as both species were extremely polar. However, as 141 was found to have a much higher
affinity for water than 142, a pure sample of benzylaminodiphenyl-2-pyridylphosphonium triflate 141 was obtained by solvent partitioning of the crude residue between water and ethyl acetate. Analysis of 141 by $^1$H NMR spectroscopy showed a signal that was a characteristic doublet of doublets at $\delta$ 4.29 ppm, which collapsed to a doublet with phosphorus decoupling. Analysis by $^{31}$P NMR spectroscopy showed a singlet at $\delta$ 30.8 ppm. In the FTIR spectrum, medium absorbances observed at 638 cm$^{-1}$ and 1029 cm$^{-1}$ were attributable to the respective stretches of the carbon-phosphorus and carbon-nitrogen bonds. Mass spectrometry of 141 showed both the benzylaminodiphenyl-2-pyridylphosphonium cation and triflate anions in positive and negative modes respectively. High resolution mass spectral data for 141 matched the molecular weight of the benzylaminodiphenyl-2-pyridylphosphonium cation.

4.2 Reactions using diphenyl-2-pyridylphosphonium anhydride triflate 137

4.2.1 Esterification of primary alcohols

Diphenyl-2-pyridylphosphonium anhydride triflate 137 was initially investigated for use in the simple esterification of a primary alcohol. Treatment of a DCM solution of diphenyl-2-pyridylphosphine oxide 137 at 0°C with triflic anhydride generated the reagent 137 after stirring for one hour. Subsequent addition of 4-nitrobenzyl alcohol and 4-nitrobenzoic acid, followed by stirring at room temperature overnight, gave a mixture of bis(4-nitrobenzyl)ether 142, 4-nitrobenzyl alcohol and 4-nitrobenzyl 4-nitrobenzoate 61 (ratio 54 : 38 : 8) after analysis by $^1$H NMR spectroscopy (Scheme 62). Although the reaction did not reach completion, the preference was towards ether 142 rather than ester 61 formation. The formation of ethers is described in section 4.2.3.
To examine whether the reagent 137 could form other esters in good yield, additional esterification reactions were performed and both benzyl 4-nitrobenzoate 143 and benzyl benzoate 144 were synthesised in high yields (Table 7). Thus, when diphenyl-2-pyridylphosphonium anhydride triflate 137 was employed, only the coupling of 4-nitrobenzyl alcohol with 4-nitrobenzoic acid was unusual, giving the ether 142 in preference to the ester 61. Presumably ether formation is kinetically faster with the slightly more acidic 4-nitrobenzyl alcohol (relative to benzyl alcohol).

**Table 7.** Esters formed using diphenyl-2-pyridylphosphonium anhydride triflate 137.

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Alcohol</th>
<th>Acid</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-NO₂-C₆H₄-CH₂-OH</td>
<td>4-NO₂-C₆H₄-COOH</td>
<td>4-Nitrobenzyl 4-nitrobenzoate 61</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>C₆H₄-CH₂-OH</td>
<td>4-NO₂-C₆H₄-COOH</td>
<td>Benzyl 4-nitrobenzoate 143</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>C₆H₄-CH₂-OH</td>
<td>C₆H₄-COOH</td>
<td>Benzyl benzoate 144</td>
<td>84</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reaction conditions: diphenyl-2-pyridylphosphonium anhydride triflate 137 (1.0 equiv.), alcohol (1.0 equiv.), acid (1.0 equiv.), DCM (10 mL).<br><sup>b</sup>Reaction times were room temperature overnight. <sup>c</sup>Isolated yields.

### 4.2.2 Esterification of secondary alcohols

Next, the use of the reagent 137 for esterification of secondary alcohols with inversion was examined. A DCM solution of diphenyl-2-pyridylphosphonium anhydride triflate
was treated with (−)-menthol and 4-nitrobenzoic acid and heated to 40°C overnight. Analysis of the reaction mixture by GC/MS revealed the presence of 2- and 3-menthene 36 and 37 (ratio 1 : 2 following analysis by $^1$H NMR spectroscopy) and neomenthyl 4-nitrobenzoate 67 (ratio 19 : 1) (Scheme 63). Hence, although the use of a reagent containing an internal base such as 137 did simplify the work-up procedure by allowing aqueous extraction of the phosphine oxide by-product, it did not tip the balance of the reaction in favour of substitution over elimination.

![Scheme 63](image)

**4.2.3 Ether formation**

Although the reaction between diphenyl-2-pyridylphosphonium anhydride triflate 137, 4-nitrobenzyl alcohol and 4-nitrobenzoic acid formed bis(4-nitrobenzyl)ether 142 in higher yields than that of the desired ester 4-nitrobenzyl 4-nitrobenzoate 61, it did demonstrate the potential ability of the reagent 137 to form acyclic dialkyl ethers. Under Mitsunobu conditions, acyclic dialkyl ethers are not generally formed due to competing alkylation of the hydrazinedicarboxylate by-product. Treatment of diphenyl-2-pyridylphosphonium anhydride triflate 137 with two equivalents of 4-nitrobenzyl alcohol formed bis(4-nitrobenzyl)ether 142 in high yield (87%) after stirring at room temperature overnight (Table 8). Interestingly, attempts to form bis(4-nitrobenzyl)-
ether 142 using the Hendrickson reagent 27 gave unreacted 4-nitrobenzyl alcohol after stirring at room temperature overnight. This difference in reactivity may be due to some ‘pre-organisation’ in the transition state for reaction in the case of 137. Once the alkoxyphosphonium intermediate has been formed, hydrogen bonding between the pyridyl nitrogen and the second alcohol molecule would facilitate the SN2 displacement process (Figure 16). It should be noted that this is analogous to a 7-endo-tet process (only 5-6-endo-tet processes are disfavoured by Baldwin rules). In addition, the pyridyl group does make the phosphorus atom in diphenyl-2-pyridylphosphonium anhydride triflate 137 more oxophilic than the phosphorus atom in the corresponding triphenyl analogue 27. However, in the case of more activated primary alcohols, the Hendrickson reagent 27 may be capable of forming the respective acyclic dialkyl ethers.

\[
\text{Figure 16} \quad \text{Figure 17}
\]

Other examples of ether formation were tried using diphenyl-2-pyridylphosphonium anhydride triflate 137. Dibenzyl ether 145 also was formed in high yield (90%) after stirring 137 with benzyl alcohol in DCM at room temperature overnight. Addition of two equivalents of 1-hexanol to 137 gave dihexyl ether 146 after stirring at room temperature for two days. The slower reaction in the case of n-hexyl versus benzyl may indicate a degree of SN1 character in the ether forming step (Figure 17). The reaction had not reached completion after stirring overnight at room temperature. In all cases, the phosphine oxide could be removed by extraction with mild acid and recovered following neutralisation and DCM extraction of the acid washes.
Table 8. Ethers formed using diphenyl-2-pyridylphosphonium anhydride triflate 137.

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Alcohol</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-NO&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;-CH&lt;sub&gt;2&lt;/sub&gt;-OH</td>
<td>Bis(4-nitrobenzyl)ether 142</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;-CH&lt;sub&gt;2&lt;/sub&gt;-OH</td>
<td>Dibenzyl ether 145</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;5&lt;/sub&gt;-OH</td>
<td>Dihexyl ether 146</td>
<td>96</td>
</tr>
<tr>
<td>4&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4-OMe-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;-CH&lt;sub&gt;2&lt;/sub&gt;-OH</td>
<td>Bis(4-methoxybenzyl)ether 147</td>
<td>57&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>4-OMe-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;-OH/MeOH</td>
<td>1,4-Dimethoxybenzene 153</td>
<td>65</td>
</tr>
<tr>
<td>6</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;11&lt;/sub&gt;-OH</td>
<td>Dicyclohexyl ether 154</td>
<td>2&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reaction conditions: diphenyl-2-pyridylphosphonium anhydride triflate 137 (1.0 equiv.), alcohol (2.0 equiv.; for entry 5, 1.0 equiv. of each alcohol was used), DCM (10 mL).<br><sup>b</sup>Reaction times: entries 1, 2, 4 and 5 (room temperature overnight), entry 3 (2 days at room temperature), entry 6 (3 days at reflux).<br><sup>c</sup>Isolated yields.<br><sup>d</sup>Diisopropylethylamine (1.1 equiv.) added.<br><sup>e</sup>Yield from <sup>1</sup>H NMR integration.<br><sup>f</sup>Yield from GC/MS analysis.

Interestingly, treatment of a DCM solution of diphenyl-2-pyridylphosphonium anhydride triflate 137 with two equivalents of 4-methoxybenzyl alcohol yielded a complex mixture of products after stirring at room temperature overnight. Analysis of the reaction mixture by <sup>1</sup>H NMR spectroscopy showed a very broad multiplet from δ 3.4 – 4.1 ppm, where the benzyl singlets of the starting material 4-methoxybenzyl alcohol, and product bis(4-methoxybenzyl)ether 147, would normally be found. Attempts to separate the reaction products by chromatography were not successful as no separation could be achieved on TLC. When the reaction was repeated in the presence of two equivalents of diisopropylethylamine, a mixture of products was obtained following analysis of the crude reaction mixture by <sup>1</sup>H NMR spectroscopy. The products were isolated by chromatography and found to be bis(4-methoxybenzyl)ether 147, 4-methoxybenzyl 4-methoxybenzoate 148 and 4-methoxybenzyl alcohol (ratio 57 : 26 : 17 from <sup>1</sup>H NMR spectrum). Thus, in the presence of base, the desired ether 147 was formed in moderate yield (57%). The formation of the minor product, 4-methoxybenzyl 4-methoxybenzoate 148, was totally unexpected. A possible mechanism for its formation is suggested in Scheme 64. Formation of the oxyphosphonium ion intermediate 149, followed by an electrocyclic fragmentation process (analogous to that
in the Moffatt\textsuperscript{245} or Swern\textsuperscript{245} oxidations \textit{150}) would give the corresponding aldehyde \textit{151}. Reaction with a second molecule of the alcohol would give the hemiacetal \textit{152}, which could be oxidised via conversion to the oxyphosphonium salt analogous to \textit{149}. One test for this mechanism would be the formation of diphenyl-2-pyridylphosphine, which could have possibly been lost during the aqueous work-up (see concluding comments, Chapter Six). It is not clear why oxidation was only observed in the case of the most electron rich alcohol, 4-methoxybenzyl alcohol. Possibly it is a function of the 4-methoxy group donating electron density into the (developing) C=O group (resonance interaction) if the transition state \textit{149} resembles the products.

![Chemical structure](image)

\textbf{Scheme 64}

The formation of ethers from phenols also was investigated using diphenyl-2-pyridylphosphonium anhydride triflate \textit{137}. Addition of 4-methoxyphenol and methanol to a solution of \textit{137} in DCM afforded 1,4-dimethoxybenzene \textit{153} in moderate
yield (65%) after stirring at room temperature overnight (Table 8). In addition, ether formation from a secondary alcohol was examined. A solution of diphenyl-2-pyridylphosphonium anhydride trflate 137 in DCM was treated with two equivalents of cyclohexanol and left to stir at room temperature for two days. Analysis of the reaction mixture by both GC/MS and $^1$H NMR spectroscopy revealed unreacted cyclohexanol. The reaction was repeated and after heating at reflux for three days, analysis of the reaction mixture by GC/MS indicated the presence of cyclohexanol, cyclohexene 75 and dicyclohexyl ether 154 (ratio 51 : 47 : 2). Thus, as with the attempted esterification of (–)-menthol with 4-nitrobenzoic acid using 137, the major product obtained was that of elimination.

4.2.4 Amide formation

Initially, the addition of 4-nitrobenzoic acid and benzylamine to a DCM solution of 137 gave none of the desired amide $N$-benzyl 4-nitrobenzamide 112 after stirring at room temperature overnight. Analysis of the crude residue by $^1$H NMR spectroscopy revealed the presence of benzylaminodiphenyl-2-pyridylphosphonium trflate 141 as evidenced by a doublet of doublets at δ 4.15 ppm. Presumably, the unreacted acid was lost during the work-up procedure used to remove the diphenyl-2-pyridylphosphine oxide 138. The reaction was repeated with heating at reflux overnight, however analysis of the reaction mixture by $^1$H NMR spectroscopy again revealed none of the desired amide 112. It is possible that the lack of reaction was caused by the pyridyl nitrogen coordinating to the positively charged phosphorus atom (see Scheme 61), thereby reducing its basicity. Hence, the reaction was repeated in the presence of 2.3 equivalents of diisopropylethylamine. After stirring at room temperature overnight, $N$-benzyl 4-nitrobenzamide 112 was isolated in good yield (70%) (Scheme 65). As a suggestion for further work, the reactivity of diphenyl-2-pyridylphosphonium anhydride
triflate 137 towards amide formation could possibly be improved by employing the 3- or 4-pyridyl analogue, which should not coordinate to the positively charged phosphorus so readily. The 3- or 4-pyridyl analogue also would provide some evidence for the ‘pre-organisation’ mechanistic hypothesis given in section 4.2.3. If the hypothesis is valid, the 4-pyridyl analogue would be most unlikely to result in ether formation. Conversely, if ether formation occurs, it is likely that the oxidation observed in the case of 4-methoxybenzyl alcohol (Scheme 64) should be precluded.

Scheme 65

5.0 General conclusions

Four acyclic analogues of the Hendrickson reagent, tributylphosphonium anhydride triflate 120, tricyclohexylphosphonium anhydride triflate 130, triphenylphosphonium anhydride tetrafluoroborate 42, and diphenyl-2-pyridylphosphonium anhydride triflate 137, were synthesised. Analogues 120, 130 and 137 were characterised as their more stable aminophosphonium salts 122, 132 and 141. When the reagents 120, 130 and 137 were used in the esterification of (–)-menthol, the major reaction pathway observed was that of syn elimination, giving a mixture of 2- and 3-menthene 36 and 37 in a ratio of 1 : 2 respectively. Problems were encountered with alkylation side products during attempts to esterify a primary alcohol using 42 and thus, it was not pursued as a method for esterification of (–)-menthol. In the reactions employing reagents 120 and 130, stable oxyphosphonium intermediates, (–)-menthylxytributylphosphonium triflate 123 and (–)-menthylxytricyclohexylphosphonium triflate 133 were isolated and characterised. Attempts to achieve an S_N2 type displacement by changing the counter-
ion of (−)-menthloxytributylphosphonium triflate 123 were not successful. The most interesting reagent, diphenyl-2-pyridylphosphonium anhydride triflate 137, was found to be a useful reagent for the synthesis of acyclic dialkyl ethers from primary alcohols. Although simpler to perform than the recently published ether synthesis procedure of Mukaiyama,246 it is not as general, as the Mukaiyama procedure can be used with secondary alcohols.
CHAPTER FOUR

POLYMER-SUPPORTED REAGENTS
Following the exploration of both cyclic and acyclic analogues of the Hendrickson reagent 27 in Chapters Two and Three, the five-membered cyclic analogue 90 was identified as a potential candidate for polymer attachment. One disadvantage with using the Hendrickson reagent 27 is that two moles of triphenylphosphine oxide are liberated per dehydration reaction compared with only one mole in the Mitsunobu reaction. This exacerbates the problem of separation of the product by chromatography. By employing the five-membered cyclic analogue 90 tethered to a polymer support, the two phosphine oxide moieties would remain attached to the polymer support after reaction. The potential advantages of such a reagent would be considerable: (a) removal of the phosphine oxide should be achieved simply by filtration of the polymer beads; (b) the recovered phosphine oxide could be readily converted back into the phosphonium anhydride by treatment with triflic anhydride; (c) azodicarboxylates would not required; (d) competing Mitsunobu-type side reactions such as alkylation of the hydrazine-dicarboxylate should be eliminated. This chapter will investigate the synthesis and use of the polymer-supported five-membered cyclic derivative 56. In addition, the synthesis and use of a reagent, more readily prepared from polymer-supported triphenylphosphine oxide and triflic anhydride will be examined.

1.0 Polymer-supported five-membered cyclic analogue 56

It was anticipated that the polymer-supported five-membered cyclic analogue 56 could be prepared by addition of triflic anhydride to polymer-supported 1,2-bis-
(diphenylphosphinyl)ethane 57. Polymer-supported 1,2-bis(diphenylphosphinyl)ethane 57 could be obtained by attachment of 1,2-bis(diphenylphosphino)ethane to a brominated poly(styrene-co-divinylbenzene) resin, followed by subsequent oxidation. Lightly cross-linked poly(styrene-co-divinylbenzene) resin was chosen as support because of its stability, reasonably high loading capacity and good swelling characteristics, as well as the literature precedence for attachment of phosphines to poly(styrene-co-divinylbenzene) resins.

1.1 Synthesis and characterisation of polymer-supported 1,2-bis(diphenylphosphinyl)ethane 57

1.1.1 Bromination of poly(styrene-co-divinylbenzene)

Polymer-supported 1,2-bis(diphenylphosphinyl)ethane 57 was prepared from brominated poly(styrene-co-divinylbenzene) 59. Although commercially available, the brominated poly(styrene-co-divinylbenzene) 59 was readily prepared in-house. Treatment of a solution of washed poly(styrene-co-divinylbenzene) resin in carbon tetrachloride with thallium (III) acetate, followed by addition of bromine gave brominated poly(styrene-co-divinylbenzene) 59 after heating at reflux for 2.5 hours (Scheme 66). The incorporation of bromine was found to be 3.53 mmol/g (28.21%) as determined by elemental analysis (51% of phenyl rings brominated).

\[
\text{Tl(OAc)}_3, \text{Br}_2 \\
\text{CCl}_4 \\
2.5 \text{ hr, reflux}
\]

Scheme 66

A mixture of thallium (III) acetate and bromine is known to be a mild and efficient catalyst for electrophilic aromatic substitution, giving predominately monobromination and para bromination in monosubstituted benzenes.\textsuperscript{247} The mechanism, suggested by
McKillop, Bromley and Taylor\textsuperscript{247} involves formation of a π-complex between thallium (III) acetate and the aromatic ring of the polymer (Scheme 67). Subsequent reaction with bromine forms a second π-complex and then the ion pair \textbf{155}. Decomposition of \textbf{155} into bromothallium diacetate involves the simultaneous formation of the brominated poly(styrene-co-divinylbenzene) \textbf{59}.

\[ Tl(OAc)_3 + Br_2 \rightarrow [TlBr(OAc)_3]^{-} \]

Scheme 67

\textbf{1.1.2 Synthesis of polymer-supported 1,2-bis(diphenylphosphinyl)ethane 57}

With the brominated poly(styrene-co-divinylbenzene) \textbf{59} in hand, formation of polymer-supported 1,2-bis(diphenylphosphino)ethane \textbf{60} was carried out (Scheme 68). The phosphorus anion \textbf{58} was formed by treatment of 1,2-bis(diphenylphosphino)ethane with a solution of the radical anion of naphthalene (preformed \textit{in situ} by addition of sodium to a solution of naphthalene in THF). The reaction of \textbf{58} with a slurry of the brominated poly(styrene-co-divinylbenzene) resin \textbf{59} afforded polymer-supported 1,2-bis(diphenylphosphino)ethane \textbf{60} after stirring at room temperature for three days (via a S\textsubscript{RN1} mechanism).\textsuperscript{248} Subsequent oxidation with hydrogen peroxide (Chapter Two, section 1.1) gave the desired polymer-supported 1,2-bis(diphenylphosphinyl)ethane \textbf{57}. The incorporation of phosphorus into \textbf{57} was found to be 1.9 mmol/g (5.89\%) as determined by elemental analysis (30\% of phenyl rings contain a bound
PO(C₆H₅)CH₂CH₂P(O)(C₆H₅)₂ group). Analysis of the polymer-supported reagent 57 by gelphase ³¹P NMR spectroscopy confirmed the presence of the phosphine oxide (δ 33.3 ppm) (Figure 18). Analysis of the resin 57 by FTIR showed a strong absorbance at 1180 cm⁻¹ attributable to the P=O group.

![Scheme 68](image)

**Figure 18.** Gelphase ³¹P NMR spectrum (162 MHz) of polymer-supported 1,2-bis(diphenylphosphinyl)ethane 57.

### 1.2 Synthesis of polymer-supported five-membered cyclic analogue 56

Following the synthesis of polymer-supported 1,2-bis(diphenylphosphinyl)ethane 57, the corresponding polymer-supported five-membered cyclic analogue 56 was generated by addition of triflic anhydride to a DCM slurry of 57 (Scheme 69).
Due to its sensitivity to moisture, 56 was characterised by $^1$H and $^{31}$P NMR spectroscopy. Upon addition of triflic anhydride to the polymer-supported 1,2-bis(diphenylphosphinyl)ethane 57 (δ 33.3 ppm), a shift in the $^{31}$P NMR spectrum to δ 57.0 ppm, consistent with the formation of the non-polymeric five-membered cyclic analogue 90 (δ 58.6 ppm) (Chapter Two, section 1.3) was observed (Figure 19a). In addition, a single peak at δ -80.3 ppm was observed in the $^{19}$F NMR spectrum of the polymer-supported five-membered cyclic analogue 56, corresponding to the triflate anion (Figure 19b).

![Scheme 69](image-url)

**Figure 19.** Polymer-supported five-membered cyclic analogue 56. (a) Gelphase $^{31}$P NMR spectrum (162 MHz). (b) Gelphase $^{19}$F NMR spectrum (376 MHz).
1.3 Reactions using the polymer-supported five-membered cyclic analogue 56

The use of the polymer-supported cyclic reagent 56 was examined for the esterification of a primary alcohol and the formation of an amide from a primary amine. Successive addition of 4-nitrobenzyl alcohol, 4-nitrobenzoic acid and diisopropylethylamine to a stirred solution of 56 in DCM generated 4-nitrobenzyl 4-nitrobenzoate 61 in high yield (96%) after stirring for two hours at room temperature (Scheme 70). A simple filtration, followed by a sodium hydrogen carbonate wash of the filtrate to remove the diisopropylethylammonium triflate, gave the desired product 61 cleanly. N-Benzyl 4-nitrobenzamide 112 also was formed in high yield (93%) after stirring a solution of the activated species 156 with benzylamine and diisopropylethylamine for two hours at room temperature (Scheme 70).

\[ \text{Scheme 70} \]

The activated species 156 was obtained \textit{in situ} by stirring a solution of 4-nitrobenzoic acid and the polymer-supported cyclic reagent 56 in DCM for two hours at room temperature. The formation of an activated species such as 156 has been shown previously to be required for amide formation in solution-phase, as addition of a 1 : 1
mixture of 4-nitrobenzoic acid and benzylamine to the Hendrickson reagent 27, in the presence of diisopropylethylamine, formed the unreactive benzylaminotriphenylphosphonium triflate 113 (Chapter Two, section 1.3). From these simple reactions, it can be seen that the polymer-supported five-membered cyclic analogue 56 is a useful reagent for the formation of esters from primary alcohols and amides from primary amines, does not require chromatography for product purification, and avoids the use of azodicarboxylates. The use of 56 was not explored further because during the course of this work, a reagent formed from the reaction of polymer-supported triphenylphosphine oxide and triflic anhydride was shown to work just as well and was easier to prepare.

2.0 Polymer-supported triphenylphosphine ditriflate 157

During the synthesis of the polymer-supported five-membered cyclic analogue 56, the possibility of forming an oxyphosphonium species from polymer-supported triphenylphosphine oxide 158 and triflic anhydride was examined. The formation of a P-O-P linkage similar to that found in the polymer-supported five-membered cyclic analogue 56 would require the highly unlikely joining of two phosphine oxide moieties on either the same or different polymer chains (as illustrated by 159).

2.1 Synthesis and characterisation of polymer-supported triphenylphosphine ditriflate 157

Initially, commercially available polymer-supported triphenylphosphine (polystyrene cross-linked with 2% divinylbenzene) was oxidised to its corresponding phosphine oxide 158 by stirring overnight with hydrogen peroxide in DCM (Chapter Two, section
1.1). Addition of triflic anhydride to an NMR tube of swollen polymer-supported triphenylphosphine oxide 158 in CD$_2$Cl$_2$ under nitrogen showed a downfield movement in the $^{31}$P NMR spectrum from $\delta$ 27.9 ppm to $\delta$ 53.3 ppm. A $^{31}$P NMR signal at $\delta$ 42.7 ppm was generated following the addition of only 0.5 equivalents of triflic anhydride (Figure 20).

**Figure 20.** Stacked gelphase $^{31}$P NMR spectra (162 MHz) of polymer-supported triphenylphosphine oxide 158 with (a) triflic anhydride (0 equiv.), (b) triflic anhydride (0.5 equiv.), (c) triflic anhydride (1.0 equiv.) = polymer-supported triphenylphosphine ditriflate 157.

From this data, it was proposed that the structure of the reagent formed from polymer-supported triphenylphosphine oxide and triflic anhydride was most likely polymer-supported triphenylphosphine ditriflate 157. The extreme moisture sensitivity of 157 made characterisation difficult. The gelphase $^{31}$P NMR data obtained can be justified by the existence of a rapid equilibrium (on the $^{31}$P NMR timescale) between the
phosphine oxide moiety 158, triflic anhydride and the phosphine ditriflate 157, with the equilibrium lying very much towards the ditriflate 157 (Scheme 71).

![Scheme 71](image)

If two polymer chains were to join together to form the P-O-P bond linkage (as illustrated by 159), one would anticipate a gelphase $^{31}$P NMR signal much closer to that of the solution-phase Hendrickson reagent 27 ($\delta$ 75.6 ppm). Interestingly, the original structure proposed by Hendrickson$^{84}$ for 27 was ‘triphenylphosphine ditriflate’ 160, i.e. a structure analogous to 157. It was only later that this structure was shown to be incorrect by a Norwegian group$^{85}$ and that the product formed upon treatment of triphenylphosphine oxide with triflic anhydride was in fact 27. Although the phosphonium ditriflate 160 is almost certainly formed first, it can be rapidly attacked by a second molecule of triphenylphosphine oxide to form the phosphonium anhydride 27. In the case of polymer-supported triphenylphosphine oxide 158, once the ditriflate 157 has been formed, phosphonium anhydride formation cannot occur unless there is a second phosphine oxide moiety in close proximity on another (or the same) polymer chain (which is highly unlikely).

![27 and 160](image)

Attempts to form 160 in solution were carried out by addition of 0.2 equivalents of triphenylphosphine oxide to a CD$_2$Cl$_2$ solution containing triflic anhydride. In this case,
the Hendrickson reagent 27 was formed immediately, as evidenced by a $^{31}$P NMR singlet at $\delta$ 79.6 ppm. In an effort to find additional supporting evidence for the proposed structure 157, obtained from addition of triflic anhydride to polymer-supported triphenylphosphine oxide 158, attempts were made to synthesise structures analogous to 160 with less reactive anhydrides. It was anticipated that structures such as 161 and 162, formed from the less reactive acid anhydrides trifluoroacetic anhydride and acetic anhydride, would be less likely to be rapidly attacked by triphenylphosphine oxide and form the corresponding phosphonium anhydride. However, addition of either trifluoroacetic anhydride or acetic anhydride to an NMR tube containing triphenylphosphine oxide in CD$_2$Cl$_2$ gave no reaction following analysis by $^{31}$P NMR spectroscopy. Thus, it was difficult to form species analogous to 160 in solution.

![Chemical Structures](attachment:structures.png)

Analysis of polymer-supported triphenylphosphine ditriflate 157 by gelphase $^{19}$F NMR showed a broad singlet at $\delta$ –80.1 ppm, which is further upfield and significantly broader than that observed for triflic anhydride ($\delta$ –73.6 ppm) or triflic acid ($\delta$ –78.3 ppm) in the presence of poly(styrene-co-divinylbenzene). A protonated phosphine oxide 163 with similar gelphase $^{31}$P NMR ($\delta$ 52.1 ppm) and $^{19}$F NMR ($\delta$ -80.3 ppm) shifts to 157 was obtained following treatment of a slurry of polymer-supported triphenylphosphine oxide 158 in CD$_2$Cl$_2$ with triflic acid. An attempt to form 4-toluic anhydride 164 from its corresponding acid in the presence of the polymer-supported protonated phosphine oxide 163 and diisopropylethylamine yielded unreacted acid, thus verifying that the structure of 157 was not merely the protonated phosphine oxide 163 (Scheme 72).
By comparison, tetrabutylammonium triflate has a $^{19}$F NMR shift at $\delta$ -80.6 ppm. A time-averaged $^{19}$F NMR shift of $\delta$ -80.1 ppm, which is between that of triflic acid ($\delta$ – 78.3 ppm) and free triflate ion ($\delta$ -80.6 ppm), does not seem unreasonable for structure 157. Equilibration of the fluorines could be achieved via the rapid equilibrium shown in Scheme 71, or via a (transient) symmetrical phosphorane intermediate 165 in equilibrium with 157 (Scheme 73).

The species 157 also was characterised as its more stable benzylaminophosphonium triflate 166, following reaction with benzylamine in the presence of diisopropylethylamine (Scheme 74). Two peaks were observed in the gelphase $^{31}$P NMR spectrum at $\delta$ 39.8 ppm (compound 166) and $\delta$ 30.0 ppm (polymer-supported triphenylphosphine oxide 158) in a ratio of 9 : 1. The non-polymeric benzylaminotriphenylphosphonium triflate 113 gave a $^{31}$P NMR signal at $\delta$ 39.4 ppm (Chapter Two, section 1.3). The formation of polymer-supported benzylaminotriphenylphosphonium triflate 166 also helped to eliminate structures similar to 159 because in those cases, the
formation of the polymer-supported aminophosphonium triflate 166 would show a 1 : 1 ratio of the oxide 158 to the aminophosphonium triflate 166 following the addition of benzylamine and diisopropylethylamine. This was not observed in the present case. The formation of approximately 10% phosphine oxide (9 : 1 ratio of $^{31}$P NMR peaks) is most likely due to the equilibrium shown in Scheme 71, with approximately 10% 158.

![Scheme 74](image)

**Scheme 74**

### 2.2 Reactions using polymer-supported triphenylphosphine ditriflate 157

A range of dehydration reactions were carried out using polymer-supported triphenylphosphine ditriflate 157 to demonstrate its versatility as a dehydrating reagent. A small excess of the polymer-supported phosphine oxide 158 was used in all examples for consistency with previous reactions (see Chapter One, section 1.0).

#### 2.2.1 Ester formation from primary alcohols

Initially, treatment of 157 with 4-nitrobenzyl alcohol, 4-nitrobenzoic acid and diisopropylethylamine gave the ester, 4-nitrobenzyl 4-nitrobenzoate 61, in high yield (95%) after stirring for two hours at room temperature (Table 9, entry 1). The product was obtained cleanly following filtration and washing of the filtrate with sodium hydrogen carbonate to remove the diisopropylethylammonium triflate. The reagent 157 was very sensitive to moisture and thus, attempts to isolate 157 by filtration before resuspension in DCM and subsequent addition of 4-nitrobenzyl alcohol, 4-nitrobenzoic
acid and diisopropylethylamine gave none of the desired ester, 4-nitrobenzyl 4-nitrobenzoate 61. Thus, 157 appears to be best prepared and used directly in situ.

2.2.2 Amide formation

A library of amides was prepared using polymer-supported triphenylphosphine ditriflate 157 (Table 9, entries 2-13). In a similar manner to the use of the polymer-supported five-membered cyclic analogue 56, addition of 4-nitrobenzoic acid to polymer-supported triphenylphosphine ditriflate 157 in DCM preformed the acyloxyphosphonium salt. Subsequent addition of benzylamine and diisopropylethylamine formed N-benzyl 4-nitrobenzamide 112 in good yield (96%) after two hours at room temperature (Table 9, entry 2). Recycling of the recovered polymer-supported triphenylphosphine oxide 158 three times gave reproducible yields, all greater than 90%, in the synthesis of N-benzyl 4-nitrobenzamide 112. N-Benzyl-4-methoxybenzamide 167 was obtained in a similar fashion in high yield (88%) via dehydration with polymer-supported triphenylphosphine ditriflate 157 (Table 9, entry 3). Interestingly, the use of two equivalents of 4-nitrobenzoic acid with 157, benzylamine and diisopropylethylamine gave N-benzyl-N-(4-nitrobenzoyl)-4-nitrobenzamide 168 in high yield (90%) after stirring at room temperature overnight (Scheme 75) (Table 9, entry 4). The main difference observed in the 1H NMR spectra between N-benzyl 4-nitrobenzamide 112 and N-benzyl-N-(4-nitrobenzoyl)-4-nitrobenzamide 168 was the downfield shift and loss of multiplicity in the benzyl protons (from a doublet at δ 4.57 ppm for 112 to a singlet at δ 5.23 ppm for 168). This example shows that 157 generated a highly reactive acylating reagent, capable of acylating an amide under mild conditions.
**Scheme 75**

**Table 9.** Useful synthetic transformations using polymer-supported triphenylphosphine ditriflate 157.

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Substrate</th>
<th>Nucleophile</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-NO₂-C₆H₄-CH₂-COOH</td>
<td>4-NO₂-C₆H₄-COOH</td>
<td>4-Nitrobenzyl 4-nitrobenzoate 61</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>4-NO₂-C₆H₄-CH₂-COOH</td>
<td>C₆H₄-CH₂-NH₂</td>
<td>N-Benzyl-4-nitrobenzamide 112</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>4-MeO-C₆H₄-CH₂-COOH</td>
<td>C₆H₄-CH₂-NH₂</td>
<td>N-Benzyl-4-methoxybenzamide 167</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>4-NO₂-C₆H₄-COOH&lt;sup&gt;d&lt;/sup&gt;</td>
<td>C₆H₄-CH₂-NH₂</td>
<td>N-Benzyl-4-(4-nitrobenzoyl)-4-nitrobenzamide 168</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>4-MeO-C₆H₄-CH₂-COOH</td>
<td>4-NO₂-C₆H₄-NH₂</td>
<td>N-(4-Nitrophenyl)-4-methoxybenzamide 169</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td>4-NO₂-C₆H₄-CH₂-COOH</td>
<td>4-OMe-C₆H₄-NH₂</td>
<td>N-(4-Methoxyphenyl)-4-nitrobenzamide 170</td>
<td>72</td>
</tr>
<tr>
<td>7</td>
<td>4-MeO-C₆H₄-CH₂-COOH</td>
<td>4-OMe-C₆H₄-NH₂</td>
<td>N-(4-Methoxyphenyl)-4-methoxybenzamide 171</td>
<td>71</td>
</tr>
<tr>
<td>8</td>
<td>4-NO₂-C₆H₄-CH₂-COOH</td>
<td>C₆H₄-NH</td>
<td>N-(4-Nitrobenzoyl)piperidine 172</td>
<td>84</td>
</tr>
<tr>
<td>9</td>
<td>4-MeO-C₆H₄-CH₂-COOH</td>
<td>C₆H₄-NH</td>
<td>N-(4-Methoxybenzoyl)piperidine 173</td>
<td>90</td>
</tr>
<tr>
<td>10</td>
<td>4-NO₂-C₆H₄-CH₂-COOH</td>
<td>tPr₂NH</td>
<td>N₄,N₄-Diisopropyl-4-nitrobenzamide 174</td>
<td>86</td>
</tr>
<tr>
<td>11</td>
<td>4-MeO-C₆H₄-CH₂-COOH</td>
<td>tPr₂NH</td>
<td>N₄,N₄-Diisopropyl-4-methoxybenzamide 175</td>
<td>77</td>
</tr>
<tr>
<td>12</td>
<td>4-NO₂-C₆H₄-CH₂-COOH</td>
<td>4-NO₂-C₆H₄-NH₂</td>
<td>N-(4-Nitrophenyl)-4-nitrobenzamide 176</td>
<td>63</td>
</tr>
<tr>
<td>13</td>
<td>C₆H₄-COOH</td>
<td>C₆H₄-SO₂-NH₂</td>
<td>N-Benzylbenzenesulfonamide 178</td>
<td>71</td>
</tr>
<tr>
<td>14&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Z-Gly-Phe-OH</td>
<td>H-Val-OMe.HCl</td>
<td>L-L-Z-Gly-Phe-Val-OMe 180</td>
<td>65</td>
</tr>
<tr>
<td>15</td>
<td>C₆H₄-C(Ο)-NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>—</td>
<td>Benzonitrile 182</td>
<td>88</td>
</tr>
<tr>
<td>16</td>
<td>&lt;i&gt;MeSo&lt;/i&gt;-hydrobenzoin</td>
<td>—</td>
<td>(E)-Stilbene oxide 30</td>
<td>85</td>
</tr>
<tr>
<td>17</td>
<td>C₆H₄-CH₂-OH</td>
<td>C₆H₄-CH₂-OH</td>
<td>Dibenzyl ether 145</td>
<td>73</td>
</tr>
<tr>
<td>18</td>
<td>4-NO₂-C₆H₄-CH₂-COOH</td>
<td>4-NO₂-C₆H₄-CH₂-COOH</td>
<td>Bis(4-nitrobenzoyl)ether 142</td>
<td>42</td>
</tr>
<tr>
<td>19</td>
<td>4-NO₂-C₆H₄-CH₂-COOH</td>
<td>MeO-C₆H₄-OH</td>
<td>O-(4-Nitrobenzoyl)-4-methoxyphenol 66</td>
<td>88</td>
</tr>
<tr>
<td>20</td>
<td>CH₃-C₆H₄-COOH</td>
<td>CH₃-C₆H₄-COOH</td>
<td>4-Toluic anhydride 164</td>
<td>95</td>
</tr>
<tr>
<td>21</td>
<td>4-Cl-C₆H₄-CH₂-OH</td>
<td>Na₅&lt;sup&gt;f&lt;/sup&gt;</td>
<td>4-Chlorobenzyl azide 65</td>
<td>89</td>
</tr>
<tr>
<td>22</td>
<td>4-Cl-C₆H₄-CH₂-OH</td>
<td>CH₃-C(Ο)-SH</td>
<td>4-Chlorobenzyl thiocacetate 64</td>
<td>91</td>
</tr>
<tr>
<td>23</td>
<td>HO-C(CH₃)₂-COOH</td>
<td>—</td>
<td>Oxacycloundecan-2-one 186</td>
<td>36</td>
</tr>
<tr>
<td>24&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4-NO₂-C₆H₄-COOH</td>
<td>Cyclohexanol</td>
<td>O-(4-Nitrobenzoyl)-cyclohexanol 76</td>
<td>85</td>
</tr>
<tr>
<td>25&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4-NO₂-C₆H₄-COOH</td>
<td>(–)-Menthol</td>
<td>O-(4-Nitrobenzoyl)-(–)-menthol 69</td>
<td>84</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reaction conditions: polymer-supported triphenylphosphine oxide 158 (1.35 equiv.), triflic anhydride (1.0 equiv.), substrate (1.0 equiv.), nucleophile (1.0 equiv.), diisopropylethylamine (3.5 equiv.), DCM (10 mL).<br><sup>b</sup>Reaction times: entries 1-3 (2 hr, RT), entries 4-11, 13-17 and 19-25 (overnight, RT), entries 12 and 18 (1 week, RT).<br><sup>c</sup>Isolated yields. <sup>d</sup>Acid (2.0 equiv.) was used. <sup>e</sup>HOBt (1.0 equiv.) and excess diisopropylethylamine (5.5 equiv.) were used.
A large number of the amides prepared by dehydration with polymer-supported triphenylphosphine ditriflate 157 (Table 9, entries 5-11, 169-175) were obtained in reasonable yields (71-90%), yet did require longer reaction times (overnight at room temperature) to reach completion. The combination of 4-nitrobenzoic acid and 4-nitroaniline (Table 9, entry 12, 176) was particularly sluggish, requiring one week at room temperature to reach completion. This could result from the deactivating electron withdrawing nitro groups on both reactants or possibly, there is a competing (equilibrium) O-acylation of the nitro group of 4-nitroaniline by the activated acid 177, which deactivates the amino group (as suggested in Scheme 76). In addition, N-benzoyl-benzenesulfonamide 178 was obtained in a 71% yield by the coupling of benzoic acid and benzenesulfonamide 179 (prepared from benzenesulfonyl chloride and ammonia) with 157 (Table 9, entry 13). From these examples, polymer-supported triphenylphosphine ditriflate 157 appears to be a simple and useful procedure for the formation of amides from acids and amines.
2.2.3 Peptide formation

The use of polymer-supported triphenylphosphine ditriflate 157 for peptide bond formation also was examined. The extent of racemization was examined using Arteunis’ test\(^\text{249}\) (the coupling of Z-Gly-Phe-OH and Val-OMe.HCl). Initially, the reaction was carried out in the standard manner by consecutive addition of Val-OMe.HCl and diisopropylethylamine to a slurry of the activated acid (preformed by stirring Z-Gly-Phe-OH and 157 at room temperature in DCM for two hours). However, following work-up and analysis by \(^1\)H NMR spectroscopy, it was established that the Z protecting group was not stable under such acidic reaction conditions. Thus, the order of addition was changed and the activated acid generated in the presence of base (diisopropylethylamine). Subsequent addition of H-Val-OMe.HCl formed the desired tripeptide Z-Gly-Phe-Val-OMe 180 after stirring at room temperature overnight, yet a 1:1 mixture of epimers was detected by \(^1\)H NMR spectroscopy, with characteristic peaks of the L,L-epimer (δ 0.74, 2 × d, (CH\(_3\))\(_2\)CH and δ 3.65, s, CH\(_3\)O) and D,L-epimer (δ 0.82 + 0.85, 2 × d, (CH\(_3\))\(_2\)CH and δ 3.64, s, CH\(_3\)O) consistent with those previously reported in the literature.\(^\text{249}\) In spite of this, the use of racemization-suppressing agent HOBT did allow Z-Gly-Phe-Val-OMe 180 (Table 9, entry 14) to be synthesised cleanly from polymer-supported triphenylphosphine ditriflate 157 as a single epimer (L,L) (none of the D,L-epimer was observed by \(^1\)H NMR spectroscopy) in reasonable yield (65%) (Scheme 77). In this reaction, the activated acid is generated first by the attack of Z-Gly-Phe-OH on the polymer-supported triphenylphosphine ditriflate 157. The acid is rapidly displaced in the present of HOBT to give the corresponding HOBT activated ester 181. Nucleophilic attack by H-Val-OMe.HCl on the active ester 181 then generates the desired tripeptide Z-Gly-Phe-Val-OMe 180.
2.2.4 General transformations

A range of other general transformations were performed using the polymer-supported triphenylphosphine ditriflate 157. Benzonitrile 182 (Table 9, entry 15) was formed by refluxing benzamide with 157 and diisopropylethylamine in DCM overnight. The epoxide, \((E)\)-stilbene oxide 30 (Table 9, entry 16), was obtained in good yield (85%) by stirring a slurry of polymer-supported triphenylphosphine ditriflate 157 in DCM with meso-hydrobenzoin and diisopropylethylamine at room temperature overnight (Scheme 78). Notably, the reagent 157 gave the epoxide 30 exclusively as its \(\textit{trans}\) isomer though an \(\text{S}_\text{N}2\)-type displacement.

Addition of two equivalents of benzyl alcohol to polymer-supported triphenylphosphine ditriflate 157 and diisopropylethylamine generated the symmetrical ether, dibenzyl ether 145 (Table 9, entry 17), in reasonable yield (73%) after stirring at room temperature overnight.
temperature overnight in DCM. The formation of bis(4-nitrobenzyl)ether 142 (Table 9, entry 18) from 4-nitrobenzyl alcohol and 157, occurred in 42% yield after stirring for one week at room temperature. The presence of electron withdrawing NO2 groups on both reactants may again be the cause of such a sluggish reaction.

Interestingly, a mixed ether-forming reaction coupling 4-nitrobenzyl alcohol with 4-methoxyphenol, yielded O-(4-nitrobenzyl)-4-methoxyphenol 66 (Table 9, entry 19) in high yield (88%) after stirring overnight at room temperature. 4-Toluic anhydride 164 (Table 9, entry 20) also was formed in good yield (95%), following the reaction of two equivalents of 4-toluic acid with polymer-supported triphenylphosphine ditriflate 157 and diisopropylethylamine in DCM at room temperature overnight. Consecutive addition of sodium azide (as a suspension in DMF) and diisopropylethylamine to a slurry of 157 and 4-chlorobenzyl alcohol in DCM generated 4-chlorobenzyl azide 65 (Table 9, entry 21) after stirring at room temperature overnight. 4-Chlorobenzyl thioacetate 64 (Table 9, entry 22) was obtained by treatment of a mixture of polymer-supported triphenylphosphine ditriflate 157 and 4-chlorobenzyl alcohol in DCM with thiolacetic acid and diisopropylethylamine. The synthesis of a nitrile, an epoxide, ethers, an anhydride, an azide and a thioacetate demonstrates the ability of polymer-supported triphenylphosphine ditriflate 157 to bring about a wide variety of simple transformations.

2.2.5 Electrophilic aromatic acylation

In addition to the general transformations performed in section 2.2.4, polymer-supported triphenylphosphine ditriflate 157 was investigated as a means for
electrophilic aromatic acylation. It was anticipated that an activated acid such as 177 could act as an acylating agent for activated aromatics such as anisole to give ketone 183 (Scheme 79). Treatment of a DCM solution of polymer-supported triphenylphosphine ditriflate 157 with 4-nitrobenzoic acid would presumably generate the activated acid 177 after stirring at room temperature for two hours. However, subsequent addition of anisole gave no reaction after stirring at room temperature overnight. This was confirmed by analysis of the crude reaction mixture by $^1$H NMR spectroscopy. Repeating the reaction at reflux for two days also gave unreacted anisole following analysis of the crude reaction mixture by $^1$H NMR spectroscopy.

![Scheme 79](image)

**Scheme 79**

### 2.2.6 Macrocyclic lactone formation

The preparation of medium-sized lactones (ring size of eight to eleven) is an important aspect of organic synthesis, particularly because such skeletons are a feature of many biologically active natural products. Numerous approaches to these macrocyclic species have been made and are detailed elsewhere. The activation energy to ring close is dependent on the strain energy of the final ring product. Therefore, the formation of these highly strained lactones has been a challenging topic for some time because of the negative entropy required for their formation. The heat of formation and
relative (to cyclohexane) strain energy of medium ring hydrocarbons is displayed in Table 10.

Table 10. Heats of formation and relative (to cyclohexane) strain energies of cycloalkanes.\textsuperscript{254,255}

<table>
<thead>
<tr>
<th>Ring size</th>
<th>Heat of formation ((\Delta H^\circ f)) kcal/mol</th>
<th>Strain energy kcal/mol</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>-29.5</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>-28.2</td>
<td>6.2</td>
</tr>
<tr>
<td>8</td>
<td>-29.7</td>
<td>9.6</td>
</tr>
<tr>
<td>9</td>
<td>-31.7</td>
<td>12.5</td>
</tr>
<tr>
<td>10</td>
<td>-36.3</td>
<td>12.9</td>
</tr>
<tr>
<td>11</td>
<td>-42.9</td>
<td>11.2</td>
</tr>
<tr>
<td>12</td>
<td>-55.0</td>
<td>4.0</td>
</tr>
</tbody>
</table>

In general, the synthesis of macrocyclic lactones is carried out by intramolecular dehydration of \(\omega\)-hydroxycarboxylic acids. The crucial problem in lactonising a \(\omega\)-hydroxycarboxylic acid 184 is to avoid polymerisation (intermolecular reactions) and direct the reaction towards the desired monomeric (macrolide) or dimeric (diolide) lactone (Scheme 80). In general, polymerisation can be overcome, to a certain extent, by employing high dilution conditions.

![Scheme 80]
It was considered that tethering a $\omega$-hydroxycarboxylic acid 184 to a polymer support may mimic such dilute conditions by site isolation and bring about the desired intramolecular cyclisation. Thus, the reaction of polymer-supported triphenylphosphine ditriflate 157 with 10-hydroxydecanoic acid may generate the activated species 185, allowing intramolecular cyclisation to occur. Accordingly, 10-hydroxydecanoic acid and diisopropylethylamine were added to a DCM solution of polymer-supported triphenylphosphine ditriflate 157 and the solution stirred overnight at room temperature (Scheme 81).

**Scheme 81**

Analysis of the crude reaction mixture by $^1$H NMR spectroscopy indicated the presence of the desired macrocyclic lactone, oxacycloundecane-2-one 186 and unreacted 10-hydroxydecanoic acid in a 1 : 1 ratio respectively. Following chromatography, oxacycloundecane-2-one 186 was obtained in a 36% yield (Table 9, entry 23). Although it initially appeared from analysis by $^1$H NMR spectroscopy that a 50% yield of oxacycloundecane-2-one 186 could have been obtained, some of the 10-
hydroxydecanoic acid may still be attached to the polymer as part of the activated species 185 and could have therefore been lost during the filtration step of the work-up. Nonetheless, this preliminary experiment indicates that the use of polymer-supported triphenylphosphine ditriflate 157 may be a viable method for the synthesis of macropolymer lactones, which eliminates the need to use high-dilution conditions.

2.2.7 Ester formation from secondary alcohols

Polymer-supported triphenylphosphine ditriflate 157 has been shown to be an effective dehydrating reagent in the formation of an ester 61 from a primary alcohol (Chapter Four, section 2.2.1). The reagent 157 was therefore investigated for the esterification of optically active alcohols with inversion of configuration. However, when a solution of polymer-supported triphenylphosphine ditriflate 157 in DCM was refluxed overnight with (–)-menthol, 4-nitrobenzoic acid and diisopropylethylamine, the presence of 2- and 3-menthene 36 and 37, (–)-menthol and neomenthyl 4-nitrobenzoate 67 were identified following analysis by GC/MS in a ratio of 79 : 16 : 5 respectively (Scheme 82). Thus, (–)-menthol was undergoing elimination rather than the desired S_N_2 substitution in the presence of polymer-supported triphenylphosphine ditriflate 157.

Scheme 82
In order to avoid competing elimination, the order of addition was altered and DMAP was employed as an activating agent (a similar approach was adopted in Chapter One, section 6.0 using the Hendrickson reagent 27). The use of polymer-supported triphenylphosphine ditriflate 157 and DMAP was initially tested on the formation of O-(4-nitrobenzoyl)-cyclohexanol 76. Addition of DMAP to the polymer-supported acyloxyphosphonium salt (preformed by addition of 4-nitrobenzoic acid to 157 in DCM) presumably generates the activated ester of 4-nitrobenzoic acid 89. Subsequent treatment with cyclohexanol and diisopropylethylamine gave O-(4-nitrobenzoyl)-cyclohexanol 76 in good yield (85%) after stirring at room temperature overnight (Table 9, entry 24). The product was obtained cleanly after a sodium hydrogen carbonate wash to remove the DMAP and diisopropylethylammonium triflate by-products. The use of a catalytic amount of DMAP (0.1 equiv.) also was explored, however after stirring at room temperature overnight, analysis by GC/MS indicated the presence of cyclohexene 75, O-(4-nitrobenzoyl)-cyclohexanol 76 and cyclohexanol in a ratio of 68 : 18 : 14. The formation of cyclohexene 75 implies competitive attack on 157 by cyclohexanol and indicates that at least one equivalent of DMAP is required to prevent elimination.

The synthesis of O-(4-nitrobenzoyl)-(–)-menthol 69 also was attempted using polymer-supported triphenylphosphine ditriflate 157. After stirring (–)-menthol with the activated ester of 4-nitrobenzoic acid 89 (preformed from 157, 4-nitrobenzoic acid and DMAP) in DCM overnight, O-(4-nitrobenzoyl)-(–)-menthol 69 was obtained in good yield (84%) (Table 9, entry 25) and retention of configuration was observed (Scheme 83). A comparison of the purity of O-(4-nitrobenzoyl)-(–)-menthol 69 obtained using the Hendrickson reagent 27, after isolation by chromatography and using polymer-
supported triphenylphosphine ditriflate 157, after a sodium hydrogen carbonate wash is shown in Figure 21.

Scheme 83

Figure 21. $^1$H NMR spectra (200 MHz) comparing $O$-(4-nitrobenzoyl)-(--)-menthol 69 prepared using (a) the Hendrickson reagent 27 following chromatography and (b) polymer-supported triphenylphosphine ditriflate 157.
3.0 General conclusions

Polymer-supported 1,2-bis(diphenylphosphinyl)ethane 57 was synthesised from brominated poly(styrene-co-divinylbenzene) 59 in two steps. The reaction of 57 with triflic anhydride yielded the polymer-supported five-membered cyclic analogue 56, which was subsequently shown to be useful for the synthesis of a simple ester and amide in good yield.

A new dehydrating reagent, polymer-supported triphenylphosphine ditriflate 157, was synthesised more conveniently from the oxidised form of commercially available polymer-supported triphenylphosphine and triflic anhydride. A large array of simple amides, a tripeptide, esters (from primary and secondary alcohols), a nitrile, an epoxide, ethers, an anhydride, an azide, a thioacetate and a macrocyclic lactone were synthesised using 157 to demonstrate that 157 is a general dehydrating-type reagent. Attempts to acylate an activated aromatic ring using polymer-supported triphenylphosphine ditriflate 157 were not successful. In the case of secondary alcohol esterification, elimination was avoided by changing the order of addition of reactants and employing and activating agent. Esters were obtained from optically active alcohols with retention.

The advantage of both the polymer-supported triphenylphosphine ditriflate 157 and the polymer-supported five-membered cyclic reagent 56 is that the main by-product, the phosphine oxide, remains attached to the polymer support. Following filtration of the polymer beads, all products can be cleanly obtained with a sodium hydrogen carbonate wash of the filtrate to remove the diisopropylethylammonium triflate. An additional advantage of these polymeric reagents 56 and 157 is that after reaction, the polymer is returned as its oxide, ready for recycling. The re-use of 157 several times showed no
loss of activity. Thus, \textbf{56} and \textbf{157} are effective dehydrating reagents which avoid the
use of azodicarboxylates and chromatography to remove the phosphine oxide.
CHAPTER FIVE

FURTHER CONSIDERATIONS OF THE MITSUNOBU AND HENDRICKSON REAGENTS
1.0 Phosphitylation via the Hendrickson reagent 27

During the course of the work described in previous chapters, some preliminary investigations of other novel transformations using the Hendrickson Reagent 27 were explored. Phosphitylation of alcohols using 27 was considered as an extension of the work previously carried out by Jenkins,\textsuperscript{256} where the Mitsunobu reaction was used to phosphitylate primary, secondary and tertiary alcohols. Trivalent phosphorus esters are important and versatile intermediates for the synthesis glycosyl phosphates\textsuperscript{257} and oligodeoxyribonucleotides.\textsuperscript{258} Phosphorylation of less reactive alcohols such as nucleosides is now commonly performed by phosphitylation followed by oxidation.\textsuperscript{259}

Following initial examination of alcohol phosphitylation by the Hendrickson reagent 27, it was anticipated that the use of polymer-supported triphenylphosphine ditriflate 157 could be applied. The latter reagent 157, would allow phosphitylation reactions to be performed without requiring chromatography to remove the phosphine oxide by-product. The initial phosphitylation reactions attempted using the Hendrickson reagent 27 are illustrated in Scheme 84.

![Scheme 84](image-url)
Reaction of the Hendrickson reagent 27 with dimethyl phosphite 187 should generate the oxyphosphonium salt 188. Subsequent reaction with 4-nitrobenzyl alcohol and diisopropylethylamine in DCM gave a complex mixture of products after stirring at room temperature overnight. Analysis of the crude reaction mixture by $^{31}$P NMR spectroscopy indicated the presence triphenylphosphine oxide (δ 29.8 ppm), dimethyl-4-nitrobenzyl phosphite 189 (δ 141.2 ppm), dimethyl phosphite 187 (δ 10.9 ppm), methyl-4-nitrobenzylphosphite 190 (δ 9.7 ppm), methyl-bis(4-nitrobenzyl) phosphite 191 (δ 140.8 ppm) and trimethyl phosphite 192 (δ 141.5 ppm, Lit. δ 141-139.6 ppm) in a ratio of 75 : 8 : 6 : 6 : 2 : 1 respectively. The desired product, assigned as 189, was based on the shift in the $^{31}$P NMR spectrum of δ 141.2 ppm, which is similar to analogous compounds in the literature. Species 191 and 192 were thought to arise by exchange of the methoxy ligand of 189 with 4-nitrobenzyl alcohol, while 190 would have arisen by reaction of the liberated methanol with 188.

Similar results were obtained with benzyl alcohol. Addition of dimethyl phosphite, benzyl alcohol and diisopropylethylamine to a CD$_2$Cl$_2$ solution of the Hendrickson reagent 27 and analysis by $^{31}$P NMR spectroscopy showed the immediate formation of triphenylphosphine oxide (δ 29.3 ppm), benzylidimethyl phosphite 193 (δ 140.7 ppm, Lit. δ 141.28 ppm), dimethyl phosphite 187 (δ 10.9 ppm), benzylmethyl phosphite 194 (δ 9.5 ppm), trimethyl phosphite 192 (δ 141.1 ppm, Lit. δ 141-139.6 ppm) and methylidibenzyl phosphite 195 (δ 140.3 ppm) in a ratio of 73 : 17 : 4 : 2 : 2 : 2 respectively (Scheme 84). When the order of addition was changed and dimethyl phosphite 187 added to a solution of benzyloxytriphenylphosphonium triflate 196 (preformed by addition of benzyl alcohol to a solution of the Hendrickson reagent 27 in CD$_2$Cl$_2$), none of the desired benzylidimethyl phosphite 193 was detected following immediate analysis of the sample by $^{31}$P NMR spectroscopy. Instead, the $^{31}$P NMR
spectrum showed triphenylphosphine oxide (δ 29.0 ppm), dimethyl phosphite 187 (δ 10.8 ppm) and benzyloxytriphenylphosphonium triflate 196 (δ 63.0 ppm) in a ratio of 44 : 29 : 27 respectively (Scheme 85). Dimethyl phosphite 187 was apparently unreactive towards 196.

![Scheme 85](image)

Under Mitsunobu conditions, trialkyl phosphites were formed cleanly from their corresponding dialkyl phosphites.256 The mechanism of phosphitylation via the Mitsunobu reaction is however, thought to proceed through a phosphoramidite intermediate such as 197.256 Therefore, it was anticipated that alcohols might be cleanly phosphitylated using the Hendrickson reagent 27 if the reaction proceeded through a phosphoramidite intermediate.

To test phosphoramidite formation with the Hendrickson reagent 27, a preliminary $^{31}$P NMR experiment was carried out. Addition of dimethyl phosphite 187 and diethylamine to a solution of the Hendrickson reagent 27 in CD$_2$Cl$_2$ (δ 76.0 ppm) generated dimethyl N,N-diethylphosphoramidite 198 (δ 149.9 ppm, Lit.262 δ 151.02 ppm) and triphenylphosphine oxide (δ 29.0 ppm) in a 3 : 17 ratio (Scheme 86). Following successful preparation of the desired phosphoramidite 198, benzyl alcohol and
diisopropylethylamine were added to a fresh solution containing the phosphoramidite 198. After stirring at room temperature overnight, analysis of the crude reaction mixture by $^{31}$P NMR spectroscopy revealed the presence of triphenylphosphine oxide ($\delta$ 30.1 ppm), benzylmethyl phosphite 194 ($\delta$ 9.4 ppm), dimethyl phosphite 187 ($\delta$ 10.8 ppm), benzyldimethyl phosphite 193 ($\delta$ 140.9 ppm, Lit. $\delta$ 141.28 ppm), methylidibenzyl phosphite 195 ($\delta$ 140.4 ppm) and trimethyl phosphite 192 ($\delta$ 141.4 ppm, Lit. $\delta$ 141-139.6 ppm) in a ratio of 79 : 9 : 6 : 4 : 1 : 1 respectively. This ratio was comparable to that obtained earlier (see Scheme 84).

As the various attempts at alcohol phosphitylation using the Hendrickson reagent 27 did not give the desired phosphites 189 or 193 cleanly, the transformation was not attempted with the polymer-supported triphenylphosphine ditriflate 157. It was concluded from these preliminary investigations that the Mitsunobu reaction was far superior to the Hendrickson reagent 27 as a procedure for the phosphitylation of alcohols.

2.0 Methylation of catechols using the Mitsunobu reaction

The methylenedioxy group has special importance in organic synthesis due to its occurrence in natural products and use as a protecting group. Older literature procedures for the methylation of catechols gave only low yields (~10-60%), however more recent methods have improved the yields significantly (~75-95%).

As both the Hendrickson reagent 27 and the Mitsunobu reaction allow dehydration reactions to be achieved under mild conditions, a preliminary investigation of acetal formation using a catechol and an aldehyde under Mitsunobu conditions was carried out (Scheme 87).
Addition of catechol and formaldehyde (generated by heating paraformaldehyde to 150°C) to a THF solution containing triphenylphosphine and DIAD gave a complex mixture of products by $^1\text{H}$ NMR spectroscopy after stirring at room temperature overnight. Attempts to identify species within the mixture following separation by chromatography or mass spectral analysis of TLC samples were not successful. The desired 1,3-benzodioxole 199 was not present in the $^1\text{H}$ NMR spectrum of the crude mixture. The reaction was repeated with the portion-wise addition of formaldehyde over 130 minutes. However, after stirring at room temperature overnight, analysis of the crude reaction mixture by $^1\text{H}$ NMR spectroscopy revealed a complex mixture of products, which could not be separated by HPLC/MS.

In contrast, when 3-methoxycatechol was stirred at room temperature overnight with formaldehyde in the presence of triphenylphosphine and DIAD, analysis of the crude reaction mixture by $^1\text{H}$ NMR spectroscopy indicated the presence of 4-methoxy-1,3-benzodioxole 200 and 3-methoxycatechol in a 3 : 2 ratio (Scheme 87). In an attempt to improve the conversion of 3-methoxycatechol to 200, the reaction was repeated with a slight excess of 3-methoxycatechol and the portion-wise addition of formaldehyde to the reaction over 130 minutes. After stirring at room temperature overnight, analysis of the reaction mixture by $^1\text{H}$ NMR spectroscopy indicated the presence of 4-methoxy-1,3-benzodioxole 200 and 3-methoxycatechol in a 4 : 1 ratio. Separation of the desired product 200 from the mixture by chromatography gave 4-methoxy-1,3-benzodioxole.
In a final example, 3-methoxycatechol was reacted with benzaldehyde in the presence of a THF solution of triphenylphosphine and DIAD. After heating to reflux for two days, analysis of the crude reaction mixture revealed the presence of unreacted 3-methoxycatechol and none of the desired 4-methoxy-2-phenyl-1,3-benzodioxole \textbf{201} (Scheme 87).

A suggested mechanism for the formation of 1,3-benzodioxoles from catechols via the Mitsunobu reaction is illustrated in Scheme 88. Addition of 3-methoxycatechol to the betaine (preformed from triphenylphosphine and DIAD) should generate the protonated betaine \textbf{82} and the anion \textbf{202}. Attack of the protonated betaine \textbf{82} by the anion \textbf{202} should generate \textbf{203}, which is in equilibrium with the phosphorane \textbf{204}. Addition of DIAD to an NMR tube containing triphenylphosphine and 3-methoxycatechol did form the phosphorane \textbf{204} as the major product, as evidenced by a singlet in the $^{31}$P NMR spectrum at $\delta$ -17.9 ppm. The analogous phosphorane formed from catechol had a $^{31}$P NMR shift at $\delta$ -22 ppm.$^{40}$ Addition of formaldehyde to \textbf{203} could then give species \textbf{205} which is in equilibrium with the oxyphosphonium salt \textbf{206}. Subsequent ring closure of \textbf{206} would give the desired 1,3-benzodioxole \textbf{200} with the loss of triphenylphosphine oxide.

It is not clear why the reaction with formaldehyde worked so well with 3-methoxycatechol, but failed completely with catechol. Possibly with catechol, the phosphorane (analogous to \textbf{204}) is very stable, whereas with \textbf{204} the buttressing effect of the OMe group favours formation of the zwitterion \textbf{203}, required for reaction with formaldehyde. The lack of reaction with benzaldehyde could reflect the importance of steric factors, although formaldehyde is well know to be more reactive than benzaldehyde. As employing the Mitsunobu reaction for the methylenation of catechol
itself failed to give the desired 1,3-benzodioxole, it does not appear to be a general procedure for 1,3-benzodioxole formation and hence, was not explored with the Hendrickson reagent 27. Nonetheless, the specific preparation of 200 using the Mitsunobu reaction was successful. This is the first example of 1,3-benzodioxole formation from catechols using the Mitsunobu reaction.

Scheme 88

3.0 Alternatives to azodicarboxylates in the Mitsunobu reaction

The focus of the work presented in this thesis has been on developing new organophosphorus-based reagents which would allow Mitsunobu conversions to be carried out without the use of the azodicarboxylate reagent and would avoid the use of chromatography for the removal of the phosphine oxide by-product. There are difficulties associated with the use of azodicarboxylates, including their expense and tendency to explode.271 Alternatives to azodicarboxylates have been the subject of many studies in the literature (see Introduction, section 1.3). This work stimulated a
brief examination of potential alternatives to azodicarboxylates in the Mitsunobu reaction. In the first example, the use of tributylphosphine and fumaronitrile was examined for the simple esterification of a primary alcohol (Scheme 89).

![Scheme 89](image_url)

To investigate the formation of intermediate 207, fumaronitrile was added to an NMR tube containing tributylphosphine in d$_6$-benzene. Upon addition of fumaronitrile, no reaction was observed by $^{31}$P NMR spectroscopy. Although this $^{31}$P NMR experiment was inconclusive in providing evidence for 207, when 4-nitrobenzyl alcohol and 4-nitrobenzoic acid were added to a solution of benzene containing tributylphosphine and fumaronitrile, the ester nitrobenzyl 4-nitrobenzoate 61 did form. Analysis of the crude reaction mixture by $^1$H NMR spectroscopy revealed 55% conversion of 4-nitrobenzyl alcohol to 4-nitrobenzyl 4-nitrobenzoate 61 (Table 11, entry 1). This result suggests that species 207 was indeed present, though presumably the equilibrium lies well to the left. However, it may be accounted for by the longer reaction time used in the synthesis of 4-nitrobenzyl 4-nitrobenzoate 61 as compared to the short reaction time (~ five minutes) used in the $^{31}$P NMR experiment. Repeating the synthesis of 4-nitrobenzyl 4-nitrobenzoate 61 using tributylphosphine and fumaronitrile in toluene at room temperature for one week gave 57% conversion to 61 (Table 11, entry 2).
**Table 11.** Synthesis of 4-nitrobenzyl 4-nitrobenzoate 61 using alternative Mitsunobu reagents 207, 208 and 211.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Conditions</th>
<th>Conversion (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PBu&lt;sub&gt;3&lt;/sub&gt;/fumaronitrile 207</td>
<td>Benzene, RT, O/N</td>
<td>55</td>
</tr>
<tr>
<td>2</td>
<td>PBu&lt;sub&gt;3&lt;/sub&gt;/fumaronitrile 207</td>
<td>Toluene, RT, 1 week</td>
<td>57</td>
</tr>
<tr>
<td>3</td>
<td>PBu&lt;sub&gt;3&lt;/sub&gt;/fumaronitrile 207</td>
<td>Toluene, reflux, 3 hr</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>PBu&lt;sub&gt;3&lt;/sub&gt;/N-phenylmaleimide 208</td>
<td>Benzene, RT, O/N</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>PBu&lt;sub&gt;3&lt;/sub&gt;/N-phenylmaleimide 208</td>
<td>Benzene, RT, 1 week</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>PBu&lt;sub&gt;3&lt;/sub&gt;/3-phenylsydnone 211</td>
<td>Toluene, reflux, 3 hr</td>
<td>7</td>
</tr>
<tr>
<td>7</td>
<td>PBu&lt;sub&gt;3&lt;/sub&gt;/3-phenylsydnone 211</td>
<td>Toluene, RT, 1 week</td>
<td>4</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reaction conditions: tributylphosphine (1.0 equiv.), fumaronitrile/N-phenylmaleimide/3-phenylsydnone 209 (1.0 equiv.), 4-nitrobenzyl alcohol (1.0 equiv.), 4-nitrobenzoic acid (1.0 equiv.).

<sup>b</sup>Conversion ratio of 4-nitrobenzyl alcohol to 4-nitrobenzyl 4-nitrobenzoate 61 determined by <sup>1</sup>H NMR integration.

A blank reaction was performed to ensure esterification did not occur in the absence of 207. Addition of 4-nitrobenzoic acid to a toluene solution containing 4-nitrobenzyl alcohol gave no ester 61 after stirring at room temperature for one week. When the reaction employing 207 was heated at reflux for three hours, analysis of the crude mixture by <sup>1</sup>H NMR spectroscopy indicated 73% conversion to 61 (Table 11, entry 3). In this case, the ester 61 was isolated by chromatography in a 72% yield (Scheme 89).

However, as the reaction required rather forcing conditions to form an ester from a primary alcohol, the esterification of secondary alcohols was not attempted. Polymerisation of the fumaronitrile may be causing the sluggish reactions observed.

The use of N-phenylmaleimide also was explored as an azodicarboxylate alternative. Reaction of 4-nitrobenzyl alcohol and 4-nitrobenzoic acid with a benzene solution of intermediate 208 (presumably formed from tributylphosphine and N-phenylmaleimide – Scheme 90) gave no reaction after stirring at room temperature overnight (Table 11,
entry 4). When the reaction time was increased to one week, only 1% conversion to the ester 4-nitrobenzyl 4-nitrobenzoate 61 was detected following analysis of the crude reaction mixture by $^1$H NMR spectroscopy (Table 11, entry 5). The reaction was not heated to reflux in order to prevent polymerisation of the $N$-phenylmaleimide. As only a small amount of ester 61 was formed using the tributylphosphine/$N$-phenylmaleimide reagent, the reaction was not further investigated.

In the final example, 3-phenylsydnone 209 was investigated as an azodicarboxylate alternative. 3-Phenylsydnone 209 was prepared as follows. Reaction of phenylglycine and sodium nitrite followed by addition of concentrated hydrochloric acid gave $N$-nitroso-$N$-phenylglycine 210. Heating 210 with acetic anhydride gave 3-phenylsydnone 209 as an easily isolated solid (Scheme 91).

Reaction of 4-nitrobenzyl alcohol and 4-nitrobenzoic acid with a toluene solution of intermediate 211 (presumably formed from tributylphosphine and 3-phenylsydnone – Scheme 92) gave only 7% conversion to the desired ester 61 after heating at reflux for three hours (Table 11, entry 6). When the reaction was stirred at room temperature for one week, only 4% conversion to the desired ester 4-nitrobenzyl 4-nitrobenzoate 61 was observed following analysis of the crude reaction mixture by $^1$H NMR spectroscopy. Of the three azodicarboxylate alternatives examined, only fumaronitrile was successful in
forming the ester of a primary alcohol, however even in this case, forcing reaction conditions were required.

\[
\text{PBU}_3 + \text{Ph} \text{N} \text{N} \text{O} \text{O} \text{Bu}_3 \text{P} \text{N} \text{N} \text{O} \text{O} \text{toluene} \rightarrow \text{Ph} \text{N} \text{N} \text{O} \text{O} \text{Bu}_3 \text{P} \text{N} \text{N} \text{O} \text{O}
\]

**Scheme 92**

### 4.0 General conclusions

Use of the Hendrickson reagent 27 for phosphitylation of alcohols gave the desired phosphites 189 and 193 but in addition, the species 190-192, 194 and 195 were formed by ligand exchange reactions. Attempts to eliminate the by-products resulting from ligand exchange by redirecting the reaction though the phosphoramidite intermediate 198 were not successful. An investigation of methylenation of catechols using the Mitsunobu reaction showed that 1,3-benzodiazoles can be formed from 3-methoxycatechol but not from catechol itself. The use of fumaronitrile as a replacement for azodicarboxylates in the Mitsunobu reaction gave the ester 61 in good yield, however forcing reaction conditions were required. Attempts to use *N*-phenylmaleimide or 3-phenylsydnone 209 as azodicarboxylate alternatives in the Mitsunobu reaction were not successful as very little (<5%) of the desired ester 61 was formed.
CHAPTER SIX

CONCLUDING COMMENTS
In the search for an alternative Mitsunobu protocol, which would allow conversions to be carried out without the use of azodicarboxylates and would avoid the use of chromatography for the removal of the phosphine oxide, the Hendrickson reagent 27 was examined and a novel polymer-supported analogue 56 of the Hendrickson reagent 27 designed.

\[
\begin{align*}
\text{Ph}_3\text{P} \quad \text{O} \quad \text{PPh}_3 \\
2\text{CF}_3\text{SO}_2\text{O}^- \\
27 \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph} \quad \text{P} \quad \text{O} \quad \text{P} \quad \text{Ph} \\
\text{Ph} \\
2\text{CF}_3\text{SO}_2\text{O}^- \\
56 \\
\end{align*}
\]

In Chapter One, the Hendrickson reagent 27 was shown to be a useful method for simple conversions such as the esterification of primary alcohols and synthesis of primary azides. However, when the Hendrickson reagent 27 was used with secondary alcohols such as (−)-menthol, the major reaction pathway was elimination, instead of esterification with inversion via an S\(_{N}2\) displacement. Elimination was shown to result from the more ‘ionic’ reaction conditions brought about by the presence of diisopropylethylammonium triflate. However, it was shown that by employing an activating agent, esterification of secondary alcohols with retention of configuration could be achieved.

The synthesis of the novel polymer-supported analogue 56 of the Hendrickson reagent 27 was pursued, as the reagent 27 was useful for a wide range of condensations and for the esterification of secondary alcohols with retention of configuration. Prior to the synthesis of 56, the synthesis, characterisation and use of novel solution-phase cyclic analogues 90-92 of the Hendrickson reagent 27 were carried out (Chapter Two). Cyclic analogues 90-92 of the Hendrickson reagent 27 were found to be useful for the synthesis of simple esters and amides with the advantage over the Hendrickson reagent 27 that the bis-phosphine oxide by-product was more easily removed by chromatography.
Investigations of reaction rates revealed the esterification of a primary alcohol using the Hendrickson reagent 27 to be faster in non-polar solvents. The fastest rate of esterification was obtained using the five-membered ring compound 90, due to the ease of formation of the putative phosphorane intermediate 105. Some preliminary investigations of other cyclic analogues (the four- and nine-membered rings) revealed that the systems were more complex and clearly require further investigation.

In addition to the cyclic analogues 90-92 described in Chapter Two, selected acyclic analogues of the Hendrickson reagent 27 were investigated (Chapter Three). Analogues possessing tributyl 120 and tricyclohexyl 130 and diphenyl-2-pyridyl 137 (an internal base) functionalities were synthesised, however use of these reagents in the esterification of (−)-menthol again gave elimination as the major reaction pathway.

Interestingly, the reaction outcome with diphenyl-2-pyridylphosphonium anhydride triflate 137 was found in some instances to depend on the nature of the substrate employed. The esters benzyl 4-nitrobenzoate 143 and benzyl benzoate 144 were formed cleanly with 137, however the reaction of 137 with 4-nitrobenzyl alcohol and 4-nitrobenzoic acid gave bis(4-nitrobenzyl)ether 142 as the major product. Diphenyl-2-pyridylphosphonium anhydride triflate 137 was subsequently found to be a useful reagent for the synthesis of acyclic dialkyl ethers from primary alcohols, although during the synthesis of bis(4-methoxybenzyl)ether 147, 4-methoxybenzyl 4-
methoxybenzoate 148 was formed as a minor product. It would be interesting in the future to further probe the mechanism of formation of 148, and to explore the use of various analogues of 137 (such as the 3-pyridyl analogue or the tris-pyridyl analogue).

Following the exploration of both cyclic and acyclic analogues of the Hendrickson reagent 27, the five-membered cyclic analogue 90 was identified as a suitable candidate for polymer attachment. In Chapter Four, the polymer-supported five-membered cyclic analogue 56 was prepared and it was shown to be a useful reagent for the synthesis of simple esters and amides.

Perhaps the most useful development to come out of this work was the discovery that polymer-supported triphenylphosphine ditriflate 157 is an easily prepared (Scheme 93) and versatile dehydrating reagent. To demonstrate that 157 is a general dehydrating-type reagent, an array of simple amides, a tripeptide, esters (from primary and secondary alcohols), a nitrile, an epoxide, ethers, an anhydride, an azide, a thioacetate and a macrocyclic lactone were synthesised. In the case of secondary alcohol esterification, elimination was avoided by changing the order of addition of reactants and employing an activating agent to give esters with retention of configuration.

The novel reagents 56 and 157 are effective dehydrating reagents which avoid the use of azodicarboxylates and chromatography to remove the phosphine oxide by-product.
A general dehydrating reagent like polymer-supported triphenylphosphine ditriflate 157, which is capable of numerous synthetic transformations would be particularly useful to an organic chemist. It was readily prepared and it was demonstrated that it could be recycled several times without loss of efficiency. The use of 157 for peptide and macroyclic lactone synthesis could be examined further. In addition, 157 has potential for application in combinatorial chemistry and in multistep one pot reactions.

During the course of this study, other novel transformations using the Hendrickson and Mitsunobu reagents were explored in a preliminary manner in Chapter Five. Use of the Hendrickson reagent 27 for phosphitylation of alcohols gave the desired phosphites 189 and 193 but unfortunately, the reaction was accompanied by extensive ligand exchange. An interesting methylation of 3-methoxycatechol using the Mitsunobu reaction was discovered, however this method does not appear to be general. A brief examination of potential alternatives to azodicarboxylates in the Mitsunobu reaction was carried out. The use of fumaronitrile as a replacement for azodicarboxylates in the Mitsunobu reaction gave the ester 61 in good yield, however forcing reaction conditions were required. Attempts to use N-phenylmaleimide or 3-phenylsyađnone 209 as azodicarboxylate alternatives in the Mitsunobu reaction were not successful as very little (<5%) of the desired ester 61 formed.
The work described in this thesis has shown that phosphorus-based reagents can be useful and versatile reagents in organic synthesis. The reactions are often finely balanced, with small changes in the structures, reaction conditions or solvent causing quite dramatic changes in the outcome. This work should stimulate further exploration of the use of Hendrickson analogues and other alternatives to Mitsunobu protocols in synthetic organic chemistry.
EXPERIMENTAL
General procedures

Air sensitive reactions were carried out in flame-dried glassware under an inert atmosphere. THF was freshly distilled from sodium benzophenone ketal, toluene from sodium and DCM from calcium hydride. Triflic anhydride was distilled from a small amount of P₂O₅ before use. Diisopropylethylamine was distilled from potassium hydroxide and stored over molecular sieves. All other reagents were purchased from commercial suppliers and used without further purification. Flash chromatography was carried out using either Merck silica gel 60 (70-230 mesh, ATM) or a Biotage system with pre-packed silica columns. Analytical thin layer chromatography (TLC) utilized precoated Merck aluminium plates coated with silica gel 60 F₂₅₄ (0.2 mm). TLC plates were visualised by means of visible or UV light.

All NMR spectra were recorded on Varian Gemini 200 or Varian Unity 400 spectrometers with chemical shifts reported in parts per million. ¹H NMR spectra were obtained at either 200 or 400 MHz and referenced to the appropriate solvent proton signal (CDCl₃, δ 7.27 ppm; CD₂Cl₂, δ 5.32 ppm; d₆-DMSO, δ 2.52 ppm). ¹³C NMR spectra were recorded at either 50 or 100 MHz and referenced to either δ 77.0 ppm (CDCl₃) or δ 54.0 ppm (CD₂Cl₂). ³¹P NMR spectra were recorded at 162 MHz with an external reference of phosphoric acid (H₃PO₄) referenced to δ 0.0 ppm. ³¹P NMR spectra obtained at -70°C or -80°C were referenced to 1,2-bis(diphenylphosphinyl)ethane 93 at δ 33.4 ppm. ¹⁹F NMR spectra were recorded at 376 MHz, with an external reference of hexafluorobenzene in CD₂Cl₂ referenced to δ – 164.9 ppm.

GC/MS analyses were performed on a Perkin-Elmer Autosystem × 1 Gas Chromatograph (20m db-5ms capillary column) connected to a Perkin-Elmer
Turbomass spectrometer using electron impact ionisation. Turbomass software was used to acquire and process GC/MS data. With injection port temperature 250°C; oven temperature 60°C (2 min), 60-250°C (15°C/min), 250°C (3.33 min), 250-300°C (20°C/min), 300°C (10 min), retention times (Rt, min) were: 2-menthene 36 (3.8), 3-menthene 37 (3.8), (1R,2S,5R)-(−)-menthol (6.2), neomethyl azide 71 (6.7), neomethyl thioacetate 70 (8.6), neomethyl 4-methoxybenzoate 68 (13.2), neomethyl 4-nitrobenzoate 67 (13.8). With injection port temperature 150°C; oven temperature 40°C (2 min), 40-150°C (10°C/min), 150°C (5 min), 150-300°C (20°C/min), 300°C (5 min), retention times (min) were: cyclohexene 75 (1.5), cyclohexanol (4.5), O-(4-nitrobenzoyl)-cyclohexanol 76 (21.4). The identity of products was confirmed by 1H NMR spectroscopy, which agreed with those reported in the literature, and by means of co-injection of authentic samples.

Melting points were measured on a Gallenkamp Variable Temperature Apparatus by the capillary method and are uncorrected. Fourier transform infrared (FTIR) spectra were recorded on a Thermo Nicolet-Nexus FTIR apparatus as KBr disks or nujol mulls. Signals were recorded with the following abbreviations: w=weak, m=medium, s=strong. Mass spectra were recorded on a Fisons VG-Platform II, using electrospray as the ionisation technique and Mass Lynx Version I (IBM) software to acquire and process data. Elemental analyses were carried out by the University of Queensland Microanalytical Service. High resolution mass spectra were carried out by the University of Tasmania Organic Mass Spectrometry Facility. Kinetic studies were performed using a Thermohaake C40P temperature controlled bath containing ethanol/water 1:1.
Note on nomenclature

The nomenclature and numbering used within the experimental is in accordance with IUPAC nomenclature of organic chemistry. A selected example is displayed below with numbering.

![Chemical structure diagram](image-url)
CHAPTER ONE

Use of the Hendrickson reagent in an alternative Mitsunobu protocol

1.0 Reaction of the Hendrickson reagent 27 with primary alcohols

1.1 Typical example for the synthesis of 4-nitrobenzyl 4-nitrobenzoate 61 using 1.0 equivalent of Hendrickson reagent 27

Addition of triflic anhydride (0.5 mL, 3 mmol) to a solution of triphenylphosphine oxide (2 g, 7.2 mmol) in dry DCM (10 mL) at 0°C generated a white precipitate that was left to stir for 30 minutes. 4-Nitrobenzyl alcohol (0.46 g, 3 mmol), 4-nitrobenzoic acid (0.5 g, 3 mmol) and diisopropylethylamine (1.15 mL, 6.6 mmol) were added in succession to form a yellow solution. After stirring for 2 hours at room temperature, the mixture was washed with sodium hydrogen carbonate (saturated aqueous solution, 2 × 20 mL) and water (2 × 20 mL). The organic layers were combined, dried (anhydrous MgSO₄), filtered and concentrated in vacuo. Analysis by ¹H NMR spectroscopy revealed 97.5% conversion of 4-nitrobenzyl alcohol to 4-nitrobenzyl 4-nitrobenzoate 61. Purification by flash chromatography (DCM/hexane 1:1) afforded 4-nitrobenzyl 4-nitrobenzoate 61 as a yellow solid (0.86 g, 95%). Mp 165-167°C (Lit. 275 168°C). ¹H NMR (200 MHz, CDCl₃) δ 5.51 (s, 2H, CH₂), 7.63 (d, J = 8.8 Hz, 1H, H₂', H₆'), 8.22-8.4 (m, 6H, H₂, H₃, H₅, H₆, H₃', H₅'). ESMS (+ve mode) MH⁺, 302 (15%).

1.2 Generation of the Hendrickson reagent 27 using catalytic triphenylphosphine oxide: attempted synthesis of 4-nitrobenzyl 4-nitrobenzoate 61

Addition of triflic anhydride (0.5 mL, 3 mmol) to a solution of triphenylphosphine oxide (0.2 g, 0.72 mmol), 4-nitrobenzyl alcohol (0.46 g, 3 mmol) and 4-nitrobenzoic acid (0.5 g, 3 mmol) in dry DCM (10 mL) at 0°C under nitrogen generated an orange
solution. With the addition of diisopropylethylamine (1.15 mL, 6.6 mmol), a precipitate appeared almost immediately. The solution was stirred at room temperature overnight and then worked up according to procedure 1.1. Analysis by $^1$H NMR spectroscopy revealed complete conversion to the ester, 4-nitrobenzyl 4-nitrobenzoate 61. The above procedure was repeated in the absence of triphenylphosphine oxide. Analysis by $^1$H NMR spectroscopy revealed complete conversion to the ester, 4-nitrobenzyl 4-nitrobenzoate 61.

1.3 Synthesis of 4-chlorobenzyl thioacetate 64 using the Hendrickson reagent 27 and thiolacetic acid

The Hendrickson reagent 27 (2 mmol) was prepared as described in procedure 1.1. 4-Chlorobenzyl alcohol (0.29 g, 2 mmol), thiolacetic acid (0.143 mL, 2 mmol) and diisopropylethylamine (0.77 mL, 4.4 mmol) were added to generate a homogeneous solution that was warmed to room temperature overnight. The mixture was worked up according to procedure 1.1. The resulting yellow residue was purified by flash chromatography (DCM/hexane 1:1) to yield 4-chlorobenzyl thioacetate 64 as a yellow oil (0.39 g, 97%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.36 (s, 3H, CH$_3$), 4.08 (s, 2H, CH$_2$), 7.17 (d, $J = 8.7$ Hz, 2H, H2, H6), 7.27 (d, $J = 8.7$ Hz, 2H, H3, H5). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 30.3 (CH$_3$), 32.7 (CH$_2$), 128.7 (C4), 130.1 (C3, C5), 133.0 (C2, C6), 136.2 (C1), 194.8 (C=O). IR (Nujol) 1703 (s, C=O), 1133 (m, C-S), 1094 cm$^{-1}$ (s, Ph-Cl). ESMS (+ve mode) M$^+$($^{35}$Cl) 199 (10%), M$^+$($^{37}$Cl) 201 (3%). Anal. calcd for C$_9$H$_9$ClOS: C, 53.86; H, 4.52. Found: C, 53.62; H, 4.53.

1.4 Synthesis of 4-chlorobenzyl azide 65 using the Hendrickson reagent 27 and NaN$_3$

The Hendrickson reagent 27 (2 mmol) was prepared as described in procedure 1.1. 4-Chlorobenzyl alcohol (0.29 g, 2 mmol), a suspension of sodium azide (0.2 g, 3 mmol) in
DMF (3 mL) and diisopropylethylamine (0.77 mL, 4.4 mmol) were added consecutively and the solution left to warm to room temperature overnight. The mixture was worked up according to procedure 1.1. The resulting residue was submitted to flash chromatography (DCM/hexane 1:1) to afford 4-chlorobenzyl azide 65 as a colourless oil (0.31 g, 93%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.33 (s, 2H, CH$_2$), 7.26 (d, $J = 8.5$ Hz, 2H, H2, H6), 7.37 (d, $J = 8.5$ Hz, 2H, H3, H5). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 54.0 (CH$_2$), 129.0 (C1), 129.5 (C2, C6), 133.9 (C3, C5), 134.2 (C4). IR (Nujol) 2100 cm$^{-1}$ (s, N=N$^+$=N$^-$). $n_D^{15}$ 1.5556 (Lit. $n_D^{15}$ 1.5600). (HRMS) Found: 167.0250. C$_7$H$_6$N$_3$Cl requires 167.0250.

1.5 Attempted synthesis of 4-chlorobenzyl azide 65 using triphenylphosphine, DIAD and NaN$_3$

Sodium azide (0.27 g, 4 mmol) in DMF (4 mL) was added to a solution of triphenylphosphine (1 g, 3.81 mmol) and 4-chlorobenzyl alcohol (0.46 g, 3.2 mmol) in DCM (10 mL). The heterogeneous mixture was cooled on ice and DIAD (0.75 mL, 3.81 mmol) added slowly. After 30 minutes, the solution was left to warm to room temperature overnight. The mixture was worked up according to procedure 1.1. Analysis of the resulting pale yellow product by $^1$H NMR spectroscopy revealed unreacted 4-chlorobenzyl alcohol.

1.6 Synthesis of O-(4-nitrobenzyl)-4-methoxyphenol 66 using the Hendrickson reagent 27

The Hendrickson reagent 27 (3 mmol) was prepared as described in procedure 1.1. 4-Nitrobenzyl alcohol (0.465 g, 3 mmol), 4-methoxyphenol (0.375 g, 3 mmol) and diisopropylethylamine (1.15 mL, 6.6 mmol) were added and the solution warmed to room temperature overnight. The mixture was worked up according to procedure 1.1. Purification by flash chromatography (DCM) yielded O-(4-nitrobenzyl)-4-
methoxyphenol 66 as a yellow solid (0.65 g, 84%). Mp 88-90°C (Lit.277 88°C). \( ^1\)H NMR (200 MHz, CDCl\(_3\)) \( \delta \) 3.78 (s, 3H, OMe), 5.13 (s, 2H, CH\(_2\)), 6.8-6.95 (m, 4H, Ar-HOME), 7.6 (d, \( J = 8.8 \) Hz, 2H, Ar-H\( \text{NO}_2 \)), 8.24 (d, \( J = 8.8 \) Hz, 2H, Ar-H\( \text{NO}_2 \)). GC/MS m/z (relative intensity) 259 (M, 7%), 123 (O-C\(_6\)H\(_4\)-OCH\(_3\), 100%).

1.7 Preparation of authentic samples for GC/MS analysis

1.7.1 Synthesis of 2- and 3-menthene 36 and 37

2- and 3-Menthene 36 and 37 were prepared according to the procedure described by Quast.\(^{223}\) A solution of (1R,2S,5R)-(−)-menthol (3.13 g, 20 mmol), triphenylphosphate (7.18 g, 22 mmol) and calcium hydride (0.1 g, 2 mmol) was prepared in N-methyl-2-pyrrolidone (20 mL) under a nitrogen atmosphere. The mixture was heated to reflux and the nitrogen supply replaced with a calcium chloride drying tube. After heating the mixture for 19 hours at reflux, the dark red solution was cooled to room temperature and the alkenes distilled (under house vacuum) until the boiling point of N-methyl-2-pyrrolidone was reached. The colourless product was extracted with sulfuric acid (1M aqueous solution, 2 × 15 mL) and saturated aqueous NaHCO\(_3\) (2 × 15 mL). The combined organic layers were dried (anhydrous K\(_2\)CO\(_3\)) and filtered to yield a mixture of pure menthenes 36 and 37 (1.8 g, 65.2%). 2-Menthene 36 : 3-menthene 37 = 1 : 2 (from \(^1\)H NMR spectroscopy integrals). 2-Menthene 36: \( ^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 0.8-2.2 (m, 16H), 5.5-5.57 (m, 2H). 3-Menthene 37: \( ^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 0.8-2.2 (m, 17H), 5.35-5.38 (m, 1H). GC/MS m/z (relative intensity) 138 (M, 20%).

1.7.2 Synthesis of neomenthyl thioacetate 70 [(1S,2S,5R)-5-methyl-2-(1-methyl-ethyl)cyclohexyl thioacetate]

Neomenthyl thioacetate 70 was prepared by a modified literature procedure.\(^{30}\) A solution of triphenylphosphine (2 g, 7.6 mmol) in dry THF (20 mL) was prepared under
an atmosphere of nitrogen. The mixture was cooled to 0°C and DIAD (0.8 mL, 4 mmol) added slowly. After 30 minutes, (1R,2S,5R)-(−)-menthol (2.4 g, 15.3 mmol) was added to the yellow solution and the mixture stirred at 0°C for 66 hours. After dropwise addition of thiolacetic acid (0.55 mL, 0.58 g, 7.6 mmol) in THF (10 mL), the solution was warmed to room temperature overnight. Concentration of the reaction mixture in vacuo and subsequent purification by flash chromatography (using DCM as eluent and visualised with PdCl$_2$/HCl dip) yielded neomenthyl thioacetate 70 as a dark orange oil (0.39 g, 24%) [based on 1 equivalent of (1R,2S,5R)-(−)-menthol]. $^1$H NMR (400 MHz, CDCl$_3$) δ 0.8-1.9 (m, 18H, H$_2$-H$_6$, H1', 6 × H2', 5-CH$_3$), 2.33 (s, 3H, CH$_3$), 4.06-4.1 (m, 1H, H1). ESMS (+ve mode) MNa$^+$, 221 (30%). The $^1$H NMR spectrum obtained for neomenthyl thioacetate 70 was identical to that reported previously.$^{278}$

### 1.7.3 Synthesis of Neomenthyl-4-methoxybenzoate 68 [(1S,2S,5R)-5-methyl-2-(1-methylethyl)cyclohexyl 4-methoxybenzoate]

Triphenylphosphine (1.05 g, 4 mmol), (1R,2S,5R)-(−)-menthol (0.31 g, 2 mmol) and anisic acid (0.3 g, 2 mmol) were placed in dry DCM (10 mL) under an atmosphere of nitrogen. The solution was cooled to 0°C and DIAD (0.8 mL, 4 mmol) added slowly. The resulting orange mixture was stirred overnight at room temperature. The solvent was then removed under reduced pressure and the residue submitted to flash chromatography (DCM/hexane 1:1). Neomenthyl-4-methoxybenzoate 68 was afforded as a colourless oil (0.44 g, 76%). $^1$H NMR (200 MHz, CDCl$_3$) δ 0.75-2.2 (m, 18H, H$_2$-H$_6$, H1', 6 × H2', 5-CH$_3$), 3.87 (s, 3H, OCH$_3$), 5.43 (br s, 1H, H1), 6.97 (d, $J$ = 8.8 Hz, 2H, H3', H5'), 8.01 (d, $J$ = 8.8 Hz, 2H, H2', H6'). ESMS (+ve mode) MNa$^+$, 313 (40%); MLi$^+$, 297 (15%). The $^1$H NMR spectrum obtained for neomenthyl-4-methoxybenzoate 68 was identical to that reported previously.$^{44}$
1.7.4 Synthesis of neomenthyl azide 71 [(1S,2S,5R)-5-methyl-2-(1-methylethyl)-cyclohexyl azide]

Neomenthyl azide 71 was prepared according to the procedure of Viaud. The zinc azide/bis pyridine complex Zn(N\(_3\))\(_2\).2Py was prepared as follows: a 2M aqueous solution of sodium azide (2.6 g in 20 mL water) was added dropwise to a stirred solution of 2M aqueous zinc nitrate (5.95 g made up to 10 mL with water). The pale pink suspension was brought to 50°C and pyridine (3.4 mL, 41.2 mmol) added dropwise. The mixture was allowed to cool to room temperature and a dense white precipitate formed. The salt was filtered, washed with minimal ice-cold water and dried to yield Zn(N\(_3\))\(_2\).2Py as a white solid (4.1 g, 67%). IR (KBr disk) 2079 cm\(^{-1}\) (s, N=N\(^+=\)=N\(^-\)). The zinc azide/bis pyridine complex (0.46 g, 1.5 mmol), (1R,2S,5R)-(−)-menthol (0.31 g, 2 mmol) and triphenylphosphine (1.05 g, 4 mmol) were added to anhydrous toluene (10 mL). DIAD (0.8 mL, 4 mmol) was added slowly to the mixture at room temperature. After stirring at room temperature for 2.5 hours, the solution was concentrated \textit{in vacuo} to yield an orange gum. Purification of the residue by flash chromatography (DCM/hexane 1:1) gave neomenthyl azide 71 as a yellow oil (0.32 g, 88%). \(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta\) 1.8-2.1 (m, 18H, H\(_2\)-H\(_6\), H\(_1\)', 6 × H\(_2\)'), 5-CH\(_3\)), 3.98 (br s, 1H, H1). GC/MS \(m/z\) (relative intensity) 138 (M, 50%). The \(^1\)H NMR spectrum obtained for neomenthyl azide 71 was identical to that reported previously.

1.7.5 Synthesis of O-(4-nitrobenzoyl)-cyclohexanol 76

Anhydrous THF (15 mL) was charged with triphenylphosphine (2 g, 7.6 mmol), cyclohexanol (0.2 mL, 0.19 g, 1.9 mmol) and 4-nitrobenzoic acid (1.27 g, 7.6 mmol) under a nitrogen atmosphere. DIAD (1.5 mL, 7.6 mmol) was added slowly to the ice-cooled solution and the resulting mixture left to warm to room temperature overnight. Removal of the solvent at reduced pressure and purification of the resulting residue by
chromatography (DCM) afforded O-(4-nitrobenzoyl)-cyclohexanol 76 as a pale yellow solid (0.4 g, 84.5%). Mp 49-51°C (Lit. 279 47-48°C). $^1$H NMR (400 MHz, CDCl$_3$) δ 1.3-2.1 (m, 5H, H2-H6), 5.04-5.1 (m, 1H, H1), 8.21 (d, $J = 9.2$ Hz, 2H, H2', H6'), 8.29 (d, $J = 9.2$ Hz, 2H, H3', H5'). ESMS (+ve mode) MH$^+$, 250 (25%).

2.0 Reactions of the Hendrickson reagent 27 with secondary alcohols

2.1 Representative example for the reaction of the Hendrickson reagent 27 with a secondary alcohol and nucleophile: attempted synthesis of neomenthyl 4-nitrobenzoate 67 [(1$S$,2$S$,5$R$)-5-methyl-2-(1-methylethyl)-cyclohexyl 4-nitrobenzoate]

The Hendrickson reagent 27 (3 mmol) was prepared as described in procedure 1.1. The DCM was removed in vacuo and the remaining solid re-suspended in dry toluene (10 mL). Addition of (1$R$,2$S$,5$R$)-(−)-menthol (0.46 g, 3 mmol) to the slurry generated a clear solution over 5 minutes, to which 4-nitrobenzoic acid (0.5 g, 3 mmol) and diisopropylethylamine (1.15 mL, 6.6 mmol) were added. The resulting yellow solution was warmed at 40°C for 24 hours. The reaction mixture was then quenched using sodium hydrogen carbonate (saturated aqueous solution) and an aliquot of the organic phase analysed directly by GC/MS (a ratio of 2- and 3-menthene 36+37 : neomenthyl 4-nitrobenzoate 67 : (1$R$,2$S$,5$R$)-(−)-menthol : = 68 : 10 : 22 was obtained). The identity of the products generated was confirmed by $^1$H NMR spectroscopy.

2.2 Sonication of a concentrated sample of the Hendrickson reagent 27 with (1$R$,2$S$,5$R$)-(−)-menthol and 4-nitrobenzoic acid

A solution of triphenylphosphine oxide (2 g, 7.2 mmol) in dry DCM (3 mL) was cooled to 0°C. Addition of triflic anhydride (0.5 mL, 3 mmol) generated a thick white
precipitate which was sonicated for 30 minutes. Addition of (1R,2S,5R)-(−)-menthol (0.42 g, 2.64 mmol) to the reaction generated a clear yellow solution to which 4-nitrobenzoic acid (0.44 g, 2.64 mmol) and diisopropylethylamine (1.15 mL, 6.6 mmol) were added. The solution was sonicated for 6 hours and then stirred at room temperature for 12 hours. Analysis of the crude mixture by GC/MS revealed 2- and 3-menthene 36 and 37 (ratio 1 : 2 by 1H NMR spectroscopy) and neomenthyl 4-nitrobenzoate 67 in a ratio of 93 : 7 respectively. The presence of these species was confirmed by 1H NMR spectroscopy.

2.3 Attempted inversion of (1R,2S,5R)-(−)-menthol by tosic acid using the Hendrickson reagent 27

The Hendrickson reagent 27 (3 mmol) was prepared as described in procedure 1.1. (1R,2S,5R)-(−)-Menthol (0.46 g, 3 mmol) was added and after 5 minutes, addition of tosic acid monohydrate (0.57 g, 3 mmol) (dried by refluxing with toluene in a Dean and Stark apparatus) and diisopropylethylamine (1.05 mL, 0.78 g, 6 mmol) generated a clear solution which was heated to reflux for 24 hours. The solution was cooled and worked up according to procedure 1.1. Analysis of the residue by 1H NMR spectroscopy revealed 2-menthene 36, 3-menthene 37, (1R,2S,5R)-(−)-menthol, neomenthyl tosylate 72 (characteristic 1H NMR (400 MHz, CDCl3) shift at δ 5.0 ppm, br s, H1; Lit.280 δ 5.02 ppm) and (1R,2S,5R)-(−)-menthloxytriphenylphosphonium trifluoromethanesulfonate 35 (73%) in a ratio of 4 : 9 : 6 : 73 respectively.

2.4 NMR spectroscopy study of (1R,2S,5R)-(−)-menthloxytriphenylphosphonium trifluoromethanesulfonate 35 formation

A solution of triphenylphosphate oxide (0.1 g, 0.36 mmol) was dissolved in dry CD2Cl2 (0.75 mL) in a 5 mm NMR tube. The tube was cooled on ice and triflic anhydride (29
µL, 0.17 mmol) added. A white solid formed immediately and after 10 minutes, (1R,2S,5R)-(−)-menthol (0.027 g, 0.17 mmol) was added. Brief vortex mixing generated a clear solution which showed (by \(^1\)H NMR spectroscopy) complete conversion of (1R,2S,5R)-(−)-menthol to (1R,2S,5R)-(−)-menthyloxytriphenylphosphonium trifluoromethanesulfonate. The \(^{31}\)P NMR spectrum revealed a 1:1 mixture of (1R,2S,5R)-(−)-menthyloxytriphenylphosphonium trifluoromethanesulfonate and protonated triphenylphosphine oxide. \(^{31}\)P NMR (162 MHz, CD\(_2\)Cl\(_2\)) \(\delta\) 51.4 (br s), 59.5 (s). \(^1\)H NMR (400 MHz, CD\(_2\)Cl\(_2\)) \(\delta\) 4.25 (ddddd, \(J = 10.7, 10.7, 6.6, 4.6\) Hz, 1H, H3). The key \(^{31}\)P and \(^1\)H NMR peaks for (1R,2S,5R)-(−)-menthyloxytriphenylphosphonium trifluoromethanesulfonate were in agreement with the literature.

3.0 Base alternatives in the Hendrickson reagent 27 reactions

3.1 Sodium hydride in DCM/DMSO

The Hendrickson reagent 27 (2 mmol) was prepared as described in procedure 1.1. The ice-bath was removed and dry DMSO (1 mL) added. 4-Nitrobenzyl alcohol (0.31 g, 2 mmol), 4-nitrobenzoic acid (0.34 g, 2 mmol) and powdered sodium hydride (0.11 g, 4.4 mmol) were added and the cloudy white solution stirred at room temperature for 48 hours. The mixture was worked up according to procedure 1.1. Analysis by \(^1\)H NMR spectroscopy showed 6% conversion to the desired ester, 4-nitrobenzyl 4-nitrobenzoate.

3.2 Sodium hydride in DCM/THF

The Hendrickson reagent 27 (2 mmol) was prepared as described in procedure 1.1. The ice-bath was removed and dry THF (30 mL) added. 4-Nitrobenzyl alcohol (0.31 g, 2 mmol), 4-nitrobenzoic acid (0.34 g, 2 mmol) and powdered sodium hydride (0.2 g, 8 mmol) added. A white solid formed immediately and after 10 minutes, (1R,2S,5R)-(−)-menthol (0.027 g, 0.17 mmol) was added. Brief vortex mixing generated a clear solution which showed (by \(^1\)H NMR spectroscopy) complete conversion of (1R,2S,5R)-(−)-menthol to (1R,2S,5R)-(−)-menthyloxytriphenylphosphonium trifluoromethanesulfonate. The \(^{31}\)P NMR spectrum revealed a 1:1 mixture of (1R,2S,5R)-(−)-menthyloxytriphenylphosphonium trifluoromethanesulfonate and protonated triphenylphosphine oxide. \(^{31}\)P NMR (162 MHz, CD\(_2\)Cl\(_2\)) \(\delta\) 51.4 (br s), 59.5 (s). \(^1\)H NMR (400 MHz, CD\(_2\)Cl\(_2\)) \(\delta\) 4.25 (ddddd, \(J = 10.7, 10.7, 6.6, 4.6\) Hz, 1H, H3). The key \(^{31}\)P and \(^1\)H NMR peaks for (1R,2S,5R)-(−)-menthyloxytriphenylphosphonium trifluoromethanesulfonate were in agreement with the literature.
mmol) were added and the cloudy beige solution stirred at room temperature for 48 hours. Water (30 mL) was then added and the THF removed in vacuo. DCM (20 mL) was added to the remaining aqueous phase and the mixture was worked up according to procedure 1.1. Analysis by $^1$H NMR spectroscopy showed 23% conversion to the desired ester, 4-nitrobenzyl 4-nitrobenzoate 61.

3.3 Potassium fluoride in DCM/THF

The Hendrickson reagent 27 (2 mmol) was prepared as described in procedure 1.1. The ice-bath was removed and THF (30 mL) added. 4-Nitrobenzyl alcohol (0.31 g, 2 mmol), 4-nitrobenzoic acid (0.34 g, 2 mmol) and potassium fluoride (0.16 g, 16 mmol) were added and the cloudy solution was stirred at room temperature for 24 hours. The solvents were removed at reduced pressure and the residue re-suspended in DCM (20 mL). The mixture was worked up according to procedure 1.1. Analysis by $^1$H NMR spectroscopy revealed unreacted 4-nitrobenzyl alcohol.

3.4 Potassium carbonate in DCM

The Hendrickson reagent 27 (3 mmol) was prepared as described in procedure 1.1. The ice-bath was removed and 4-nitrobenzyl alcohol (0.4 g, 2.64 mmol), 4-nitrobenzoic acid (0.44 g, 2.64 mmol) and potassium carbonate (1.24 g, 9 mmol) added. The white heterogeneous solution was stirred for 24 hours at room temperature. The mixture was then filtered, the solvent removed at reduced pressure and resulting residue dried under high vacuum. Analysis by $^1$H NMR spectroscopy revealed unreacted 4-nitrobenzyl alcohol.
3.5 Polymer-supported diisopropylethylamine in DCM

3.5.1 Primary alcohol

A solution of triphenylphosphine oxide (0.5 g, 1.8 mmol) in dry DCM (15 mL) was placed in an ice-bath under an atmosphere of nitrogen. Slow addition of triflic anhydride (0.125 mL, 0.75 mmol) generated a clear yellow solution over 30 minutes. The ice-bath was removed and polymer-supported diisopropylethylamine (0.85 g, 3 mmol, 3.5 mmol/g) added. The resin was allowed to swell with gentle stirring for 2 hours. 4-Nitrobenzyl alcohol (0.1 g, 0.67 mmol) and 4-nitrobenzoic acid (0.11 g, 0.67 mmol) were then added and the resulting slurry stirred for 24 hours at room temperature. The polymer beads were collected by filtration and washed with DCM (3 × 50 mL). The combined filtrates were dried (anhydrous MgSO$_4$), concentrated in vacuo and the resulting residue dried under high vacuum. Analysis by $^1$H NMR spectroscopy revealed 80% conversion to the corresponding ester, 4-nitrobenzyl 4-nitrobenzoate 61.

3.5.2 Secondary alcohol

The Hendrickson reagent 27 (0.75 mmol) was prepared according to procedure 3.5.1. The ice-bath was removed and polymer-supported diisopropylethylamine (0.85 g, 3 mmol, 3.5 mmol/g) added. The resin was allowed to swell with gentle stirring for 2 hours. (1R,2S,5R)-(-)-menthol (0.1 g, 0.67 mmol) was added and 30 minutes later, 4-nitrobenzoic acid (0.11 g, 0.67 mmol) added. The resulting slurry stirred for 24 hours at 40°C. The polymer beads were collected by filtration and washed with DCM (3 × 50 mL). The combined filtrates were concentrated in vacuo and the resulting residue dried briefly under high vacuum. Analysis by $^1$H NMR spectroscopy showed the presence of
2- and 3-menthene 36 and 37 (ratio 1 : 2) and (1R,2S,5R)-(−)-menthoxyptriphenylphosphonium trifluoromethanesulfonate 35 in a ratio of 55 : 45 respectively.

**4.0 Addition of diisopropylethylammonium and tetrabutylammonium triflates to the standard Mitsunobu reaction**

**4.1 Formation of 2-menthene 36 and neomenthyl 4-nitrobenzoate 67 [(1S,2S,5R)-5-methyl-2-(1-methylethyl)-cyclohexyl 4-nitrobenzoate] (Organic Syntheses Mitsunobu procedure)**

A solution of triphenylphosphine (4.02 g, 15.3 mmol), (1R,2S,5R)-(−)-menthol (0.6 g, 3.8 mmol) and 4-nitrobenzoic acid (2.58 g, 15.4 mmol) in dry THF (30 mL) was cooled on ice. DIAD (3.03 mL, 15.4 mmol) was added slowly and the reaction left to warm to room temperature overnight. A sample of the reaction mixture was removed for analysis by GC/MS which showed 2-menthene 36 : neomenthyl 4-nitrobenzoate 67 = 12 : 88. The remaining solution was diluted with ether (30 mL) and washed with saturated aqueous sodium bicarbonate (2 × 20 mL). The aqueous layers were combined and extracted with ether (20 mL). The combined ethereal layers were dried (anhydrous MgSO₄) and concentrated in vacuo. The resulting solid was suspended in ether (10 mL) and allowed to stand overnight. Hexane (5 mL) was added slowly to the stirring mixture and the precipitated white solid removed by filtration. The solvent was removed from the filtrate and the resulting residue submitted to column chromatography (8% ether/hexanes) to yield neomenthyl 4-nitrobenzoate 67 as a pale yellow crystalline solid (0.96 g, 82%). Mp 92-94°C (Lit. 222 93-95°C). H NMR (400 MHz, CDCl₃) δ 0.87-2.14 (m, 18H, H2-H6, 5-CH₃, H1', 6 × H2'), 5.51 (s, 1H, H1), 8.17 (d, J = 9.1 Hz, 2H, H2", H6"), 8.26 (d, J = 9.1 Hz, 2H, H3", H5'"). GC/MS m/z (relative intensity) 138 (2- and 3-menthene 36 and 37, 20%).
4.2 $^{31}$P NMR spectroscopy study of the Mitsunobu reaction between (1R,2S,5R)-(−)-menthol and 4-nitrobenzoic acid in the presence of diisopropylethlammonium trifluoromethanesulfonate

A solution of triflic acid (28 µL, 0.32 mmol) and diisopropylethylamine (56 µL, 0.32 mmol) in CD$_2$Cl$_2$ (0.75 mL) was prepared in a 5 mm NMR tube. Triphenylphospine (0.1 g, 0.38 mmol), (1R,2S,5R)-(−)-menthol (0.05 g, 0.32 mmol) and 4-nitrobenzoic acid (0.055 g, 0.32 mmol) were added. A chilled solution of DIAD (75 µL, 0.38 mmol) was then added to the tube at 0°C. The tube was stoppered and sealed with Parafilm®. A $^{31}$P NMR spectrum was obtained at 25°C after brief vortex mixing and again after standing at room temperature 24 hours. The above procedure was repeated using an excess of diisopropylethylamine (168 µL, 0.96 mmol) and in the absence of diisopropylethlammonium triflate.

At 25°C: $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$) δ 29.1 (s), 52.6 (s), 2 : 3 respectively; At 25°C after 24 hours: $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$) δ 29.1 (s), 52.6 (s), 59.5 (s), 47 : 42 : 11 respectively; With an excess of diisopropylethylamine at 25°C: $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$) δ 29.1 (s), 52.6 (s), 53 : 47 respectively; With an excess of diisopropylethylamine at 25°C after 24 hours: $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$) δ 29.1 (s), 52.6 (s), 59.5 (s), 55 : 21 : 33 respectively; In the absence of diisopropylethlammonium triflate at 25°C after 24 hours: $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$) δ 29.1 (s), 59.5 (s), 9: 1 respectively.

4.3 $^{31}$P NMR spectroscopy study of the Mitsunobu reaction between (1R,2S,5R)-(−)-menthol and 4-nitrobenzoic acid in the presence of tetrabutylammonium trifluoromethanesulfonate

A solution of triphenylphospine (0.1 g, 0.38mmol) in CD$_2$Cl$_2$ (0.75 mL) was prepared in a 5 mm NMR tube. Tetrabutylamnomium triflate (0.1 g, 0.38 mmol), (1R,2S,5R)-(−)-menthol (0.05 g, 0.32mmol) and 4-nitrobenzoic acid (0.055 g, 0.32 mmol) were added.
A chilled solution of DIAD (75 µL, 0.38 mmol) was then added to the tube at 0°C. The tube was stoppered, sealed with Parafilm® and briefly vortexed. A $^{31}$P NMR spectrum was obtained after a few minutes at 25°C and again after standing at room temperature for 24 hours.

At 25°C: $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$) δ 29.1 (s), 44.2 (s), 59.5 (s) ~ 1 : 3 : 1 respectively; At 25°C after 24 hours: $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$) δ 29.1 (s), 52.6 (s), 59.5 (s), ~ 5 : 1 : 1 respectively.

4.4 General procedure for the addition of tetrabutylammonium trifluoromethanesulfonate to the Mitsunobu reaction between (1R,2S,5R)-(−)-menthol and 4-nitrobenzoic acid

A solution of triphenyl phosphine (1 g, 3.8 mmol), (1R,2S,5R)-(−)-menthol (0.5 g, 3.2 mmol) and 4-nitrobenzoic acid (0.55 g, 3.2 mmol) was prepared in dry DCM (8 mL). Tetrabutylammonium triflate (0.01-2.0 equiv., 0.038-7.6 mmol) in DCM (2 mL) was added. Slow addition of DIAD (0.75 mL, 3.8 mmol) to the ice-cooled liquid generated a yellow solution that was left to warm to room temperature over 24 hours. An aliquot of the reaction mixture was removed for analysis by GC/MS.

4.5 Reaction of 2-menthene 36 with triflic acid and diisopropylethylamine (testing for isomerisation to 3-menthene 37)

4.5.1 Preparation of 2-menthene 36

Triphenylphosphine (2 g, 7.6 mmol) and (1R,2S,5R)-(−)-menthol (1 g, 6.4 mmol) were dissolved in dry THF (20 mL) under an atmosphere of nitrogen. The solution was cooled on ice and DIAD (1.4 mL, 7.1 mmol) added. The orange solution was allowed to warm to room temperature overnight. The solvent was carefully removed by distillation and the temperature increased slowly such that a pure sample of 2-menthene
2-Menthene 36 was collected by distillation. 2-Menthene 36 was obtained as a colourless oil (0.4 g, 45%). Bp 65°C (760 mmHg). 1H NMR (400 MHz, CDCl3) δ 0.8-2.2 (m, 16H), 5.5-5.56 (m, 2H).

4.5.2 Reaction of 2-menthene 36 with triflic acid and diisopropylethylamine

A solution of 2-menthene 36 (0.05 g, 0.36 mmol), triflic acid (32 µL, 0.36 mmol) and diisopropylethylamine (63 µL, 0.36 mmol) in DCM (1 mL) was stirred overnight at room temperature. The resulting mixture was concentrated in vacuo. Analysis by 1H NMR spectroscopy revealed 2-menthene 36 (95%) and 3-menthene 37 (5%).

4.6 Addition of excess triphenylphosphine oxide to a standard Mitsunobu reaction (in the absence of 4-nitrobenzoic acid)

A solution of triphenylphosphine (1 g, 3.8 mmol), triphenylphosphine oxide (4.45 g, 16 mmol) and (1R,2S,5R)-(−)-menthol (0.5 g, 3.2 mmol) was prepared in dry THF (25 mL) and cooled to 0°C. Addition of DIAD (0.75 mL, 3.8 mmol) generated a yellow solution which was left to warm to room temperature overnight. A sample was then removed for analysis by GC/MS and the remaining solution concentrated in vacuo. Analysis by both GC/MS and 1H NMR spectroscopy confirmed complete conversion of (1R,2S,5R)-(−)-menthol to 2-menthene 36.

5.0 Investigation of the influence of the menthyl leaving group on the reaction outcome – elimination versus substitution

5.1 Attempted esterification of (1R,2S,5R)-(−)-menthol through a triflate intermediate

Triflic anhydride (0.5 mL, 3 mmol) and diisopropylethylamine (1.15mL, 6.6mmol) were added to a solution of 4-nitrobenzoic acid (0.5 g, 3 mmol) and (1R,2S,5R)-(−)-
menthol (0.465 g, 3 mmol) in dry DCM (10 mL) under a nitrogen atmosphere at 0°C. 
The orange solution was stirred overnight at room temperature overnight and a pale
yellow precipitate formed. An aliquot of the reaction mixture was removed for analysis
by GC/MS and the remainder washed with sodium hydrogen carbonate (saturated
aqueous solution, 2 × 20 mL). The organic layers were combined, dried (anhydrous
MgSO₄), filtered and the solvent removed at reduced pressure. Analysis by GC/MS
revealed the presence of 2- and 3-menthene 36 and 37 (ratio 1 : 2 by ¹H NMR
spectroscopy) and neomenthyl 4-nitrobenzoate 67 and O-(4-nitrobenzoyl)-(−)-menthol
69 (ratio 1 : 3 by ¹H NMR spectroscopy) in a ratio of 36+37 : 67+69 = 91 : 9.

5.2 Attempted esterification of (1R,2S,5R)-(−)-menthol through a tosylate
intermediate

5.2.1 Preparation of (1R,2S,5R)-(−)-menthyl tosylate 87
(1R,2S,5R)-(−)-Menthyl tosylate 87 was prepared according to the procedure of
Winstein.²⁸¹ A solution of (1R,2S,5R)-(−)-menthol (2.5 g, 16 mmol) in pyridine (10
mL) was cooled to 0°C. Tosyl chloride (3 g, 16 mmol) was added and the solution
stirred at 0°C for 6 hours. The mixture was left to stand in a freezer at -18°C for 5 days.
The solution was filtered and water (15 mL) added to the filtrate. The precipitated solid
was collected by filtration, recrystallised from ethanol and dried under high vacuum to
yield (1R,2S,5R)-(−)-menthyl tosylate 87 as a white solid (3.8 g, 77%). Mp 92-94°C
(Lit.²⁸¹ 93.5-94). ¹H NMR (400 MHz, CDCl₃) δ 0.53 (d, J = 7.2 Hz, 3H, 5-CH₃), 0.78-
0.9 (m, 7H), 0.92-1.02 (m, 1H), 1.15-1.24 (m, 2H), 1.6-1.7 (m, 2H), 1.85-1.95 (m, 1H),
2.1-2.2 (m, 1H), 2.45 (s, 3H, CH₃), 4.41 (ddd, J = 10.8, 10.8, 4.5 Hz, 1H, H1), 7.32 (d, J
= 8.0 Hz, 2H, H3", H5") , 7.80 (d, J = 8.3 Hz, 2H, H2", H6") . ESMS (+ve mode) MH⁺,
311 (10%).
5.2.2 Reaction of \((1R,2S,5R)-(\text{-})\)-menthyl tosylate 87 with 4-nitrobenzoic acid and diisopropylethylamine: room temperature overnight

A solution of \((1R,2S,5R)-(\text{-})\)-menthyl tosylate 87 (0.45 g, 1.45 mmol) and 4-nitrobenzoic acid (0.24 g, 1.45 mmol) was prepared in DCM (15 mL) under nitrogen. Diisopropylethylamine (0.56 mL, 3.19 mmol) was added and the clear yellow solution stirred at room temperature overnight. An aliquot was removed for analysis by GC/MS. The reaction mixture was concentrated \textit{in vacuo} and dried briefly under high vacuum. Analysis by both GC/MS and \(^1\)H NMR spectroscopy indicated the presence of unreacted \((1R,2S,5R)-(\text{-})\)-menthyl tosylate 87.

5.2.3 Reaction of \((1R,2S,5R)-(\text{-})\)-menthyl tosylate 87 with 4-nitrobenzoic acid and diisopropylethylamine: reflux overnight

Procedure 5.2.2 was carried out and heated at reflux overnight. Analysis of the reaction mixture by both GC/MS and \(^1\)H NMR spectroscopy showed the presence of unreacted \((1R,2S,5R)-(\text{-})\)-menthyl tosylate 87.

5.2.4 Reaction of \((1R,2S,5R)-(\text{-})\)-menthyl tosylate 87 with the sodium salt of 4-nitrobenzoic acid and diisopropylethylamine

Sodium hydride (16 mg, 0.64 mmol, 95% powdered) was added to a solution of 4-nitrobenzoic acid (0.1 g, 0.64 mmol) in DCM (5 mL) under an atmosphere of nitrogen. The suspension was allowed to stir for 1 hour at room temperature. \((1R,2S,5R)-(\text{-})\)-Menthyl tosylate 87 (0.2 g, 0.64 mmol) was added and the solution stirred overnight at room temperature. The mixture was quenched with water (5 mL) and the DCM layer concentrated \textit{in vacuo}. Analysis by GC/MS showed the presence of 2- and 3-menthene 36 and 37 (5%) and \((1R,2S,5R)-(\text{-})\)-menthyl tosylate 87 (95%). Analysis by \(^1\)H NMR spectroscopy revealed unreacted \((1R,2S,5R)-(\text{-})\)-menthyl tosylate 87.
6.0 Esterification of secondary alcohols with retention using the Hendrickson reagent 27 and an activating agent

6.1 Synthesis of O-(4-nitrobenzoyl)-cyclohexanol 76 using the Hendrickson reagent 27 and DMAP

The Hendrickson reagent 27 (3 mmol) was prepared according to procedure 1.1. Addition of 4-nitrobenzoic acid (0.5 g, 3 mmol) was to the resulting white precipitate formed a clear solution after 15 minutes. DMAP (0.37 g, 3 mmol) was added and after 5 minutes, the solution treated with cyclohexanol (0.32 mL, 3 mmol) and diisopropylethylamine (1.15 mL, 6.6 mmol). After stirring at room temperature overnight, an aliquot was removed and examined by GC/MS, which indicated the presence of O-(4-nitrobenzoyl)-cyclohexanol 76 and cyclohexanol in a ratio of 97 : 3. The remaining solution was worked up as described in procedure 1.1. The resulting yellow residue was submitted to flash chromatography (DCM) to afford O-(4-nitrobenzoyl)-cyclohexanol 76 as a pale yellow solid (0.72 g, 96%). Mp 49-51°C (Lit.279 47-48°C). 1H NMR (400 MHz, CDCl3) δ 1.3-2.1 (m, 5H, H2-H6), 5.04-5.1 (m, 1H, H1), 8.21 (d, J = 9.2 Hz, 2H, H2’, H6’), 8.29 (d, J = 9.2 Hz, 2H, H3’, H5’). ESMS (+ve mode) MH+, 250 (25%).

6.2 Synthesis of O-(4-nitrobenzoyl)-(-)-menthol 69 using the Hendrickson reagent 27 and DMAP

The Hendrickson reagent 27 (3 mmol) was prepared according to procedure 1.1. Addition of 4-nitrobenzoic acid (0.6 g, 3.6 mmol) to the resulting white precipitate formed a clear solution after 15 minutes. DMAP (0.44 g, 3.6 mmol) was added and after 5 minutes, the solution treated with (1R,2S,5R)-(-)-menthol (0.46 g, 3 mmol) and diisopropylethylamine (1.15 mL, 6.6 mmol). After stirring at room temperature for 15 minutes, an aliquot was removed and examined by GC/MS (100% O-(4-nitrobenzoyl)-
(–)-menthol 69). The remaining solution was worked up as described in procedure 1.1. The resulting yellow residue was submitted to flash chromatography (DCM) to afford O-(4-nitrobenzoyl)-(–)-menthol 69 as a pale yellow solid (0.84 g, 92%). Mp 60-62°C. The ¹H NMR spectrum obtained for O-(4-nitrobenzoyl)-(–)-menthol 69 was identical to that reported previously.¹ H NMR (200 MHz, CDCl₃) δ 0.76-2.2 (m, 18H, H2-H6, 5-CH₃, H1', 6 × H2'), 4.98 (ddd, J = 11, 11, 4 Hz, 1H, H1), 8.21 (d, J = 9.1 Hz, 2H, H2", H6"), 8.3 (d, J = 9.1 Hz, 2H, H3", H5"). GC/MS m/z (relative intensity) 138 (2- and 3-menthene 36 and 37, 50%).
CHAPTER TWO
Cyclic analogues of the Hendrickson reagent

1.0 Synthesis and characterisation of five-, six- and seven-membered cyclic analogues 90-92

1.1 Oxidation of phosphines

1.1.1 Synthesis of 1,2-bis(diphenylphosphinyl)ethane 93

1,2-Bis(diphenylphosphino)ethane (1 g, 2.33 mmol) was dissolved in DCM (100 mL) and the solution shaken in a separating funnel with hydrogen peroxide (10 mL, 30% wt solution in water). The completion of the reaction (~ 5 min) was determined by TLC (DCM). The DCM layer was washed with water (2 × 80 mL), dried (anhydrous MgSO₄) and evaporated in vacuo. Recrystallisation of the crude residue from toluene yielded 1,2-bis(diphenylphosphinyl)ethane 93 as a white solid (1.06 g, 98%). Mp 273-275°C (Lit. 283 276-278°C). ³¹P NMR (162 MHz, CDCl₃) δ 33.0 (s).

1.1.2 Synthesis of bis(diphenylphosphinyl)methane 107

Bis(diphenylphosphinyl)methane 107 was prepared according to procedure 1.1.1 from bis(diphenylphosphino)methane (1 g, 2.6 mmol). Recrystallisation of the crude residue from ethanol yielded bis(diphenylphosphinyl)methane 107 as a white solid (1.01 g, 93%). Mp 173-176°C (Lit. 283 178-179°C). ³¹P NMR (162 MHz, CDCl₃) δ 26.4 (s).

1.1.3 Synthesis of 1,3-bis(diphenylphosphinyl)propane 94

1,3-Bis(diphenylphosphinyl)propane 94 was prepared according to procedure 1.1.1 from 1,3-bis(diphenylphosphino)propane (1 g, 2.43 mmol). 1,3-Bis(diphenyl-
phosphinyl)propane \textbf{94} was obtained as a white solid after recrystallisation of the crude residue from toluene/cyclohexane (1 : 1) (1.04 g, 97%). Mp 144-146°C (Lit.\textsuperscript{283} 142-144°C). \textsuperscript{31}P NMR (162 MHz, CDCl\textsubscript{3}) \( \delta \) 32.8 (s).

\textbf{1.1.4 Synthesis of 1,4-bis(diphenylphosphinyl)butane 95}

1,4-Bis(diphenylphosphinyl)butane \textbf{95} was prepared according to procedure 1.1.1 from bis(diphenylphosphino)butane (1 g, 2.34 mmol). 1,4-Bis(diphenylphosphinyl)butane \textbf{95} was obtained as a white solid after recrystallisation of the crude residue from ethanol (1.02 g, 95%). Mp 267-269°C (Lit.\textsuperscript{283} 264-266°C). \textsuperscript{31}P NMR (162 MHz, CDCl\textsubscript{3}) \( \delta \) 34.1 (s).

\textbf{1.2 \textsuperscript{31}P NMR spectroscopy study of five-membered cyclic analogue \textit{90} formation and subsequent reaction with alcohols}

\textbf{1.2.1 \textsuperscript{31}P NMR spectroscopy study of reaction of triflic anhydride with 1,2-bis(diphenylphosphinyl)ethane \textbf{93} at -80°C}

A solution of 1,2-bis(diphenylphosphinyl)ethane \textbf{93} (0.01 g, 0.023 mmol) in CD\textsubscript{2}Cl\textsubscript{2} (0.75 mL) was prepared in a 5 mm NMR tube under argon. A \textsuperscript{31}P NMR spectrum was obtained at –80°C. The tube was removed from the spectrometer and placed in a dry ice/ethanol slurry. Triflic anhydride (0.781 µL, 0.0046 mmol, 0.2 equiv.) was added, the tube quickly vortexed and another \textsuperscript{31}P NMR spectrum obtained at –80°C. This procedure was repeated until 1.2 equivalents of triflic anhydride has been added. With 0 equiv. triflic anhydride: \textsuperscript{31}P NMR (162 MHz, CD\textsubscript{2}Cl\textsubscript{2}, -80°C) \( \delta \) 33.4 (s); With 0.2 equiv. triflic anhydride: \textsuperscript{31}P NMR (162 MHz, CD\textsubscript{2}Cl\textsubscript{2}, -80°C) \( \delta \) 38.1 (br s); With 0.4 equiv. triflic anhydride: \textsuperscript{31}P NMR (162 MHz, CD\textsubscript{2}Cl\textsubscript{2}, -80°C) \( \delta \) 40.8 (br s), 51.9 (br s), ratio 1:1; With 0.6 equiv. triflic anhydride: \textsuperscript{31}P NMR (162 MHz, CD\textsubscript{2}Cl\textsubscript{2}, -80°C) \( \delta \) 42.5
(br s), 51.9 (br s), ratio 9:1; With 0.8 equiv. triflic anhydride: $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$, -80°C) δ 52.1 (br s); With 1.0 equiv. triflic anhydride: $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$, -80°C) δ 52.5 (br s), 59.3 (br s), ratio 1:1; with 1.2 equiv. triflic anhydride: $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$, -80°C) δ 53.7 (br s), 59.9 (br s), ratio 3:1; After standing sample with 1.2 equiv. triflic anhydride at –18°C for 26 hours: $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$, -80°C) δ 60.4 (s).

The above procedure was repeated using a drier sample of 1,2-bis(diphenylphosphinyl)ethane 93 and freshly distilled triflic anhydride. With 0.5 equiv. triflic anhydride: $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$, -80°C) δ 51.6 (br s); With 0.8 equiv. triflic anhydride: $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$, -80°C) δ 52.1 (br s), 59.3 (br s), ratio 1:2.

### 1.2.2 $^{31}$P NMR spectroscopy study of reaction of triflic acid with 1,2-bis(diphenylphosphinyl)ethane 93

1,2-Bis(diphenylphosphinyl)ethane 93 (10 mg, 0.0232 mmol) was dissolved in CD$_2$Cl$_2$ (0.75 mL) in a 5 mm NMR tube. A $^{31}$P NMR spectrum was obtained at –70°C. The tube was transferred to a slurry of dry ice/ethanol and triflic acid (0.41 µL, 0.0047 mmol) added. The tube was briefly vortexed and another $^{31}$P NMR spectrum obtained at –70°C. This procedure was repeated with the addition of another 0.2 equivalents of triflic acid (0.41 µL, 0.0047 mmol) and then a further 0.6 equivalents of triflic acid (1.23 µL, 0.0141 mmol). With 0 equiv. triflic acid: $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$, -70°C) δ 33.4 (s); With 0.2 equiv. triflic acid: $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$, -70°C) δ 34.1 (s); With 0.4 equiv. triflic acid: $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$, -70°C) δ 34.9 (s); With 1.0 equiv. triflic acid: $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$, -70°C) δ 39.8 (br s).
1.2.3 $^{31}$P NMR spectroscopy study of reaction of 1,2-bis(diphenylphosphinyl)ethane with 1,1,3,3-tetraphenyl-2-oxa-1,3-phospholanium bis(trifluoromethanesulfonate) 90

1,1,3,3-Tetraphenyl-2-oxa-1,3-phospholanium bis(trifluoromethanesulfonate) 90 was prepared by addition of triflic anhydride (3.9 µL, 0.023 mmol) to an ice-cooled 5 mm NMR tube containing 1,2-bis(diphenylphosphinyl)ethane 93 (10 mg, 0.023 mmol) in CD$_2$Cl$_2$ (0.75 mL) under argon. The tube was vortexed briefly and a $^{31}$P NMR spectrum acquired at –70°C. The tube was placed in a dry ice/ethanol slurry and a solution of 1,2-bis(diphenylphosphinyl)ethane 93 (2 mg, 0.0046 mmol) in CD$_2$Cl$_2$ (40 µL) added. The tube was briefly vortexed and another $^{31}$P NMR spectrum obtained at –70°C. This procedure was repeated with the addition of further 1,2-bis(diphenylphosphinyl)ethane 93 (3 mg, 0.07 mmol). With 0 equiv. 1,2-bis(diphenylphosphinyl)ethane 93: $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$, -70°C) δ 60.2 (s); With 0.2 equiv. 1,2-bis(diphenylphosphinyl)ethane 93: $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$, -70°C) δ 50.6 (br s), 60.2 (s), ratio 1 : 8; With 0.5 equiv. 1,2-bis(diphenylphosphinyl)ethane 93: $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$, -70°C) δ 52.2 (br s), 60.1 (s), ratio 4 : 1.

1.2.4 $^{31}$P NMR spectroscopy study of reaction of 4-chlorophenol with 1,1,3,3-tetraphenyl-2-oxa-1,3-phospholanium bis(trifluoromethanesulfonate) 90

1,1,3,3-Tetraphenyl-2-oxa-1,3-phospholanium bis(trifluoromethanesulfonate) 90 (0.023 mmol) was prepared according to procedure 1.2.3 in a 5 mm NMR tube. The tube was cooled to –80°C in a dry ice/ethanol slurry. A solution of 4-chlorophenol (1.5 mg, 0.012 mmol) in CD$_2$Cl$_2$ (20 µL) was added and the tube vortexed briefly until a clear solution resulted. A $^{31}$P NMR spectrum was obtained at –80°C. With 0 equiv. 4-chlorophenol: $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$, -80°C) δ 60.2 (s); With 0.5 equiv. 4-
chlorophenol: $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$, -80°C) $\delta$ 59.9 (d, $J = 59.8$ Hz), 60.3 (s), 76.8 (d, $J = 58.6$ Hz), 68.9 (d, $J = 62$ Hz), ratio 1 : 2 : 1.

1.2.5 $^{31}$P NMR spectroscopy study of reaction of cyclohexanol with 1,1,3,3-tetraphenyl-2-oxa-1,3-phospholanium bis(trifluoromethanesulfonate) 90

1,1,3,3-Tetraphenyl-2-oxa-1,3-phospholanium bis(trifluoromethanesulfonate) 90 (0.023 mmol) was prepared according to procedure 1.2.3 in a 5 mm NMR tube. The tube was cooled to −80°C in a dry ice/ethanol slurry. A solution of cyclohexanol (1.23 µL, 0.012 mmol) in CD$_2$Cl$_2$ (13 µL) was added and the tube vortexed briefly until a clear solution resulted. A $^{31}$P NMR spectrum was obtained at −80°C. With 0 equiv. cyclohexanol: $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$, -80°C) $\delta$ 60.2 (s); With 0.5 equiv. cyclohexanol: $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$, -80°C) $\delta$ 60.3 (s), 60.7 (d, $J = 58.6$ Hz), 68.9 (d, $J = 58.6$ Hz), ratio 2 : 1 : 1.

1.3 Synthesis and characterisation of cyclic analogues 90-92

1.3.1 Synthesis of 1,1,3,3-tetraphenyl-2-oxa-1,3-phospholanium bis(trifluoromethanesulfonate) 90

In a 5 mm NMR tube, a sample containing 1,2-bis(diphenylphosphinyl)ethane 93 (10 mg, 0.023 mmol) in dry CD$_2$Cl$_2$ (0.75 mL) was prepared under argon. The tube was cooled to 0°C and triflic anhydride (3.9 µL, 0.023 mmol) added via syringe. The resulting cloudy white solution was left to stand in a freezer at −18°C for 24 hours to give 1,1,3,3-tetraphenyl-2-oxa-1,3-phospholanium bis(trifluoromethanesulfonate) 90. $^1$H NMR (400 MHz, CD$_2$Cl$_2$) $\delta$ 3.0-3.1 (4H, m, 2 × CH$_2$), 7.65-7.7 (8H, m, Ar-H), 7.75-7.9 (12H, m, Ar-H). $^{13}$C NMR (100 MHz, CD$_2$Cl$_2$) 20.7 (CH$_2$), 122.8 (q, $J = 320$ Hz,
193

CF3), 123.0 (C), 130.6 (CH), 131.9 (CH), 135.7 (CH). 31P NMR (162 MHz, CD2Cl2) 58.6 (s).

1.3.2 Synthesis of 1,1,3,3-tetraphenyl-2-oxa-1,3-phosphinanium bis(trifluoromethanesulfonate) 91

1,1,3,3-Tetraphenyl-2-oxa-1,3-phosphinanium bis(trifluoromethanesulfonate) 91 was prepared according to procedure 1.3.1 from 1,3-bis(diphenylphosphinyl)propane 94 (10.2 mg, 0.023 mmol) and triflic anhydride (3.9 µL, 0.023 mmol). 1,1,3,3-Tetraphenyl-2-oxa-1,3-phosphinanium bis(trifluoromethanesulfonate) 91: 1H NMR (400 MHz, CD2Cl2) δ 3.0-3.2 (2H, m, CH2), 3.75-3.85 (4H, m, 2 × CH2), 7.65-7.75 (8H, m, Ar-H), 7.85-7.95 (12H, m, Ar-H). 13C NMR 131P, 1H (100 MHz, CD2Cl2) δ 18.7 (CH2), 20.7 (CH2), 116.5 (C), 120.0 (q, J = 320 Hz, CF3), 131.5 (CH), 133.8 (CH), 139.0 (CH). 31P NMR (162 MHz, CD2Cl2) δ 85.7 (s).

1.3.3 Synthesis of 1,1,3,3-tetraphenyl-2-oxa-1,3-phosphateanum bis(trifluoromethanesulfonate) 92

1,1,3,3-Tetraphenyl-2-oxa-1,3-phosphateanum bis(trifluoromethanesulfonate) 92 was prepared according to procedure 1.3.1 from 1,4-bis(diphenylphosphinyl)butane 95 (10.5 mg, 0.023 mmol) and triflic anhydride (3.9 µL, 0.023 mmol). 1,1,3,3-Tetraphenyl-2-oxa-1,3-phosphateanum bis(trifluoromethanesulfonate) 92: 1H NMR (400 MHz, CD2Cl2) δ 2.5-2.65 (4H, m, 2 × CH2), 3.55-3.65 (4H, m, 2 × CH2), 7.7-7.8 (16H, m, Ar-H), 7.95-8.05 (4H, m, Ar-H). 13C NMR 131P, 1H (100 MHz, CD2Cl2) δ 21.9 (CH2), 26.4 (CH2), 116.6 (C), 119.7 (q, J = 320 Hz, CF3), 131.8 (CH), 133.3 (CH), 139.2 (CH). 31P NMR (162 MHz, CD2Cl2) δ 91.5 (s).
1.3.4\(^{31}\)P NMR spectroscopy study of attempted formation of 1,1,3,3-tetraphenyl-2-oxa-1,3-phosphetanium bis(trifluoromethanesulfonate) 106

1.3.4.1 With 1.0 equivalent of triflic anhydride

Bis(diphenylphosphinyl)methane 107 (0.02 g, 0.048 mmol) was dissolved in CD\(_2\)Cl\(_2\) (0.75 mL) in a 5 mm NMR tube under an atmosphere of nitrogen. The tube was cooled to 0\(^\circ\)C and triflic anhydride (8.08 µL, 0.048 mmol) added. After brief mixing by vortex, a \(^{31}\)P NMR spectrum was recorded at 25\(^\circ\)C. With 0 equiv. triflic anhydride: \(^{31}\)P NMR (162 MHz, CD\(_2\)Cl\(_2\)) δ 24.2 (s); with 1.0 equiv. triflic anhydride: \(^{31}\)P NMR (162 MHz, CD\(_2\)Cl\(_2\)) δ 48.8 (br s), 56.4 (br s), 61.1 (br s), 71.2 (br s); ratio 41 : 9 : 25 : 25.

1.3.4.2 With 1.2 equivalents of triflic anhydride

Procedure 1.3.4.1 was repeated using triflic anhydride (9.7 µL, 0.058 mmol). After brief mixing by vortex, a \(^{31}\)P NMR spectrum was recorded at 25\(^\circ\)C. With 0 equiv. triflic anhydride: \(^{31}\)P NMR (162 MHz, CD\(_2\)Cl\(_2\)) δ 24.2 (s); with 1.2 equiv. triflic anhydride: \(^{31}\)P NMR (162 MHz, CD\(_2\)Cl\(_2\)) δ 48.8 (br s), 61.0 (br s), 71.1 (br s); ratio 60 : 19 : 21.

1.3.4.3 With 2.0 equivalents of triflic anhydride

Procedure 1.3.4.1 was repeated using triflic anhydride (16.15 µL, 0.096 mmol). After brief mixing by vortex, a \(^{31}\)P NMR spectrum was recorded at 25\(^\circ\)C. With 0 equiv. triflic anhydride: \(^{31}\)P NMR (162 MHz, CD\(_2\)Cl\(_2\)) δ 24.2 (s); with 2.0 equiv. triflic anhydride: \(^{31}\)P NMR (162 MHz, CD\(_2\)Cl\(_2\)) δ 48.8 (br s), 61.2 (br s), 71.3 (br s); ratio 52 : 25 : 23.
1.3.4.4 Attempted synthesis of 4-nitrobenzyl 4-nitrobenzoate 61 using 1,1,3,3-tetraphenyl-2-oxa-1,3-phosphetanium bis(trifluoromethanesulfonate) 106

Bis(diphenylphosphinyl)methane 107 (0.02 g, 0.048 mmol) was dissolved in CD$_2$Cl$_2$ (0.75 mL) in a 5 mm NMR tube under an atmosphere of nitrogen. The tube was cooled to 0°C and triflic anhydride (8.08 µL, 0.048 mmol) added. After mixing by vortex, 4-nitrobenzyl alcohol (7.4 mg, 0.048 mmol), 4-nitrobenzoic acid (8 mg, 0.048 mmol) and diisopropylethylamine (18.4 µL, 0.106 mmol) were added. The tube was mixed by vortex and analysed by $^{31}$P and $^1$H NMR spectroscopy at 25°C. $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$) δ 25.1 (s), 39.7 (br s), 65.8 (s) and 69.1 (s); ratio 30 : 33 : 1 : 36. The $^1$H NMR spectrum (400 MHz, CD$_2$Cl$_2$) was a complex mixture of products.

1.3.5 Synthesis of N-benzyl-4-nitrobenzamide 112 using the Hendrickson reagent 27

Addition of triflic anhydride (0.5 mL, 3 mmol) to a solution of triphenylphosphine oxide (2 g, 7.2 mmol) in dry DCM (10 mL) at 0°C under a nitrogen atmosphere generated a white precipitate. The mixture was stirred for 30 minutes, 4-nitrobenzoic acid (0.5 g, 3 mmol) was added and the solution stirred for 15 minutes until a clear solution resulted. Successive addition of benzylamine (0.33 mL, 3 mmol) and diisopropylethylamine (1.15 mL, 6.6 mmol) formed a yellow solution which was stirred at room temperature for 2 hours. The mixture was then washed with sodium hydrogen carbonate (5% aqueous solution, 2 × 20 mL) and water (2 × 20 mL). The organic layers were combined, dried (anhydrous MgSO$_4$) and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexane 1:1) afforded N-benzyl-4-nitrobenzamide 112 as a pale yellow solid (0.72 g, 97.2%). Mp 140-143°C (Lit. 141.5-143°C). $^1$H NMR (200 MHz, CDCl$_3$) δ 4.57 (d, $J = 5.9$ Hz, 2H, CH$_2$), 6.55-6.65 (br s, 1H, NH),
7.18-7.35 (m, 5H, H2'-H5'), 7.86 (d, J = 8.8 Hz, 2H, H2, H6), 8.18 (d, J = 8.8 Hz, 2H, H3', H5'). ESMS (+ve mode) MNa⁺, 279 (25%); MLi⁺, 263 (50%).

1.3.6 Formation of benzylaminotriphenylphosphonium trifluoromethanesulfonate 113 using the Hendrickson reagent 27

The Hendrickson reagent 27 (3 mmol) was prepared as described in procedure 1.3.5. Benzylamine (0.33 mL, 3 mmol) and diisopropylethylamine (1.15 mL, 6.6 mmol) were added, forming a yellow solution which was stirred at room temperature overnight. The mixture was worked up according to procedure 1.3.5. Purification by flash chromatography (DCM) isolated a mixture of triphenylphosphine oxide and benzylaminotriphenylphosphonium trifluoromethanesulfonate 113. The oxide was removed from the desired product by further chromatography (10% acetone/diethyl ether). The solid obtained was recrystallised (ethyl acetate) to afford benzylaminotriphenylphosphonium trifluoromethanesulfonate 113 as a white crystalline solid (1.24 g, 80%). Mp 114-116°C. ¹H NMR (400 MHz, CDCl₃) δ 4.25 (dd, J = 14.3, 7.3 Hz, 2H, CH₂), 7.05-7.21 (m, 5H, H2'-H6'), 7.58-7.78 (m, 15H, 3 × H2-H6). ¹³C NMR (100 MHz, CDCl₃) δ 46.0 (d, J = 2.3 Hz, CH₂), 120.5 (q, J = 320 Hz, CF₃), 120.8 (d, J = 102.4 Hz, C), 127.6 (CH), 127.7 (CH), 128.5 (CH), 129.9 (d, J = 13.6 Hz, CH), 133.3 (d, J = 10.5 Hz, C), 134.9 (d, J = 3.0 Hz, CH), 137.7 (d, J = 3.8 Hz, CH). ³¹P NMR (162 MHz, CDCl₃) δ 39.4 (s). IR (KBr) 692, 1028 cm⁻¹ (m, P-N-C). ESMS (+ve mode) C₂₅H₂₃NP⁺, 368 (100%), (-ve mode) CF₃SO₃⁻ 149 (100%). Anal. calcd for C₂₆H₂₃F₃NO₃PS: C, 60.34; H, 4.48; N, 2.71. Found: C, 60.21; H, 4.43; N, 2.45.

1.3.7 Synthesis of benzylaminodiphenyl(2-diphenylphosphinylethyl)phosphonium trifluoromethanesulfonate 114

1,2-Bis(diphenylphosphinyl)ethane 93 (0.5 g, 1.16 mmol) was dissolved in dry DCM (15 mL) under a nitrogen atmosphere. Dropwise addition of triflic anhydride (0.195
mL, 1.16 mmol) to the solution at 0°C generated a thick white precipitate, which was left to stir for 1 hour. Following the addition of benzylamine (0.125 mL, 1.16 mmol) and diisopropylethylamine (0.45 mL, 2.55 mmol), a clear solution resulted. The solution was warmed to room temperature for 2 hours and the mixture worked up according to procedure 1.3.5. The crude pale yellow solid was submitted to flash chromatography (10% acetone/diethyl ether) and following recrystallisation (ethyl acetate) gave benzylinodiphenyl(2-diphenylphosphinylethyl)phosphonium trifluoromethanesulfonate 114 as a white crystalline solid (0.7 g, 74%). Mp 177-178°C. ¹H NMR (400 MHz, CDCl₃) δ 2.6-2.72 (m, 2H, CH₂-PO), 2.88-3.0 (m, 2H, CH₂-PN), 4.08 (dd, J = 13.6, 6.6 Hz, 2H, 2 × CH₂), 6.6-7.1 (m, 2H, Ar-H), 7.13-7.22 (m, 4H, Ar-H, NH), 7.46-7.82 (m, 20H, Ar-H). ¹³C NMR (100 MHz, CDCl₃) δ 19.0 (dd, J = 67.6, 4.9 Hz, CH₂-PO), 21.5 (dd, J = 67.6, 4.9 Hz, CH₂-PN), 46.2 (d, J = 2.5 Hz, CH₂), 119.9 (d, J = 99.7 Hz, C) 120.6 (q, J_CF = 320 Hz, CF₃), 127.8 (CH), 128.0 (CH), 128.8 (CH), 129.1 (d, J = 12.4 Hz, CH), 130.2 (d, J = 13.2 Hz, CH), 130.8 (d, J = 9.9 Hz, CH), 131.2 (d, J = 99.7 Hz, C), 132.4 (d, J = 2.5 Hz, CH), 132.6 (d, J = 10.7 Hz, CH), 135.2 (d, J = 2.5 Hz, CH), 137.5 (d, J = 4.1 Hz, CH). ³¹P NMR (162 MHz, CDCl₃) δ 33.1 (d, J = 42.2 Hz, PO), 45.5 (d, J = 42.2 Hz, PN). IR (KBr) 738, 1030 (m, P=N-C), 1271 cm⁻¹ (s, P=O). ESMS (+ve mode) (C₃₃H₃₂NOP₂⁺) 520 (100%); (-ve mode) (CF₃SO₃⁻) 149 (100%). HRMS (Found: 520.1970. C₃₃H₃₂NOP₂⁺ requires 520.1959). Anal. calcd for C₃₄H₃₂F₃NO₄P₂S: C, 60.98; H, 4.82; N, 2.09%. Found: C, 60.41; H, 4.90; N, 2.08%.

1.3.8 Synthesis of benzylinodiphenyl(2-diphenylphosphinylpropyl)phosphonium trifluoromethanesulfonate 115

Benzylinodiphenyl(2-diphenylphosphinylpropyl)phosphonium trifluoromethanesulfonate 115 was prepared according to procedure 1.3.7 from 1,3-bis(diphenylphosphinyl)propane 94 (0.52 g, 1.16 mmol), triflic anhydride (0.195 mL,
1.16 mmol), benzylamine (0.125 mL, 1.16 mmol) and diisopropylethylamine (0.45 mL, 2.55 mmol). Benzylaminodiphenyl(2-diphenylphosphinylpropyl)phosphonium trifluoromethanesulfonate 115 was obtained as a white solid (0.6 g, 62%). Mp 55-58°C. $^1$H NMR (400 MHz, CDCl$_3$) δ 1.85-2.0 (m, 2H, CH$_2$-CH$_2$-PO), 2.4-2.5 (m, 2H, CH$_2$-PO), 3.05-3.15 (m, 2H, CH$_2$-PN), 4.03 (dd, $J = 12.8$, 7.2 Hz, 2H, CH$_2$), 6.5 (dt, $J = 17.0$, 6.9 Hz, 1H, NH), 7.05-7.1 (m, 2H, Ar-H), 7.18-7.22 (m, 3H, Ar-H), 7.4-7.75 (m, 20H, Ar-H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 14.9 (dd, $J = 3.8$, 1.2 Hz, CH$_2$-CH$_2$-PO), 25.2 (dd, $J = 63.8$, 11.1 Hz, CH$_2$-PO), 28.9 (dd, $J = 71.5$, 16.7 Hz, CH$_2$-PN), 45.9 (d, $J = 2.3$ Hz, CH$_2$), 120.1 (d, $J = 99.7$ Hz, C) 120.6 (q, $J_{CF} = 320$ Hz, CF$_3$), 127.7 (CH), 127.8 (CH), 128.7 (CH), 128.8 (d, $J = 13.6$ Hz, CH), 129.9 (d, $J = 13.0$ Hz, CH), 130.6 (d, $J = 9.3$ Hz, CH), 131.7 (d, $J = 101$ Hz, C), 132.0 (CH), 132.6 (d, $J = 11.2$ Hz, CH), 134.8 (d, $J = 2.1$ Hz, CH), 137.2 (d, $J = 4.5$ Hz, CH). $^{31}$P NMR (162 MHz, CDCl$_3$) δ 34.0 (d, $J = 2.3$ Hz, PO), 44.1 (d, $J = 2.8$ Hz, PN). IR (KBr) 638, 1030 (m, P-N-C), 1259 cm$^{-1}$ (s, P=O). ESMS (+ve mode) (C$_{34}$H$_{34}$NOP$_2$)$^+$ 534 (100%); (-ve mode) (CF$_3$SO$_3$)$^-$ 149 (100%). HRMS (Found: 534.2120. C$_{34}$H$_{34}$NOP$_2$ requires 534.2116).

1.3.8 Synthesis of benzylaminodiphenyl(2-diphenylphosphinylbutyl)phosphonium trifluoromethanesulfonate 116

Benzylaminodiphenyl(2-diphenylphosphinylbutyl)phosphonium trifluoromethanesulfonate 116 was prepared according to procedure 1.3.7 using 1,4-bis(diphenylphosphinyl)butane 95 (0.54 g, 1.16 mmol), triflic anhydride (0.195 mL, 1.16 mmol), benzylamine (0.125 mL, 1.16 mmol) and diisopropylethylamine (0.45 mL, 2.55 mmol). Benzylaminodiphenyl(2-diphenylphosphinylbutyl)phosphonium trifluoromethanesulfonate 116 was obtained as a pale yellow solid (0.65 g, 66%). Mp 40-42°C. $^1$H NMR (400 MHz, CDCl$_3$) δ 1.6-1.75 (m, 2H, CH$_2$-CH$_2$-PO), 2.35-2.45 (m, 2H, CH$_2$-CH$_2$-PO), 2.6-2.8 (m, 4H, CH$_2$-PO, CH$_2$-PN), 4.04 (2H, dd, $J = 13.4$, 5.9 Hz, CH$_2$),
6.85-6.95 (1H, br s, NH), 7.1-7.2 (m, 5H, Ar-H), 7.4-7.8 (m, 20H, Ar-H). $^{13}$C NMR

(100 MHz, CDCl$_3$) $\delta$ 22.1 (dd, $J = 17.4$, 3.1 Hz, CH$_2$), 22.6 (dd, $J = 15.5$, 3.4 Hz, CH$_2$), 24.5 (d, $J = 65.0$ Hz, CH$_2$), 28.0 (d, $J = 70.6$ Hz, CH$_2$), 45.9 (d, $J = 1.9$ Hz, CH$_2$), 120.3 (d, $J = 97.9$ Hz, C), 120.6 (q, $J_{CF} = 320$ Hz, CF$_3$), 127.8 (CH), 127.9 (CH), 128.6 (CH), 128.8 (d, $J = 11.8$ Hz, CH), 130.0 (d, $J = 13.0$ Hz, CH), 130.8 (d, $J = 9.3$ Hz, CH), 131.4 (d, $J = 110.0$ Hz, C), 132.0 (CH), 132.7 (d, $J = 10.5$ Hz, CH), 134.8 (d, $J = 2.5$ Hz, CH), 137.5 (d, $J = 4.3$ Hz, CH). $^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ 33.6 (s, PO), 44.7 (s, PN).

IR (KBr) 638, 1030 (m, P-N-C), 1278 cm$^{-1}$ (s, P=O). ESMS (+ve mode) (C$_{35}$H$_{36}$NOP$_2^+$) 548 (100%); (-ve mode) (CF$_3$SO$_3^-$) 149 (100%). HRMS (Found: 548.2272. C$_{35}$H$_{36}$NOP$_2^+$ requires 548.2272).

2.0 Uses of the cyclic analogues 90-92 for ester and amide formation

2.1 Synthesis of 4-nitrobenzyl 4-nitrobenzoate 61 using cyclic analogues 90-92

2.1.1 Synthesis of 4-nitrobenzyl 4-nitrobenzoate 61 using 1,1,3,3-tetraphenyl-2-oxa-1,3-phospholanium bis(trifluoromethanesulfonate) 90

Triflic anhydride (0.34 mL, 2 mmol) was added slowly to a solution of 1,2-bis(diphenylphosphinyl)ethane 93 (1.03 g, 2.4 mmol) in dry DCM (15 mL) at 0°C under a nitrogen atmosphere. A thick white precipitate formed almost immediately. The mixture was stirred at 0°C for 1 hour. 4-Nitrobenzyl alcohol (0.31 g, 2 mmol), 4-nitrobenzoic acid (0.34 g, 2 mmol) and diisopropylethylamine (0.77 mL, 4.4 mmol) were added consecutively and the resulting yellow solution left to warm to room temperature overnight. The solution was then washed with sodium hydrogen carbonate (saturated aqueous solution, 2 × 20 mL) and water (2 × 20 mL). The combined organic layers were dried (anhydrous MgSO$_4$), filtered and the solvent removed in vacuo. The
residue was submitted to flash chromatography (DCM/hexane 1:1) to afford 4-nitrobenzyl 4-nitrobenzoate 61 as a yellow solid (0.56 g, 93%). Mp 165-167°C (Lit. 168°C). $^1$H NMR (200 MHz, CDCl$_3$) δ 5.51 (s, 2H, CH$_2$), 7.63 (d, $J$ = 8.8 Hz, 1H, H2', H6'), 8.22-8.4 (m, 6H, H2, H3, H5, H6, H3', H5'). ESMS (+ve mode) MH$^+$, 302 (15%).

2.1.2 Synthesis of 4-nitrobenzyl 4-nitrobenzoate 61 using 1,1,3,3-tetraphenyl-2-oxa-1,3-phosphinanium bis(trifluoromethanesulfonate) 91

Procedure 2.1.1 was carried out using 1,3-bis(diphenylphosphinyl)propane 94 (1.07 g, 2.4 mmol), triflic anhydride (0.34 mL, 2 mmol), 4-nitrobenzyl alcohol (0.31 g, 2 mmol), 4-nitrobenzoic acid (0.34 g, 2 mmol) and diisopropylethylamine (0.77 mL, 4.4 mmol). 4-Nitrobenzyl 4-nitrobenzoate 61 was obtained as a yellow solid (0.57 g, 94%). Mp 165-167°C (Lit. 168°C). $^1$H NMR (200 MHz, CDCl$_3$) δ 5.51 (s, 2H, CH$_2$), 7.63 (d, $J$ = 8.8 Hz, 1H, H2', H6'), 8.22-8.4 (m, 6H, H2, H3, H5, H6, H3', H5'). ESMS (+ve mode) MH$^+$, 302 (15%).

2.1.3 Synthesis of 4-nitrobenzyl 4-nitrobenzoate 61 using 1,1,3,3-tetraphenyl-2-oxa-1,3-phosphepanium bis(trifluoromethanesulfonate) 92

Procedure 2.1.1 was carried out using 1,4-bis(diphenylphosphinyl)butane 95 (1.1 g, 2.4 mmol), triflic anhydride (0.34 mL, 2 mmol), 4-nitrobenzyl alcohol (0.31 g, 2 mmol), 4-nitrobenzoic acid (0.34 g, 2 mmol) and diisopropylethylamine (0.77 mL, 4.4 mmol). 4-Nitrobenzyl 4-nitrobenzoate 61 was obtained as a yellow solid (0.5 g, 83%). Mp 170-171°C (Lit. 168°C). $^1$H NMR (200 MHz, CDCl$_3$) δ 5.51 (s, 2H, CH$_2$), 7.63 (d, $J$ = 8.8 Hz, 1H, H2', H6'), 8.22-8.4 (m, 6H, H2, H3, H5, H6, H3', H5'). ESMS (+ve mode) MH$^+$, 302 (15%).
2.2 Synthesis of N-phenyl-4-toluamide 118 using cyclic analogues 90-92

2.2.1 Synthesis of N-phenyl-4-toluamide 117 using 1,1,3,3-tetraphenyl-2-oxa-1,3-phospholanium bis(trifluoromethanesulfonate) 90

1,1,3,3-Tetraphenyl-2-oxa-1,3-phospholanium bis(trifluoromethanesulfonate) 90 (2 mmol) was prepared according to procedure 2.1.1 from 1,2-bis(diphenylphosphinyl)ethane 93 (1.02 g, 2.4 mmol) and triflic anhydride (0.34 mL, 2 mmol). Aniline (0.185 mL, 2 mmol), 4-toluic acid (0.27 g, 2 mmol) and diisopropylethylamine (0.77 mL, 4.4 mmol) were added consecutively and the solution warmed to room temperature over 2 hours. The solution was worked up as described in procedure 1.3.5. The resulting yellow residue was passed through a short silica column (ethyl acetate/hexane, 1:3) to yield N-phenyl-4-toluamide 117 as a pale yellow solid (0.34 g, 81%). Mp 147-149°C (Lit. 89 150°C). 1H NMR (200 MHz, CDCl3) δ 2.44 (s, 3H, CH3), 7.1-7.45 (m, 5H, H2' - H6'), 7.65 (d, J = 7.9 Hz, 2H, H2, H6), 7.79 (d, J = 7.9 Hz, 2H, H3, H5). ESMS (+ve mode) MH+ (212, 100%), MLi+ (218, 100%).

2.2.2 Synthesis of N-phenyl-4-toluamide 117 using 1,1,3,3-tetraphenyl-2-oxa-1,3-phosphinanium bis(trifluoromethanesulfonate) 91

Procedure 2.2.1 was carried out using 1,3-bis(diphenylphosphinyl)propane 94 (1.07 g, 2.4 mmol), triflic anhydride (0.34 mL, 2 mmol), aniline (0.185 mL, 2 mmol), 4-toluic acid (0.27 g, 2 mmol) and diisopropylethylamine (0.77 mL, 4.4 mmol) to give N-phenyl-4-toluamide 117 as a pale yellow solid (0.38 g, 90%). Mp 151-152°C (Lit. 89 150°C). 1H NMR (200 MHz, CDCl3) δ 2.44 (s, 3H, CH3), 7.1-7.45 (m, 5H, H2' - H6'), 7.65 (d, J = 7.9 Hz, 2H, H2, H6), 7.79 (d, J = 7.9 Hz, 2H, H3, H5). ESMS (+ve mode) MH+ (212, 100%), MLi+ (218, 100%).
2.2.3 Synthesis of \(N\)-phenyl-4-toluamide 117 using 1,1,3,3-tetraphenyl-2-oxa-1,3-phosphepanium bis(trifluoromethanesulfonate) 92

Procedure 2.2.1 was carried out using 1,4-bis(diphenylphosphinyl)butane 95 (1.1 g, 2.4 mmol), triflic anhydride (0.34 mL, 2 mmol), aniline (0.185 mL, 2 mmol), 4-toluic acid (0.27 g, 2 mmol) and diisopropylethylamine (0.77 mL, 4.4 mmol) to give \(N\)-phenyl-4-toluamide 117 as a pale yellow solid (0.36 g, 85%). Mp 148-149°C (Lit.\(^{89}\) 150°C). \(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta\) 2.44 (s, 3H, CH\(_3\)), 7.1-7.45 (m, 5H, H\(_2\)' - H\(_6\)'), 7.65 (d, \(J = 7.9\) Hz, 2H, H\(_2\), H\(_6\)), 7.79 (d, \(J = 7.9\) Hz, 2H, H\(_3\), H\(_5\)). ESMS (+ve mode) MH\(^+\) (212, 100%), MH\(^+\) (218, 100%).

3.0 Kinetic studies of 4-nitrobenzyl 4-nitrobenzoate 61 formation using the Hendrickson reagent 27 and cyclic analogues 90-92

3.1 Kinetic study of the effect of solvent polarity on 4-nitrobenzyl 4-nitrobenzoate 61 formation using the Hendrickson reagent 27

A solution of triphenylphosphine oxide (1.34 g, 4.8 mmol) in dry DCM, DCM/acetonitrile (1:1) or DCM/toluene (1:1) (150 mL) under nitrogen was cooled to 0°C using a temperature-controlled bath (EtOH/H\(_2\)O). Triflic anhydride (0.34 mL, 2 mmol) was added slowly and the solution stirred for 1 hour. 4-Nitrobenzyl alcohol (0.31 g, 2 mmol), 4-nitrobenzoic acid (1.7 g, 10 mmol) and diisopropylethylamine (1.74 mL, 10 mmol) were added consecutively. Aliquots (1.5 mL) were then removed periodically (at 1, 2, 3, 5, 10, 15, 30, 60 and 180 min) from the reaction mixture and quenched in sodium hydrogen carbonate (saturated aqueous solution, 2 mL). The organic phase of each aliquot was separated, dried (anhydrous MgSO\(_4\)) and concentrated \textit{in vacuo}. The ratio of 4-nitrobenzyl 4-nitrobenzoate 61 to unreacted 4-nitrobenzyl alcohol was determined by \(^1\)H NMR integration of the respective benzyl
Analysis by $^1$H NMR spectroscopy revealed the following conversions to 4-nitrobenzyl 4-nitrobenzoate \textit{61} over time.

DCM/toluene (1:1): 1 min (47.6%), 2 min (68.8%), 3 min (78.4%), 5 min (89.5%), 10 min (97.7%), 15 min (98.3%), 30 min (99.2%).

DCM: 1 min (26.1%), 2 min (42.8%), 3 min (52.0%), 5 min (63.2%), 10 min (80%), 15 min (86.5%), 30 min (96.8%), 60 min (97.5%).

DCM/acetonitrile (1:1): 1 min (13.1%), 2 min (17.0%), 3 min (20.3%), 5 min (26.4%), 10 min (38.8%), 15 min (48.8%), 30 min (66.9%), 60 min (83.3%), 180 min (100%).

3.2 Kinetic study of 4-nitrobenzyl 4-nitrobenzoate \textit{61} formation using cyclic analogues 90-92 in DCM

Procedure 3.1 was carried out with a solution of the bis-phosphine oxide 93-95 (2.4 mmol) in dry DCM (150 mL) at 0°C. The ratio of 4-nitrobenzyl 4-nitrobenzoate \textit{61} to unreacted 4-nitrobenzyl alcohol was determined by $^1$H NMR integration of the respective benzyl CH$_2$ groups. The following conversions to 4-nitrobenzyl 4-nitrobenzoate \textit{61} were recorded over time.

1,1,3,3-Tetraphenyl-2-oxa-1,3-phospholanium bis(trifluoromethanesulfonate) 90: 1 min (35.1%), 2 min (55.1%), 3 min (68.7%), 5 min (78.6%), 10 min (91.8%), 15 min (96.1%), 30 min (98.0%).

1,1,3,3-Tetraphenyl-2-oxa-1,3-phosphinanium bis(trifluoromethanesulfonate) 91: 1 min (6.4%), 2 min (8.4%), 3 min (12.1%), 5 min (17.7%), 10 min (24.5%), 15 min (31.2%), 30 min (49.7%), 60 min (67.1%), 180 min (93.1%).

1,1,3,3-Tetraphenyl-2-oxa-1,3-phospheneanum bis(trifluoromethanesulfonate) 92: 1 min (6.5%), 2 min (14.5%), 3 min (17.7%), 5 min (20.7%), 10 min (29.1%), 15 min (34.3%), 30 min (48.3%), 60 min (62.3%), 180 min (91.0%).
1.0 Tributylphosphonium anhydride trifluoromethanesulfonate 120 [µ-oxobis(tributylphosphonium) bis(trifluoromethanesulfonate)]

1.1 Synthesis and characterisation of tributylphosphonium anhydride trifluoromethanesulfonate 120

1.1.1 Synthesis of tributylphosphonium anhydride trifluoromethanesulfonate 120

Tributylphosphine oxide 121 (0.044 g, 0.2 mmol) was dissolved in CD$_2$Cl$_2$ (0.75 mL) under an atmosphere of nitrogen in a 5 mm NMR tube. The tube was cooled to 0°C and triflic anhydride (17 µL, 0.1 mmol) added. The tube was stoppered and briefly mixed using a vortex mixer to give tributylphosphonium anhydride trifluoromethanesulfonate 120, which was used directly in the next step. $^1$H NMR (400 MHz, CD$_2$Cl$_2$) δ 0.99 (t, $J = 7.2$ Hz, 18H, 6 × CH$_3$), 1.5-1.7 (m, 24H, 12 × CH$_2$), 2.78-2.88 (m, 12H, 6 × CH$_2$). $^{13}$C NMR (100 MHz, CD$_2$Cl$_2$) δ 13.5 (CH$_3$), 23.8 (CH$_2$), 24.0 (d, $J = 9.1$ Hz, CH$_2$), 24.9 (d, $J = 25.1$ Hz, CH$_2$). $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$) δ 119.2 (s).

1.1.2 $^{31}$P NMR spectroscopy study of the reaction of triflic acid with tributylphosphine oxide 121

Tributylphosphine oxide 121 (0.02 g, 0.1 mmol) was dissolved in CD$_2$Cl$_2$ (0.75 mL) in a 5 mm NMR tube. The tube was stoppered and a $^{31}$P NMR spectrum recorded. Triflic acid (8.9 µL, 0.1 mmol) was added, the tube briefly mixed by vortexing and another $^{31}$P NMR spectrum obtained. Initially at 25°C: $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$) δ 47.8 (s). Following triflic acid addition at 25°C: $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$) δ 85.2 (s).
1.1.3 Synthesis of benzylaminotributylphosphonium trifluoromethanesulfonate 122

Triflic anhydride (0.17 mL, 1 mmol) was added to a solution of tributylphosphine oxide 121 (0.48 g, 2.2 mmol) in DCM (8 mL) under nitrogen at 0°C. The clear yellow solution was stirring for 30 minutes at 0°C. Benzylamine (0.11 mL, 1.0 mmol) and diisopropylethylamine (0.38 mL, 2.2 mmol) were added and the solution was stirred overnight at room temperature. The mixture was washed with sodium hydrogen carbonate (saturated aqueous solution, 3 × 30 mL) and the combined organic layers dried (anhydrous MgSO₄), filtered and concentrated at reduced pressure. The resulting oil was dissolved in a minimum amount of boiling ethyl acetate. Addition of cold hexane formed a cloudy layer of solvent which was removed. The addition and removal of hexane was repeated five times and the remaining ethyl acetate layer passed through a short silica plug (ethyl acetate) to yield benzylaminotributylphosphonium trifluoromethanesulfonate 122 as a white solid (0.3 g, 66%). Mp 47-48°C. ¹H NMR (400 MHz, CDCl₃) δ 0.9 (t, J = 7.1 Hz, 9H, 3 × CH₃), 1.32-1.48 (m, 12H, 6 × CH₂), 1.98-2.08 (m, 6H, 3 × CH₂), 4.12 (dd, J = 15.5, 7.3 Hz, 2H, CH₂), 5.76 (dt, J = 7.7, 7.3 Hz, 1H, NH), 7.28-7.38 (m, 5H, Ar-H). ¹³C NMR (100 MHz, CDCl₃) δ 13.2 (C4), 21.5 (d, J = 58.8 Hz, C1), 22.9 (d, J = 3.8 Hz, C2), 23.6 (d, J = 16.0 Hz, C3), 45.4 (d, J = 2.7 Hz, CH₂), 120.5 (q, J = 319.3 Hz, CF₃), 127.6 (C4'), 128.1 (s, C2', C6'), 128.9 (s, C3', C5'), 138.2 (d, J = 2.7 Hz, C1'). ³¹P NMR (162 MHz, CDCl₃) δ 59.3 (s). IR (KBr) 640 (m, P-N), 1031 cm⁻¹ (m, C-N). ESMS (+ve mode) C₁₉H₃₅NP⁺, 308 (100%), (-ve mode) CF₃SO₃⁻, 149 (100%). Anal. calcd for C₂₀H₃₅F₃NO₃PS: C, 52.50; H, 7.71; N, 3.06. Found: C, 52.21; H, 7.86; N, 2.92.
1.2 Reactions using tributylphosphonium anhydride trifluoromethanesulfonate 120

1.2.1 Formation of 4-nitrobenzyl 4-nitrobenzoate 61

Tributylphosphonium anhydride trifluoromethanesulfonate 120 (1.44 mmol) was prepared according to procedure 1.1.3. 4-Nitrobenzyl alcohol (0.22 g, 1.44 mmol), nitrobenzoic acid (0.24 g, 1.44 mmol) and diisopropylethylamine (0.56 mL, 3.2 mmol) were added consecutively and the solution stirred at room temperature for 2 hours. The mixture was washed with sodium hydrogen carbonate (saturated aqueous solution, 2 × 20 mL) and the combined organic layers dried (anhydrous MgSO₄) and concentrated in vacuo. The resulting residue was submitted to flash chromatography (DCM/hexane 1:1). 4-Nitrobenzyl 4-nitrobenzoate 61 was obtained as a yellow solid (0.39 g, 90%). Mp 165-167°C (Lit. 168°C). ¹H NMR (200 MHz, CDCl₃) δ 5.51 (s, 2H, CH₂), 7.63 (d, J = 8.8 Hz, 1H, H₂', H₆'), 8.22-8.4 (m, 6H, H₂, H₃, H₅, H₆, H₃', H₅'). ESMS (+ve mode) MH⁺, 302 (15%).

1.2.2 Attempted synthesis of neomenthyl 4-nitrobenzoate 67 [(1S,2S,5R)-5-methyl-2-(1-methylethyl)cyclohexyl 4-nitrobenzoate]

1.2.2.1 Room temperature overnight

Tributylphosphonium anhydride trifluoromethanesulfonate 120 (1.44 mmol) was prepared according to procedure 1.1.3. (1R,2S,5R)-(−)-Menthol (0.23 g, 1.44 mmol) was added and after a clear solution formed, 4-nitrobenzoic acid (0.24 g, 1.44 mmol) and diisopropylethylamine (0.56 mL, 3.2 mmol) were added. The solution was stirred at room temperature overnight. An aliquot was removed for analysis by GC/MS. The remaining solution was worked up according to procedure 1.2.1. Analysis by GC/MS revealed the presence of 2- and 3-menthene 36 and 37 and unreacted (1R,2S,5R)-(−)-
menthol in a 1 : 9 ratio respectively. Analysis by $^1$H NMR spectroscopy revealed unreacted (1R,2S,5R)-(−)-menthol.

1.2.2.1 Reflux overnight

Procedure 1.2.2.1 was repeated with heating at reflux overnight. Analysis of an aliquot by GC/MS revealed the presence of 2- and 3-menthene 36 and 37 and neomethyl 4-nitrobenzoate 67 in a 9 : 1 ratio respectively. The combined DCM layers were dried (anhydrous MgSO$_4$), filtered and concentrated at reduced pressure. Analysis by $^1$H NMR spectroscopy revealed the presence of (1R,2S,5R)-(−)-menthlyoxytributylphosphonium trifluoromethanesulfonate 123 and 2- and 3-menthene 36 and 37 in a ratio of 17 : 3 respectively. The ratio of 36 : 37 following analysis by $^1$H NMR spectroscopy was 1 : 2 respectively. The minor UV active components were removed by column chromatography (DCM/hexane 1 : 1). The product 123 was isolated from tributylphosphine oxide 121 using column chromatography (1% acetone/chloroform, vanillin and heat visualisation) to yield (1R,2S,5R)-(−)-menthlyoxytributylphosphonium trifluoromethanesulfonate 123 as a white crystalline solid (0.1 g, 19.5%). Mp 111.5-112.5°C. $^1$H NMR (400 MHz, CDCl$_3$) δ 0.81 (d, 3H, $J_{2',1'} = 7.0$ Hz, 3 × H2'), 0.84-0.92 (m, 1H, H4$_{eq}$), 0.95 (d, 3H, $J_{2',1'} = 7.0$ Hz, 3 × H2'), 0.96 (d, 3H, $J = 6.5$ Hz, 5-CH$_3$), 0.98 (t, 9H, $J_{4'',3''} = 7.0$ Hz, 9 × H4''), 1.02-1.14 (m, 1H, H3$_{ax}$), 1.21 (ddd, 1H, $J_{6ax,6eq} = 12.0$ Hz, $J_{6ax,5ax} = J_{6ax,1ax} = 11.0$ Hz, H6$_{ax}$), 1.41 (dddd, 1H, $J_{2,1'} = 2.5$ Hz, $J_{2,3eq} = 3.5$ Hz, $J_{2,1} = 10.0$ Hz, $J_{2,3ax} = 13.0$ Hz, H2), 1.48-1.66 (m, 13H, 6 × H2'', 6 × H3'', H5), 1.68-1.76 (m, 2H, H3$_{eq}$, H4$_{ax}$), 1.93 (dqq, 1H, $J_{1',2'} = 7.0$ Hz, $J_{1',1} = 2.0$ Hz, H1'), 2.09 (dddd, 1H, $J_{6eq,6ax} = 11.5$ Hz, $J_{6eq,5ax} = J_{6eq,1ax} = 4.0$ Hz, $J_{6eq,4eq} = 1.5$ Hz, H6$_{eq}$), 2.29-2.51 (m, 6H, 6 × H1''), 4.35 (dddd, 1H, $J_{1ax,6ax} = J_{1ax,2ax} = 10.5$ Hz, $J_{HP} = 5.0$ Hz, $J_{1ax,6eq} = 4.5$ Hz, H1). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 13.1 (C4''), 15.6 (C2''), 20.9 (C2''), 21.7 (5-CH$_3$), 22.4 (C3), 22.7 (d, $J = 58.0$ Hz, C1'').
22.9 (d, $J = 4.0$ Hz, C2”), 23.5 (d, $J = 16.0$ Hz, C3”), 25.4 (C1’), 31.0 (C5), 33.3 (C4),
42.9 (C6), 49.0 (d, $J = 7.0$ Hz, C2), 83.8 (d, $J = 10.0$ Hz, C1), 120.5 (q, $J = 320$ Hz,
CF3). $^{31}$P NMR (162 MHz, CDCl3) $\delta$ 95.2 (s). IR (KBr) 1269 cm$^{-1}$ (P–O). ESMS (+ve
mode) C$_{22}$H$_{46}$OP$^+$, 357 (30%), (-ve mode) CF$_3$SO$_3$–, 149 (100%). Anal. calcd for
C$_{23}$H$_{46}$F$_3$O$_4$PS: C, 54.52; H, 9.15; S, 6.33. Found: C, 54.47; H, 9.52; S, 6.32.

1.2.3 Stability tests of (1R,2S,5R)-(–)-menthyloxytributylphosphonium trifluoromethanesulfonate 123

1.2.3.1 Water in THF

(1R,2S,5R)-(–)-Menthyloxytributylphosphonium trifluoromethanesulfonate 123 (0.025
g, 0.139 mmol) was stirred in a mixture of water (2 mL, pH 6) and THF (2 mL) at room
temperature overnight. The solution was extracted with DCM (2 × 5 mL) and the
combined DCM layers dried (anhydrous MgSO$_4$) and concentrated *in vacuo*. Analysis
of the residue by $^1$H and $^{31}$P NMR spectroscopy revealed unreacted (1R,2S,5R)-(–)-
menthyloxytributylphosphonium trifluoromethanesulfonate 123 (0.023 g, 92%).

1.2.3.1 Sodium hydrogen carbonate in THF

(1R,2S,5R)-(–)-Menthyloxytributylphosphonium trifluoromethanesulfonate 123 (0.025
g, 0.139 mmol) was stirred in a mixture of sodium hydrogen carbonate (2 mL, saturated
aqueous solution) and THF (2 mL) at room temperature overnight. The solution was
extracted with DCM (2 × 5 mL) and the combined DCM layers dried (anhydrous
MgSO$_4$) and concentrated *in vacuo*. Analysis by $^1$H and $^{31}$P NMR spectroscopy
revealed (1R,2S,5R)-(–)-menthol and tributylphosphine oxide 121 (0.22 g).
1.2.4 Reactions with \((1R,2S,5R)-(-)-\text{menthloxytributylphosphonium trifluoromethanesulfonate 123}\)

1.2.4.1 Sodium benzoate 124 in toluene

A solution of sodium benzoate 124 (0.02 g, 0.139 mmol) was prepared in toluene (3 mL) under an atmosphere of nitrogen. \((1R,2S,5R)-(-)-\text{menthloxytributylphosphonium trifluoromethanesulfonate 123}\) (0.05 g, 0.1 mmol) was added and the solution allowed to stir at room temperature overnight. Water (10 mL) was then added and the mixture extracted with DCM (2 × 15 mL). The DCM layers were combined, dried (anhydrous MgSO₄) and concentrated at reduced pressure. After drying under high vacuum, analysis of the resulting white solid (0.04 g) by \(^1\)H and \(^{31}\)P NMR spectroscopy indicated the presence of only \((1R,2S,5R)-(-)-\text{menthloxytributylphosphonium trifluoromethanesulfonate 123}\).

1.2.4.2 Sodium benzoate 124 in DMF

Procedure 1.2.4.2 was repeated in DMF (3 mL). Analysis of the resulting white solid (0.044 g) by \(^1\)H and \(^{31}\)P NMR spectroscopy indicated the presence of only \((1R,2S,5R)-(-)-\text{menthloxytributylphosphonium trifluoromethanesulfonate 123}\).

1.2.4.3 Lithium 4-nitrobenzoate 125 in toluene

A solution of 4-nitrobenzoic acid (0.023 g, 0.139 mmol) was prepared in toluene (3 mL) under an atmosphere of nitrogen. \(n\)-Butyllithium (87 µL, 0.139 mmol, 1.6 M in hexanes) was added slowly and a cloudy yellow solution formed. \((1R,2S,5R)-(-)-\text{Menthloxytributylphosphonium trifluoromethanesulfonate 123}\) (0.05 g, 0.1 mmol) was added and the solution allowed to stir at room temperature overnight. Water (10 mL)
was added and the mixture extracted with DCM (2 × 15 mL). The DCM layers were combined, dried (anhydrous MgSO₄) and concentrated at reduced pressure. After drying under high vacuum, analysis of the resulting white solid (0.04 g) by \(^1\)H and \(^{31}\)P NMR spectroscopy indicated the presence of only (1\(R\),2\(S\),5\(R\))-(–)-menthylxytributylphosphonium trifluoromethanesulfonate 123.

### 1.2.4.4 Zinc benzoate 126 in DMF

Zinc benzoate 126 was prepared as follows according to a modified literature procedure.\(^{87,285}\) A solution of benzoic acid (0.37 g, 3 mmol) in ethanol/water (40 mL, 1 : 2) was treated with zinc carbonate (0.36 g, 2.85 mmol) and the mixture sonicated for 15 minutes at room temperature. The cloudy white solution was concentrated at reduced pressure, washed twice with benzene (30 mL) and evaporated to dryness. The dry salt was used immediately. A solution of zinc benzoate 126 (0.02 g, 0.11 mmol) was prepared in DMF (3 mL) under an atmosphere of nitrogen. (1\(R\),2\(S\),5\(R\))-(–)-Menthylxytributylphosphonium trifluoromethanesulfonate 123 (0.05 g, 0.1 mmol) was added and the solution allowed to stir at room temperature overnight. The mixture was washed with sodium hydrogen carbonate (saturated aqueous solution, 2 × 15 mL) and concentrated in vacuo. Analysis of the resulting white solid (0.042 g) by \(^1\)H and \(^{31}\)P NMR spectroscopy indicated the presence of only (1\(R\),2\(S\),5\(R\))-(–)-menthylxytributylphosphonium trifluoromethanesulfonate 123.

### 1.2.4.5 Preparation of tetrabutylammonium 4-nitrobenzoate 127

Tetrabutylammonium 4-nitrobenzoate 127 was prepared according the procedure of Pocher.\(^{286}\) Tetrabutylammonium hydroxide (3.9 mL, 6 mmol, 40% w/v) was added to a solution of 4-nitrobenzoic acid (1 g, 6 mmol) and water (20 mL). The solution was left to stir at room temperature for 2 days. The resulting solution was extracted with DCM
(2 × 30 mL), the combined DCM layers dried (anhydrous MgSO₄), filtered and concentrated in vacuo. The resulting residue was dried under high vacuum to yield tetrabutylammonium 4-nitrobenzoate 127 as a yellow solid (2.2 g, 90%). Mp 84-86°C.  

$^1$H NMR (200 MHz, CDCl₃) δ 0.97 (t, $J = 6.6$ Hz, 12H, 4 × CH₃), 1.3-1.5 (m, 8H, 4 × CH₂), 1.56-1.76 (m, 8H, 4 × CH₂), 3.26-3.42 (m, 8H, 4 × CH₂), 8.12 (d, $J = 8.8$ Hz, 2H, H₃, H₅), 8.20 (d, $J = 8.8$ Hz, 2H, H₂, H₆). ESMS (+ve mode) Bu₄N⁺ 242 (100%); (-ve mode) O₂N-C₆H₄-COO⁻, 166 (70%).

1.2.4.6 Tetrabutylammonium 4-nitrobenzoate 127 in DCM

Tetrabutylammonium 4-nitrobenzoate 127 (0.1 g, 0.25 mmol) was added to a solution of DCM (5 mL) containing (1R,2S,5R)-(−)-menthylxytributylphosphonium trifluoromethanesulfonate 123 (0.1 g, 0.2 mmol). The solution was stirred at room temperature overnight. The DCM was removed in vacuo and the resulting residue (0.09 g) dried under high vacuum. Analysis by $^1$H NMR spectroscopy indicated the presence of only (−)-menthylxytributylphosphonium trifluoromethanesulfonate 123.

1.2.4.7 Preparation of (1R,2S,5R)-(−)-menthylxytributylphosphonium iodide 128

(−)-Menthylxytributylphosphonium trifluoromethanesulfonate 123 (0.1 g, 0.197 mmol) and sodium iodide (0.036 g, 0.24 mmol) were dissolved in acetone (5 mL) and the clear solution left to stir at room temperature for 2 days until a yellow solution resulted. Diethyl ether (5 mL) was then added and after 15 minutes, the precipitated white solid removed by filtration. The remaining clear yellow solution was concentrated in vacuo to yield (1R,2S,5R)-(−)-menthylxytributylphosphonium iodide 128 as a yellow oil (76 mg, 80%). The $^1$H and $^{13}$C NMR data obtained were consistent with the data obtained for (−)-menthylxytributylphosphonium trifluoromethanesulfonate 123. The absence of
the triflate counter-ion was confirmed by $^{13}$C NMR spectroscopy. ESMS (+ve mode) C$_{22}$H$_{46}$OP$^+$, 357 (5%), (-ve mode) I, 127 (20%).

1.2.4.8 Attempted preparation of neomenthyl iodide 129

(1$R$,2$S$,5$R$)-(--)-Menthylxytributylphosphonium iodide 128 (76 mg, 0.158 mmol) was refluxed in DCM (7 mL) overnight. Concentration of the resulting solution in vacuo yielded a yellow oil (70 mg) which was shown by $^1$H NMR spectroscopy to be unreacted (1$R$,2$S$,5$R$)-(--)-menthylxytributylphosphonium iodide 128.

2.0 Tricyclohexylphosphonium anhydride trifluoromethanesulfonate 130

2.1 Synthesis and characterisation of tricyclohexylphosphonium anhydride trifluoromethanesulfonate 130

2.1.1 Synthesis of tricyclohexylphosphine oxide 131

Tricyclohexylphosphine (0.73 g, 2.6 mmol) was dissolved in DCM (100 mL) and the solution shaken with hydrogen peroxide (10 mL, 30% wt solution in water) for 5 minutes. The DCM layer was washed with water (2 × 80 mL), dried (anhydrous MgSO$_4$) and evaporated in vacuo. Recrystallisation of the crude residue from hexane yielded tricyclohexylphosphine oxide 131 as a white solid (0.72 g, 93%). Mp 157-159°C (Lit. 283 155-157°C). $^{31}$P NMR (CDCl$_3$) δ 50.7 (s).

2.1.2 Synthesis of tricyclohexylphosphonium anhydride trifluoromethanesulfonate 130

Tricyclohexylphosphonium anhydride trifluoromethanesulfonate 130 (0.1 mmol) was prepared from tricyclohexylphosphine oxide 131 (0.06 g, 0.2 mmol) and triflic
anhydride (17 µL, 0.1 mmol) according to procedure 1.1.1. The tube was stoppered and briefly mixed by vortexing to give *tricyclohexylphosphonium anhydride trifluoromethanesulfonate* 130. $^1$H NMR (400 MHz, CD$_2$Cl$_2$) δ 1.25-2.2 (m, 60H, 30 × CH$_2$), 3.1-3.25 (m, 6H, 6 × CH). $^{13}$C NMR (100 MHz, CD$_2$Cl$_2$) δ 25.4 (12 × CH$_2$), 26.2 (12 × CH$_2$), 26.4 (d, $J$ = 18 Hz, 6 × CH$_2$), 35.2 (d, $J$ = 33 Hz, 6 × CH). $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$) δ 118.8 (s).

### 2.1.3 Synthesis of benzylaminotricyclohexylphosphonium trifluoromethanesulfonate 132

Benzylaminotricyclohexylphosphonium trifluoromethanesulfonate 132 was prepared from tricyclohexylphosphine oxide 131 (0.6 g, 2 mmol), triflic anhydride (0.17 mL, 1 mmol), benzylamine (0.11 mL, 1 mmol) and diisopropylethylamine (0.38 mL, 2.2 mmol) as described in procedure 1.1.3. The resulting foamy residue was recrystallised from hot ethyl acetate, to yield *benzylaminotricyclohexylphosphonium trifluoromethanesulfonate* 132 as a white solid (0.45 g, 84%). Mp 183-185°C. $^1$H NMR (400 MHz, CDCl$_3$) δ 1.05-1.5 (m, 15H) and 1.7-1.78 (m, 6 × H4, 6 × H3, 6 × H5), 1.8-1.9 (m, 12H, 6 × H2, 6 × H6), 2.3-2.45 (m, 3H, 3 × H1), 4.17 (dd, 2H, $J$ = 10.8, 7.5 Hz, CH$_2$), 5.48 (dd, 1H, $J$ = 7.7, 7.7 Hz, NH), 7.2-7.4 (m, 5H, C$_6$H$_5$). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 25.5 (d, $J$ = 1.9 Hz, C4), 26.3 (d, $J$ = 3.1 Hz, C2, C6), 26.5 (d, $J$ = 12.6 Hz, C3, C5), 32.1 (d, $J$ = 51.9 Hz, C1), 45.9 (d, $J$ = 3.8 Hz, CH$_2$), 120.6 (q, $J$ = 320.1 Hz, CF$_3$), 127.4 (C4'), 127.8 (C2', C6'), 128.8 (C3', C5'), 138.5 (d, $J$ = 3.4 Hz, C1'). $^{31}$P NMR (162MHz, CDCl$_3$) δ 57.2 (s). IR (KBr) 636 (m, P-N), 1028 cm$^{-1}$ (m, C-N). ESMS (+ve mode) C$_{25}$H$_{41}$NP$^+$, 386 (100%), (-ve mode) CF$_3$SO$_3^-$, 149 (100%). Anal. calcd for C$_{26}$H$_{41}$F$_3$NO$_3$PS: C, 58.30; H, 7.72; N, 2.61. Found: C, 58.34; H, 7.99; N, 2.49.
2.2 Reactions using tricyclohexylphosphonium anhydride trifluoromethane-sulfonate 130

2.2.1 Formation of 4-nitrobenzyl 4-nitrobenzoate 61

Tricyclohexylphosphine oxide 131 (1 g, 3.2 mmol) was dissolved in DCM (10 mL) under an atmosphere of nitrogen. The solution was cooled to 0°C and triflic anhydride (0.24 mL, 1.44 mmol) added. A clear solution resulted after stirring for 30 minutes. 4-Nitrobenzyl alcohol (0.22 g, 1.44 mmol), 4-nitrobenzoic acid (0.24 g, 1.44 mmol) and diisopropylethylamine (0.56 mL, 3.2 mmol) were added consecutively and the solution stirred for 2 hours at room temperature. The mixture was worked up according to procedure 1.2.1 and following flash chromatography (DCM/hexane 1 : 1), 4-nitrobenzyl 4-nitrobenzoate 61 was obtained as a yellow solid (0.41 g, 95%). Mp 165-167°C (Lit. 168°C). 1H NMR (200 MHz CDCl3) δ 5.51 (s, 2H, CH2), 7.63 (d, J = 8.8 Hz, 1H, H2', H6'), 8.22-8.4 (m, 6H, H2, H3, H5, H6, H3', H5'). ESMS (+ve mode) MH+, 302 (15%).

2.2.2 Kinetic study of 4-nitrobenzyl 4-nitrobenzoate 61 formation

A solution of the tricyclohexylphosphine oxide 131 (0.75 g, 2.4 mmol) in dry DCM (150 mL) under nitrogen was cooled to 0°C using a temperature-controlled bath (EtOH/H2O, 1 : 1). Triflic anhydride (0.34 mL, 2 mmol) was added slowly and the solution stirred for 1 hour. 4-Nitrobenzyl alcohol (0.31 g, 2 mmol), 4-nitrobenzoic acid (1.7 g, 10 mmol) and diisopropylethylamine (1.74 mL, 10 mmol) were added consecutively. Aliquots (1.5 mL) were then removed periodically (1, 2, 3, 5, 10, 15, 30, 60 and 180 min) from the reaction mixture and quenched in sodium hydrogen carbonate (saturated aqueous solution, 2 mL). The organic phase of each aliquot was separated, dried (anhydrous MgSO4) and concentrated in vacuo. The ratio of 4-nitrobenzyl 4-
nitrobenzoate 61 to unreacted 4-nitrobenzyl alcohol was determined by $^1$H NMR spectroscopy integration of the respective benzyl CH$_2$ groups. The following conversions to 4-nitrobenzyl 4-nitrobenzoate 61 were recorded over time: 1 min (83.7%), 2 min (88.4%), 3 min (95.6%).

### 2.2.3 Attempted synthesis of neomenthyl 4-nitrobenzoate 67 [(1$S$,2$S$,5$R$)-5-methyl-2-(1-methylethyl)cyclohexyl 4-nitrobenzoate]

#### 2.2.3.1 Room temperature overnight

Tricyclohexylphosphonium anhydride trifluoromethanesulfonate 130 (1.44 mmol) was prepared according to procedure 2.2.1. (1$R$,2$S$,5$R$)-(-)-Menthol (0.23 g, 1.44 mmol) was added and when a clear solution resulted, 4-nitrobenzoic acid (0.24 g, 1.44 mmol) and diisopropylethylamine (0.56 mL, 3.2 mmol) were added and the solution warmed to room temperature overnight. An aliquot was removed for analysis by GC/MS. The remaining solution was worked up as described in procedure 1.2.1. Analysis by $^1$H NMR spectroscopy revealed unreacted (1$R$,2$S$,5$R$)-(−)-menthol. Analysis by GC/MS revealed the presence of 2- and 3-menthene 36 and 37 and unreacted (1$R$,2$S$,5$R$)-(−)-menthol, in a ratio of 1 : 19 respectively.

#### 2.2.3.2 Reflux overnight

Procedure 2.2.3.1 was repeated with heating at reflux overnight. Analysis of an aliquot by GC/MS revealed the presence of 2- and 3-menthene 36 and 37, (1$S$,2$S$,5$R$)-menthyloxytricyclohexylphosphonium trifluoromethanesulfonate 133 and 2- and 3-menthene 36 and 37, in a ratio of 4 : 1 respectively. The minor UV active components were removed by column chromatography (1% acetone/chloroform). The
product 133 was isolated from tricyclohexylphosphine oxide 131 using column chromatography (acetone/chloroform 1:3, vanillin and heat visualisation) to yield (1R,2S,5R)-(-)-menthloxytricyclohexylphosphonium trifluoromethanesulfonate 133 as a white crystalline solid (0.1 g, 16%). Mp 133-135°C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.8 (d, 3H, $J_{2',1'} = 7.0$ Hz, 3 × H2”), 0.83-0.91 (m, 1H, H4$_{eq}$) 0.94 (d, 3H, $J_{2',1'} = 7.0$ Hz, 3 × H2”), 0.96 (d, 3H, $J = 6.5$ Hz, 5-CH$_3$) 1.0-1.12 (m, 1H, H3$_{ax}$), 1.22-1.34 (m, 4H, 3 × H4", H6$_{ax}$), 1.35-1.63 (m, 14H, 6 × H2" or H6", 6 × H3" or H5", H5, H2), 1.64-1.74 (m, 2H, H3$_{eq}$, H4$_{ax}$), 1.75-1.83 (m, 3H, 3 × H4") 1.87-2.07 (m, 13H, 6 × H2" or H6", 6 × H3", H1”), 2.11-2.17 (m, 1H, H6$_{eq}$), 2.51 (br t, $J_{HP} = 12.0$ Hz, $J_{HH} = 13.0$ Hz, 3 × H1”), 4.43 (ddddd, $J_{HP} = 3.0$ Hz, $J_{1ax,2ax} = 10.0$ Hz, $J_{1ax,6ax} = 9.0$ Hz, $J_{1ax,6eq} = 4.0$ Hz, H1). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 16.1 (C2”), 21.0 (C2”), 21.8 (5-CH$_3$), 22.5 (C3), 25.3 (d, $J = 2.0$ Hz, C4”), 25.4 (C1’), 26.0 (d, $J = 12.5$ Hz, C3" or C5”), 26.05 (d, $J = 13.0$ Hz, C3" or C5”), 26.2 (d, $J = 3.5$ Hz, C2" or C6”), 26.4 (d, $J = 3.0$ Hz, C2" or C6”), 31.4 (C5), 33.1 (C4), 34.6 (d, $J = 50.0$ Hz, C1”), 43.1 (C6), 49.6 (d, $J = 6.0$ Hz, C2), 86.1 (d, $J = 13.0$ Hz, C1), 120.5 (q, $J = 320$ Hz, CF$_3$). $^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ 88.1 (s). IR (KBr) 1254 cm$^{-1}$ (s, P-O). ESMS (+ve mode) C$_{28}$H$_{52}$OP$^+$, 435 (100%), (-ve mode) CF$_3$SO$_3^-$, 149 (100%). Anal. calcd for C$_{29}$H$_{52}$F$_3$O$_4$PS: C, 59.57; H, 8.96; S, 5.48. Found: C, 59.55; H, 9.23; S, 5.27.

3.0 Triphenylphosphonium anhydride tetrafluoroborate 42

3.1 Attempted formation of 4-nitrobenzyl 4-nitrobenzoate 61

3.1.1 Room temperature overnight

Triethyloxonium tetrafluoroborate (6 mL, 6 mmol, 1.0 M in DCM) was added slowly to a solution of triphenylphosphine oxide (2 g, 7.19 mmol) in dry DCM (10 mL) at 0°C
under an atmosphere of nitrogen. A white precipitate formed immediately and after stirring for 30 minutes, 4-nitrobenzyl alcohol (0.46 g, 3 mmol), 4-nitrobenzoic acid (0.5 g, 3 mmol) and diisopropylethylamine (1.15 mL, 6.6 mmol) were added. The clear solution was warmed to room temperature overnight, then worked up according to procedure 1.2.1. Analysis of the crude residue by $^1$H NMR spectroscopy indicated the presence of 61, 134 and 135 in a 1 : 2 : 2 ratio. The crude residue was submitted to flash chromatography (DCM/hexane, 1 : 1) and three fractions were obtained.

Fraction 1 (Rf 0.8) 4-nitrobenzyl ethyl ether 135, $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 1.28 (t, 3H, $J$ = 7 Hz, CH$_3$), 3.58 (q, 2H, $J$ = 7 Hz, OCH$_2$CH$_3$), 4.40 (s, 2H, CH$_2$), 7.48 (d, 2H, $J$ = 8 Hz, H2, H6), 8.28 (d, 2H, $J$ = 8 Hz, H3, H5). The $^1$H NMR spectra obtained for 4-nitrobenzyl ethyl ether 135 was in agreement with the literature.$^{287}$

Fraction 2 (Rf 0.4) ethyl 4-nitrobenzoate 134, $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 1.43 (t, $J$ = 7.4 Hz, 3H, CH$_3$), 4.43 (q, $J$ = 6.4 Hz, 2H, CH2), 8.20 (d, $J$ = 8.8 Hz, 2H, H2, H6), 8.29 (d, $J$ = 8.8 Hz, 2H, H3, H5). The $^1$H NMR spectra obtained for ethyl 4-nitrobenzoate 134 was in agreement with the literature.$^{288}$

Fraction 3 (Rf 0.3) 4-nitrobenzyl 4-nitrobenzoate 61, $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 5.51 (s, 2H, CH$_2$), 7.63 (d, $J$ = 8.8 Hz, 1H, H2', H6'), 8.22-8.4 (m, 6H, H2, H3, H5, H6, H3', H5').

3.1.2 Attempted isolation and use of triphenylphosphonium anhydride tetrafluoroborate 42

Triphenylphosphonium anhydride tetrafluoroborate 42 (6 mmol) was prepared according to procedure 3.1.1. Under Schlenk conditions, the white solid was washed
with dry DCM (3 × 50 mL) and the liquid removed following each washing. The white solid was dried briefly under high vacuum and taken up in fresh DCM (10 mL). 4-Nitrobenzyl alcohol (0.46 g, 3 mmol), 4-nitrobenzoic acid (0.5 g, 3 mmol) and diisopropylethylamine (1.15 mL, 6.6 mmol) were added and the solution stirred overnight at room temperature. The resulting solution was worked up according to procedure 1.2.1. Analysis by \(^1\text{H}\) NMR spectroscopy of the crude product revealed the presence of 4-nitrobenzyl ethyl ether \textbf{135} (60%) and unreacted 4-nitrobenzyl alcohol (40%).

\textbf{4.0 Diphenyl-2-pyridylphosphonium anhydride trifluoromethanesulfonate 137}

\textbf{4.1 Synthesis and characterisation of diphenyl-2-pyridylphosphonium anhydride trifluoromethanesulfonate 137}

\textbf{4.1.1 Synthesis of diphenyl-2-pyridylphosphine oxide 138}

Diphenyl-2-pyridylphosphine oxide \textbf{138} was prepared according to procedure 2.1.1 from diphenyl-2-pyridylphosphine (1 g, 2.6 mmol) and hydrogen peroxide (10 mL, 30% wt solution in water). Recrystallisation of the crude residue from cyclohexane yielded diphenyl-2-pyridylphosphine oxide \textbf{138} as a white solid (0.95 g, 90%). Mp 112-113°C (Lit.\textsuperscript{283} 109-110°C). \(^{31}\text{P}\) NMR (162 MHz, CDCl\textsubscript{3}) \(\delta\) 21.3 (s).

\textbf{4.1.2 Synthesis of diphenyl-2-pyridylphosphonium anhydride trifluoromethanesulfonate 137}

A solution of diphenyl-2-pyridylphosphine oxide \textbf{138} (0.05 g, 0.18 mmol) in CD\textsubscript{2}Cl\textsubscript{2} (0.75 mL) was prepared in a 5 mm NMR tube under argon. The tube was stoppered and a \(^{31}\text{P}\) NMR spectrum recorded. Freshly distilled triflic anhydride (15.2 µL, 0.09 mmol)
was added to the tube at 0°C. After 30 minutes, the tube was warmed to room temperature and $^{31}$P, $^1$H and $^{13}$C NMR spectra obtained.

Initially at 25°C: $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$) δ 16.7 (s). Following triflic anhydride addition at 25°C: $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$) δ 64.7 (s); $^1$H NMR (400 MHz, CD$_2$Cl$_2$) δ 7.65-7.8 (m, 5H, Ar-H), 7.85-8.0 (m, 7H, Ar-H), 8.1-8.25 (br s, 1H, 2-pyr-H), 8.65-8.75 (br s, 1H, 2-pyr-H); $^{13}$C NMR (100 MHz, CD$_2$Cl$_2$) δ 115-117 (br s, w½h = 120 Hz, 2-pyr-CH), 121.2 (q, J = 321 Hz, CF$_3$), 130.9 (s, CH), 131.4 (s, CH), 133.3 (br s, w½h = 37 Hz, 2-pyr-CH), 135.1 (s, CH), 138.7 (s, CH), 139.6 (br s, w½h = 50 Hz, 2-pyr-CH), 142.1 (br d, J = 156 Hz, 2-pyr-C), 152.6 (br s, w½h = 50 Hz, 2-pyr-CH).

4.1.3 Synthesis of benzylaminodiphenyl-2-pyridylphosphonium trifluoromethanesulfonate 141

Benzylaminodiphenyl-2-pyridylphosphonium trifluoromethanesulfonate 141 was prepared from diphenyl-2-pyridylphosphine oxide 138 (0.75 g, 2.69 mmol), triflic anhydride (0.19 mL, 1.12 mmol) and benzylamine (0.12 mL, 1.12 mmol), as described in procedure 1.1.3. The mixture was diluted with DCM (20 mL) and washed with water (2 × 20 mL). The water layer was back extracted with DCM (2 × 20 mL) and the combined DCM layers dried (anhydrous MgSO$_4$) and concentrated in vacuo. The residue was taken up in ethyl acetate (30 mL) and washed with water (2 × 20 mL). The water layers were extracted with DCM (2 × 20 mL) and the combined DCM layers dried (anhydrous MgSO$_4$) and concentrated in vacuo. The residue was again taken up in ethyl acetate, washed with water and the water layer extracted with DCM, as previously described, until an analytically pure sample of benzylaminodiphenyl-2-pyridylphosphonium trifluoromethanesulfonate 141 was obtained. Mp 91-93°C. $^1$H NMR (400 MHz, CDCl$_3$) δ 4.29 (dd, J = 14.0, 7.0 Hz, 2H, CH$_2$), 7.1-7.3 (m, 6H, CH$_2$-C$_6$H$_5$, NH), 7.55-7.62 (m, 6H, C$_6$H$_5$, H6), 7.72-7.85 (m, 5H, C$_6$H$_5$), 8.0 (dddd, J = 7.8,
7.8, 4.9, 1.7 Hz, 1H, H5), 8.3 (dd, J = 7.5, 6.6 Hz, 1H, H4), 8.84 (dd, J = 4.6, 1.45 Hz, 1H, H1). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 46.3 (d, J = 2.6 Hz, CH$_2$), 120.4 (d, J = 103 Hz, 2 × i-C$_6$H$_5$), 120.4 (q, J = 320 Hz, CF$_3$), 127.5 (d, J = 3.1 Hz, C3), 127.7 and 128.0 and 128.6 (C5, p-C$_6$H$_5$, m-CH$_2$-C$_6$H$_5$), 130.8 (d, J = 23.8 Hz, i-CH$_2$-C$_6$H$_5$), 129.7 (d, J = 13.4 Hz) and 132.2 (d, J = 9.9 Hz) and 133.9 (d, J = 10.7 Hz) and 137.8 (d, J = 10.7 Hz, o-C$_6$H$_5$, m-C$_6$H$_5$, o-CH$_2$-C$_6$H$_5$, m-CH$_2$-C$_6$H$_5$), 134.9 (d, J = 3.1 Hz, C4), 147.6 (d, J = 134 Hz, C2), 151.2 (d, J = 21.0 Hz, C6). $^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ 30.8 (s). IR (KBr) 638, 1029 cm$^{-1}$ (s, P-N-C). ESMS (+ve mode) 369 (100%), (-ve mode) CF$_3$SO$_3^-$, 149 (100%). (HRMS) Found: 369.15114. C$_{24}$H$_{22}$N$_2$P$^+$ requires 369.15151.

4.2 Reactions using diphenyl-2-pyridylphosphonium anhydride trifluoromethanesulfonate 137

4.2.1 Attempted synthesis of 4-nitrobenzyl 4-nitrobenzoate 61

Diphenyl-2-pyridylphosphine oxide 138 (0.75 g, 2.69 mmol) was dissolved in dry DCM (8 mL) under nitrogen and the solution cooled to 0°C. Addition of triflic anhydride (0.19 mL, 1.12 mmol) generated a clear yellow solution which was left to stir for 1 hour. 4-Nitrobenzyl alcohol (0.172 g, 1.12 mmol) and 4-nitrobenzoic acid (0.186 g, 1.12 mmol) were added consecutively and the solution warmed to room temperature overnight. The solution was washed with HCl (2 M, aqueous, 3 × 20 mL) and the organic layers dried (anhydrous MgSO$_4$) and concentrated in vacuo. Analysis of the crude residue (0.26 g) by $^1$H NMR spectroscopy revealed the presence of bis(4-nitrobenzyl)ether 142 ($\delta$ 4.7 ppm, s, 2H, CH$_2$), 4-nitrobenzyl alcohol ($\delta$ 4.82 ppm, s, 2H, CH$_2$) and 4-nitrobenzyl 4-nitrobenzoate 61 ($\delta$ 5.5 ppm, s, 2H, CH$_2$) in a 54 : 38 : 8 ratio. The $^1$H NMR data obtained for 142 was consistent with that reported previously in the literature.$^{289}$
4.2.2 Synthesis of benzyl 4-nitrobenzoate 143

Diphenyl-2-pyridylphosphonium anhydride trifluoromethanesulfonate 137 (1.12 mmol) was prepared according to procedure 4.2.1. Benzyl alcohol (116 µL, 1.12 mmol) and 4-nitrobenzoic acid (0.186 g, 1.12 mmol) were added to 137 and the solution stirred at room temperature overnight. The reaction mixture was worked up according to procedure 4.2.1. Benzyl 4-nitrobenzoate 143 was obtained as a pale yellow solid (0.26 g, 90%). Mp 80-83°C (Lit. 86°C). 1H NMR (200 MHz, CDCl3) δ 5.43 (s, 2H, CH2), 7.3-7.6 (m, 5H, H2’-H6’), 8.25 (d, J = 8.1 Hz, 2H, H2, H6), 8.31 (d, J = 8.1 Hz, 2H, H3, H5). ESMS (+ve mode) MH+, 257 (10%). The phosphine oxide was recovered by treatment of the acid solution with NaOH (aqueous 3 M solution) to pH 14, and extraction with diethyl ether.

4.2.3 Synthesis of benzyl benzoate 144

Procedure 4.2.2 was carried out using diphenyl-2-pyridylphosphine oxide 138 (0.75 g, 2.69 mmol), triflic anhydride (0.19 mL, 1.12 mmol), benzoic acid (0.136 g, 1.12 mmol) and benzyl alcohol (116 µL, 1.12 mmol). Benzyl benzoate 144 was obtained as a colourless oil (0.2 g, 84%). 1H NMR (200 MHz, CDCl3) δ 5.41 (s, 2H, CH2), 7.4–7.6 (m, 8H, Ar-H), 8.13 (d, J = 8.1 Hz, 2H, H2, H6). GC/MS m/z (relative intensity) 212 (M, 10%), 105 (C6H4CO, 100%). The 1H NMR data obtained for 144 was in agreement with that previously reported.291

4.2.4 Attempted synthesis of neomenthyl 4-nitrobenzoate 67 [(1S,2S,5R)-5-methyl-2-(1-methylethyl)cyclohexyl 4-nitrobenzoate]

Diphenyl-2-pyridylphosphonium anhydride trifluoromethanesulfonate 137 (1.12 mmol) was prepared according to procedure 4.2.1. (1R,2S,5R)-(−)-Menthol (0.088 g, 0.56 mmol) and 4-nitrobenzoic acid (0.093 g, 0.56 mmol) were added to 137. After stirring 40°C overnight, an aliquot was removed for GC/MS analysis. The remaining solution
was concentrated *in vacuo* and dried under high vacuum. GC/MS analysis revealed the presence of 2- and 3-menthene 36 and 37 (ratio 1 : 2 by $^1$H NMR spectroscopy) and neomenthyl 4-nitrobenzoate 67 in a 19 : 1 ratio. The presence of these species was confirmed by $^1$H NMR spectroscopy.

### 4.2.5 Synthesis of bis(4-nitrobenzyl)ether 142

Diphenyl-2-pyridylphosphonium anhydride trifluoromethanesulfonate 137 (1.12 mmol) was prepared according to procedure 4.2.1. 4-Nitrobenzyl alcohol (0.34 g, 2.24 mmol) was added to 137 and the clear solution stirred at room temperature overnight. The reaction mixture was worked up as described in procedure 4.2.1 to yield bis(4-nitrobenzyl)ether 142 as a white fluffy solid (0.28 g, 87%). Mp 94-96°C (Lit. 97-98°C). $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 4.72 (s, 4H, 2 × CH$_2$), 7.56 (d, $J = 8.8$ Hz, 4H, H2, H6), 8.25 (d, $J = 8.8$ Hz, 4H, H3, H5). $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 71.5 (CH$_2$), 123.7 (C3, C5), 127.7 (C2, C6), 145 (C1), 147.5 (C4). IR (KBr disk) 1345 (s, NO$_2$), 1513 (s, NO$_2$), 1603 cm$^{-1}$ (C-O-C). GC/MS m/z (relative intensity) 107 (C$_6$H$_5$-CH$_2$-O-, 45%), 92 (C$_6$H$_5$-CH$_2$-, 100%).

### 4.2.6 Attempted synthesis of bis(4-nitrobenzyl)ether 142 using the Hendrickson reagent 27

Triflic anhydride (0.5 mL, 3 mmol) was added to a solution of triphenylphosphine oxide (2 g, 7.2 mmol) in DCM (10 mL) at 0°C under a nitrogen atmosphere. A white precipitate formed and the mixture was stirred for 30 minutes. Subsequent addition of 4-nitrobenzyl alcohol (0.92 g, 6 mmol) and diisopropylethylamine (1.15 mL, 6.6 mmol) formed a clear yellow solution which was warmed to room temperature overnight. The resulting solution was worked up according to procedure 1.2.1. Analysis of the crude reaction mixture by $^1$H NMR spectroscopy revealed the presence of unreacted 4-
nitrobenzyl alcohol, which was confirmed by addition of a small sample of 4-nitrobenzyl alcohol into the NMR sample.

4.2.7 Synthesis of dibenzyl ether 145

Procedure 4.2.5 was carried out using benzyl alcohol (0.23 mL, 2.24 mmol). Dibenzyl ether 145 was obtained following work-up as a colourless oil (0.2 g, 90%). $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 4.57 (s, 4H, 2 × CH$_2$), 7.3-7.4 (m, 10H, Ar-H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 72.1 (CH$_2$), 127.6 (C4), 127.8 (C2, C6), 128.4 (C3, C5), 138.8 (C1). GC/MS $m/z$ (relative intensity) 107 (C$_6$H$_5$-CH$_2$-O-, 15%), 92 (C$_6$H$_5$-CH$_2$-, 100%). The $^1$H and $^{13}$C NMR data obtained for 145 were in agreement with that previously reported.$^{292}$

4.2.8 Synthesis of dihexyl ether 146

Procedure 4.2.5 was performed using 1-hexanol (0.28 mL, 2.24 mmol). Dihexyl ether 146 was obtained after stirring at room temperature for 2 days and following work-up as a colourless oil (0.2 g, 96%). $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 0.89 (t, J = 6.6 Hz, 6H, 6 × H6), 1.2-1.4 (m, 12H, 4 × H3, 4 × H4, 4 × H5), 1.58 (t, J = 6.6 Hz, 4H, 4 × H2), 3.4 (t, J = 6.6 Hz, 4H, 4 × H1). $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 14.1 (C6), 22.7 (C5) 29.8 (C3), 31.8 (C2), 71.0 (C1). GC/MS $m/z$ (relative intensity) 85 (CH$_3$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-, 100%). The $^1$H and $^{13}$C NMR data obtained for 146 were consistent with that previously reported.$^{292}$

4.2.9 Attempted synthesis of bis(4-methoxybenzyl)ether 147

4.2.9.1 Room temperature overnight

Procedure 4.2.5 was carried out using 4-methoxybenzyl alcohol (0.28 mL, 2.24 mmol). Analysis of the crude residue by $^1$H NMR spectroscopy showed a complex mixture of products (very broad multiplet from $\delta$ 3.4 - 4.1 ppm).
4.2.9.2 Room temperature overnight with diisopropylethylamine

Procedure 4.2.9.1 was carried out using 4-methoxybenzyl alcohol (0.28 mL, 2.24 mmol) and diisopropylethylamine (0.42 mL, 2.46 mmol). Analysis of the crude residue by $^1$H NMR spectroscopy indicated the presence of 4-methoxybenzyl alcohol, 148 and 147 in a 17 : 26 : 57 ratio. Separation of the products by column chromatography (DCM) gave three fractions.

Fraction 1 (Rf 0.9) bis(4-methoxybenzyl)ether 147, $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 3.83 (s, 6H, $2 \times$ OCH$_3$), 4.49 (s, 4H, $2 \times$ CH$_2$), 6.90 (d, $J = 8.8$ Hz, H2, H6), 7.31 (d, $J = 8.1$ Hz, H3, H5), GC/MS m/z (relative intensity) 258 (M, 5%), 121 (MeO-C$_6$H$_4$-CH$_2$-, 100%). The $^1$H NMR data obtained for 147 was in agreement with that previously reported.

Fraction 2 (Rf 0.7) 4-methoxybenzyl 4-methoxybenzoate 148, $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 3.87 (s, 3H, OCH$_3$), 3.9 (s, 3H, OCH$_3$), 6.90 (d, $J = 8.8$ Hz, H2, H6), 8.0 (d, $J = 8.8$ Hz, H3, H5), GC/MS m/z (relative intensity) 166 (M, 45%), 107 (MeO-C$_6$H$_4$-CH$_2$-, 22%). The $^1$H NMR spectrum obtained for 148 was in agreement with that previously reported.

Fraction 3 (Rf 0.1) 4-methoxybenzyl alcohol, $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 3.81 (s, 3H, OCH$_3$), 4.6 (s, 2H, CH$_2$), 6.90 (d, $J = 8.8$ Hz, H2, H6), 7.29 (d, $J = 8.0$ Hz, H3, H5), GC/MS m/z (relative intensity) 121 (MeO-C$_6$H$_4$-CH$_2$-, 100%). The $^1$H NMR spectrum obtained was identical to that of an authentic sample of 4-methoxybenzyl alcohol.
4.2.10 Synthesis of 1,4-dimethoxybenzene 153

Procedure 4.2.5 was performed using methanol (0.46 mL, 1.12 mmol) and 4-methoxyphenol (0.14 g, 1.12 mmol). The solution was stirred at room temperature overnight and the DCM removed at reduced pressure. The yellow oil was taken up in a minimum amount of chloroform and allowed to stand for 24 hours, after which time it had separated into two layers. The top layer was removed, concentrated in vacuo and dried under high vacuum to yield 1,4-dimethoxybenzene 153 as a pale yellow liquid (0.1 g, 65%). $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 3.76 (s, 6H, 2 × OCH$_3$), 6.78 (s, 4H, Ar-H). GC/MS m/z (relative intensity) 107 (MeO-C$_6$H$_4^-$, 45%). The $^1$H NMR data obtained for 153 was in agreement with that previously reported. 288

4.2.11 Attempted synthesis of dicyclohexyl ether 154

4.2.11.1 Room temperature for 2 days

Procedure 4.2.5 was performed using cyclohexanol (0.22 mL, 2.2 mmol). After stirring at room temperature for 2 days, an aliquot removed for GC/MS analysis. The remaining solution was washed with HCl (2 M, aqueous, 3 × 20 mL), the organic phase dried (anhydrous MgSO$_4$) and the solvent removed in vacuo. The resulting oil was dried under high vacuum. Analysis by GC/MS and $^1$H NMR spectroscopy revealed unreacted cyclohexanol. Characteristic peak in $^1$H NMR (200MHz, CDCl$_3$) $\delta$ 3.65 (m, 1H, H1). GC/MS m/z (relative intensity) 83 (C$_6$H$_{11}^-$, 70%).

4.2.11.2 Reflux for 3 days

Procedure 4.2.11.1 was carried out by heating at reflux for 3 days. Analysis of the crude reaction mixture by GC/MS revealed cyclohexanol, cyclohexene 75 and dicyclohexyl ether 154 in a 51 : 47 : 2 ratio. Cyclohexanol (R$_T$ 5.6 min): GC/MS m/z
(relative intensity) 83 (C₆H₁₁–, 70%). Cyclohexene 75 (Rₜ 1.5 min): GC/MS m/z
(relative intensity) 83 (C₆H₁₁–, 50%). Dicyclohexyl ether 154 (Rₜ 11.8 min): GC/MS
m/z (relative intensity) 182 (M, 5%), 100 (C₆H₁₁-O–, 85%), 83 (C₆H₁₁–, 100%). The
characteristic peak in the ¹H NMR spectrum (200 MHz, CDCl₃) of the crude material
for cyclohexanol was δ 3.65 (m, 1H, H1). Cyclohexene 75 and dicyclohexyl ether 154
were not observed in the ¹H NMR spectrum.

4.2.12 Synthesis of N-benzyl 4-nitrobenzamide 112

4.2.12.1 Room temperature overnight

A solution of diphenyl-2-pyridylphosphine oxide 138 (0.75 g, 2.69 mmol) in dry DCM
(10 mL) was cooled to 0°C under a nitrogen atmosphere. A yellow solution resulted
following the addition of triflic anhydride (0.19 mL, 1.12 mmol). After stirring for 1
hour, 4-nitrobenzoic acid (0.19 g, 1.12 mmol) was added. The clear yellow solution
was stirred at room temperature for 15 minutes. Benzylamine (0.122 mL, 1.12 mmol)
was added and the resulting dark brown solution stirred overnight at room temperature.
The solvent was then removed in vacuo and the resulting oil dried under high vacuum.
Analysis of the crude residue by ¹H NMR spectroscopy indicated the absence of the
desired amide 112. Peaks corresponding to the benzylaminodiphenyl-2-
pyridylphosphonium trifluoromethanesulfonate 141, ¹H NMR (200 MHz, CDCl₃) δ 4.15
(dd, J = 13.5, 6.9 Hz, 2H, CH₂) and diphenyl-2-pyridylphosphine oxide 138, ¹H NMR
(200 MHz, CDCl₃) δ 7.3–9.0 (m, Ar-H) were observed in the ¹H NMR spectrum.

4.2.12.2 Reflux overnight

Procedure 4.2.12.1 was repeated with heating at reflux overnight. Analysis of the crude
residue by ¹H NMR spectroscopy indicated the absence of the desired amide 112.
Benzylaminodiphenyl-2-pyridylphosphonium trifluoromethanesulfonate 141, $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 4.15 (dd, $J = 13.5$, 6.9 Hz, 2H, CH$_2$) and diphenyl-2-pyridylphosphine oxide 138, $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 7.3–9.0 (m, Ar-H) were observed in the $^1$H NMR spectrum.

4.2.12.3 Room temperature overnight with diisopropylethylamine

Procedure 4.2.12.1 was repeated in the presence of diisopropylethylamine (0.46 mL, 2.6 mmol). Following work-up, the resulting brown residue was passed through a short silica plug (DCM) to yield $N$-benzyl 4-nitrobenzamide 112 as a pale yellow solid (0.1 g, 70%). Mp 140-143$^\circ$C (Lit.$^{284}$ 141.5-143$^\circ$C). $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 4.57 (d, $J = 5.9$ Hz, 2H, CH$_2$), 6.55-6.65 (br s, 1H, NH), 7.18-7.35 (m, 5H, H2'-H5'), 7.86 (d, $J = 8.8$ Hz, 2H, H2, H6), 8.18 (d, $J = 8.8$ Hz, 2H, H3, H5). ESMS (+ve mode) MNa$^+$, 279 (25%); MLi$^+$, 263 (50%).
CHAPTER FOUR

Polymer-supported reagents

1.0 Polymer-supported five-membered cyclic analogue 56

1.1 Synthesis and characterisation of polymer-supported 1,2-bis(diphenylphosphinyl)ethane 57

1.1.1 Synthesis of brominated poly(styrene-co-divinylbenzene) 59

Poly(styrene-co-divinylbenzene) resin (2% cross-linked, 200-400 mesh) was washed for 40 minutes with each of the following solutions: 1M NaOH 60°C, 1M HCl 60°C, 1M NaOH 60°C, 1M HCl 60°C, H₂O 25°C, DMF 40°C, 1M HCl 60°C, H₂O 60°C, MeOH 25°C, DCM-MeOH (2:3) 25°C, DCM-MeOH (3:1) 25°C, DCM-MeOH (9:1) 25°C, DCM 25°C. The white resin beads were dried at 125°C for 48 hours at 100 mmHg (house vacuum) on a Kugelrohr apparatus. Brominated poly(styrene-co-divinylbenzene) 59 was prepared from poly(styrene-co-divinylbenzene) (10 g, 0.096 mol) using thallium (III) acetate (0.6 g, 1.6 mmol) and bromine (6.72 g, 2.16 mL, 0.042 mol) as reported by Farrall.²⁹⁴ The beads were dried at 125°C for 48 hours at 100 mmHg (house vacuum) on a Kugelrohr apparatus to give brominated poly(styrene-co-divinylbenzene) 59 as tan coloured beads (12.2 g). Elemental analysis found 28.21% Br, corresponding to 3.53 mmol Br/g resin (51% of phenyl rings brominated).

1.1.2 Synthesis of polymer-supported 1,2-bis(diphenylphosphino)ethane 60

Diphenyl[2-(phenylphosphino)ethyl]phosphine, sodium salt 58 was prepared from sodium (3.33 g, 0.145 mol), naphthalene (15.5 g, 0.12 mol) and 1,2-
bis(diphenylphosphino)ethane (1.7 g, 0.043 mol) according to the procedure of Chou. Attachment of 58 to the poly(styrene-co-divinylbenzene) resin was carried out via the method of Pitman using brominated poly(styrene-co-divinylbenzene) resin 59 (4 g, 0.014 mol) to yield polymer-supported 1,2-bis(diphenylphosphino)ethane 60 as brown coloured beads (4.5 g). $^{31}$P NMR (162 MHz, CDCl$_3$, gelphase) –12.3 (br s).

1.1.3 Synthesis of polymer-supported 1,2-bis(diphenylphosphinyl)ethane 57

Polymer-supported 1,2-bis(diphenylphosphino)ethane 60 (2 g) was placed in DCM (25 mL) and hydrogen peroxide (15 mL, 30% wt solution in water) added. The slurry was left to stir overnight at room temperature and the resulting beads collected by filtration and washed with DCM (60 mL). The beads were dried at 125°C at 10 mmHg for 48 hours. Polymer-supported 1,2-bis(diphenylphosphinyl)ethane 57 was obtained as light yellow beads (2.5 g). Elemental analysis for P found 5.88%, corresponding to 1.9 mmol P/g resin (30% of phenyl rings contain a bound P(O)(C$_6$H$_5$)CH$_2$CH$_2$P(O)(C$_6$H$_5$)$_2$). $^{31}$P NMR (162 MHz, CDCl$_3$, gelphase) δ 33.3 (br s). IR (KBr disk) 1180 cm$^{-1}$ (s, P=O).

1.2 Synthesis of polymer-supported 1,1,3,3-tetraphenyl-2-oxa-1,3-phospholanium bis(trifluoromethanesulfonate) 56

Polymer-supported 1,2-bis(diphenylphosphinyl)ethane 57 (0.1 g, 0.19 mmol, 1.9 mmol/g) was dried by repeated azeotropic removal of water with dry toluene on a rotary evaporator. The resin was swollen in CD$_2$Cl$_2$ (0.75 mL) in a 5 mm NMR tube. Triflic anhydride (16.5 µL, 0.095 mmol) was added and the slurry mixed thoroughly by vortex to give polymer-supported 1,1,3,3-tetraphenyl-2-oxa-1,3-phospholanium bis(trifluoromethanesulfonate) 56. $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$, gelphase) δ 57.0 (br s); $^{19}$F NMR (376 MHz, CD$_2$Cl$_2$, gelphase) δ –80.3 (br s).
1.3 Reactions using polymer-supported 1,1,3,3-tetraphenyl-2-oxa-1,3-phospholanium bis(trifluoromethanesulfonate) 56

1.3.1 Synthesis of 4-nitrobenzyl 4-nitrobenzoate 61

Dry polymer-supported 1,2-bis(diphenylphosphinyl)ethane 57 (0.8 g, 1.52 mmol, 1.9 mmol/g) was swollen in DCM (15 mL) for 30 minutes. Triflic anhydride (0.13 mL, 0.75 mmol) was added and the slurry stirred for 1 hour at room temperature. Subsequent treatment with 4-nitrobenzyl alcohol (0.12 g, 0.75 mmol), 4-nitrobenzoic acid (0.13 g, 0.75 mmol) and diisopropylethylamine (0.36 mL, 2 mmol) formed a yellow slurry which was stirred at room temperature for 2 hours. The polymer beads were removed by filtration, washed with DCM (50 mL) and the filtrate washed with sodium hydrogen carbonate (saturated aqueous solution, 3 x 30 mL). The organic phases were dried (anhydrous MgSO$_4$), concentrated in vacuo and dried under high vacuum to yield 4-nitrobenzyl 4-nitrobenzoate 61 as a yellow solid (0.22 g, 96%). Mp 165-167°C (Lit.$^{275}$ 168°C). $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 5.51 (s, 2H, CH$_2$), 7.63 (d, $J$ = 8.8 Hz, 1H, H2', H6'), 8.22-8.4 (m, 6H, H2, H3, H5, H6, H3', H5'). ESMS (+ve mode) MH$^+$, 302 (15%).

1.3.2 Synthesis of N-benzyl 4-nitrobenzamide 112

A slurry of 56 was prepared according to procedure 1.3.1 from polymer-supported 1,2-bis(diphenylphosphinyl)ethane 57 (0.8 g, 1.52 mmol, 1.9 mmol/g) and triflic anhydride (0.13 mL, 0.75 mmol). 4-Nitrobenzoic acid (0.13 g, 0.75 mmol) was added and the mixture stirred for 2 hours at room temperature. Addition of benzylamine (63 µL, 0.75 mmol) and diisopropylethylamine (0.36 mL, 2 mmol) generated a yellow slurry which was stirred at room temperature for 2 hours. The polymer beads were removed by filtration, washed with DCM (50 mL) and the filtrate washed with sodium hydrogen carbonate (saturated aqueous solution, 3 x 30 mL). The organic phases were dried (anhydrous MgSO$_4$), concentrated in vacuo and dried under high vacuum to yield N-benzyl 4-nitrobenzamide 112 as a yellow solid (0.20 g, 95%). Mp 173-175°C (Lit.$^{276}$ 173°C). $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 7.15-7.3 (m, 5H, H2, H3, H5, H6, H7), 7.5-7.7 (m, 5H, H2', H3', H5', H6', H7'), 8.17 (d, $J$ = 8.8 Hz, 1H, H2'). ESMS (+ve mode) MH$^+$, 368 (15%).
carbonate (5% aqueous solution, 3 × 30 mL). The organic phase was concentrated \textit{in vacuo} and dried under high vacuum to yield \textit{N}-benzyl 4-nitrobenzamide \textbf{112} as a light yellow solid (0.18 g, 93%). Mp 138-140°C (Lit.\textsuperscript{284} 141.5-143°C). \textsuperscript{1}H NMR (200 MHz, CDCl\textsubscript{3}) \(\delta\) 4.57 (d, \(J = 5.9\) Hz, 2H, CH\textsubscript{2}), 6.55-6.65 (br s, 1H, NH), 7.18-7.35 (m, 5H, H2'-H5'), 7.86 (d, \(J = 8.8\) Hz, 2H, H2, H6), 8.18 (d, \(J = 8.8\) Hz, 2H, H3, H5). ESMS (+ve mode) MNa\textsuperscript{+}, 279 (25%); MLi\textsuperscript{+}, 263 (50%).

\textbf{2.0 Polymer-supported triphenylphosphine ditriflate 157}

\textbf{2.1 Synthesis and characterisation of polymer-supported triphenylphosphine ditriflate 157 [polymer-supported trifluoromethanesulfonyloxytriphenylphosphonium trifluoromethanesulfonate]}

\textbf{2.1.1 Synthesis of polymer-supported triphenylphosphine oxide 158}

Before use, the polymer-supported triphenylphosphine resin (2% cross-linked, 200-400 mesh, 3 mmol/g) was washed for 40 minutes with each of the following solutions: 1M NaOH 60°C, 1M HCl 60°C, 1M NaOH 60°C, 1M HCl 60°C, H\textsubscript{2}O 25°C, DMF 40°C, 1M HCl 60°C, H\textsubscript{2}O 60°C, MeOH 25°C, DCM-MeOH (2:3) 25°C, DCM-MeOH (3:1) 25°C, DCM-MeOH (9:1) 25°C, DCM 25°C. The beige resin beads were dried at 125°C for 48 hours at 100 mmHg (house vacuum) on a Kugelrohr apparatus. Hydrogen peroxide (20 mL, 30% wt solution in water) was added to polymer-supported triphenylphosphine (2 g, 9 mmol, 3 mmol/g) in DCM (50 mL) and the slurry stirred overnight at room temperature. The beads were collected by filtration, washed with DCM (60 mL) and dried under high vacuum to give polymer-supported triphenylphosphine oxide \textbf{158} as yellow beads (2.5 g). \textsuperscript{31}P NMR (162 MHz, CDCl\textsubscript{3}, gelphase) \(\delta\) 30.0 (br s).
2.1.2 Synthesis of polymer-supported triphenylphosphine ditriflate 157

In a 5 mm NMR tube, a gelphase sample of dry polymer-supported triphenylphosphine oxide 158 (0.075 g, 0.23 mmol, 3 mmol/g) was prepared in CD$_2$Cl$_2$ (0.75 mL). Triflic anhydride (19.5 µL, 0.11 mmol) was added and the slurry mixed by vortex. A $^{31}$P NMR spectrum was recorded. The addition of triflic anhydride (19.5 µL, 0.11 mmol) was repeated and $^{31}$P NMR and $^{19}$F NMR spectra obtained. With 0.5 equiv. triflic anhydride: $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$, gelphase) δ 42.7 (br s); with 1.0 equiv. triflic anhydride: $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$, gelphase) δ 53.3 (br s), $^{19}$F NMR (376 MHz, CD$_2$Cl$_2$, gelphase) δ –80.1 (br s).

2.1.3 Attempted formation of triphenylphosphine ditriflate 160

Triflic anhydride (33.6 µL, 0.2 mmol) was placed in CD$_2$Cl$_2$ (0.75 mL) in a 5 mm NMR tube under nitrogen. The tube was cooled on ice and a solution of triphenylphosphine oxide (52.5 mg, 0.2 mmol, 0.2 equiv.) in CD$_2$Cl$_2$ (20 µL, 0.04 mmol) added. The tube was mixed briefly by vortex and a $^{31}$P NMR spectrum obtained at 25°C. With 0 equiv. acetic anhydride: $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$) δ 27.6 (s); With 0.2 equiv. triphenylphosphine oxide: $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$) δ 79.6 (s).

2.1.4 Attempted formation of triphenylphosphine di(trifluoroacetate) 161

Triphenylphosphine oxide (52.5 mg, 0.2 mmol) was dissolved in CD$_2$Cl$_2$ (0.75 mL) in a 5 mm NMR tube under an atmosphere of nitrogen. A $^{31}$P NMR spectrum was recorded at 25°C. The tube was cooled on ice and trifluoroacetic anhydride added (28 µL, 0.2 mmol). After vortexing briefly, another $^{31}$P NMR spectrum was obtained at 25°C. With 0 equiv. trifluoroacetic anhydride: $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$) δ 27.5 (s); With 1.0 equiv. trifluoroacetic anhydride: $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$) δ 27.5 (s).
2.1.5 Attempted formation of triphenylphosphine diacetate 162

Triphenylphosphine oxide (52.5 mg, 0.2 mmol) was dissolved in CD$_2$Cl$_2$ (0.75 mL) in a 5 mm NMR tube under an atmosphere of nitrogen. A $^{31}$P NMR spectrum was recorded at 25°C. The tube was cooled on ice and acetic anhydride added (22 µL, 0.2 mmol). After vortexing briefly, another $^{31}$P NMR spectrum was obtained at 25°C. With 0 equiv. acetic anhydride: $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$) δ 27.6 (s); With 1.0 equiv. acetic anhydride: $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$) δ 27.6 (s).

2.1.6 $^{19}$F NMR of triflic acid in the presence of poly(styrene-co-divinylbenzene)

A sample of poly(styrene-co-divinylbenzene) (0.2 g, 200-400 mesh) was swollen in CD$_2$Cl$_2$ (1.5 mL) in a 10 mm NMR tube. Triflic acid (50 µL, 0.56 mmol) was added and the tube mixed thoroughly by vortex. $^{19}$F NMR (376 MHz, CD$_2$Cl$_2$) δ -78.3 (br s).

2.1.7 $^{19}$F NMR of triflic anhydride in the presence of poly(styrene-co-divinylbenzene)

A sample of poly(styrene-co-divinylbenzene) (0.2 g, 200-400 mesh) was swollen in CD$_2$Cl$_2$ (1.5 mL) in a 10 mm NMR tube. Triflic anhydride (50 µL, 0.29 mmol) was added and the tube mixed thoroughly by vortex. $^{19}$F NMR (376 MHz, CD$_2$Cl$_2$) δ -73.6 (br s).

2.1.8 Synthesis of protonated polymer-supported triphenylphosphine oxide 163

A gelphase NMR sample of polymer-supported triphenylphosphine oxide 158 (0.075 g, 0.225 mmol) in CD$_2$Cl$_2$ (0.75 mL) was prepared in a 5 mm NMR tube. Triflic acid (20 µL, 0.225 mmol) was added and the tube vortexed briefly. $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$) δ 52.1 (br s). $^{19}$F NMR (376 MHz, CD$_2$Cl$_2$) δ -80.3 (br s).
2.1.9 Attempted synthesis of 4-toluic anhydride 164 using protonated polymer-supported triphenylphosphine oxide 163

Polymer-supported triphenylphosphine oxide 158 (0.15 g, 0.45 mmol) was swollen in DCM (5 mL) under an atmosphere of nitrogen. Triflic acid (29.3 µL, 0.33 mmol) was added and the slurry stirred at room temperature for 1 hour. Subsequent addition of 4-toluic acid (0.088 g, 0.66 mmol) and diisopropylethylamine formed a yellow slurry which was stirred at room temperature overnight. The reaction mixture was worked up according to procedure 1.3.2 to yield a pale yellow solid (0.08 g). Analysis of the crude residue by $^1$H NMR spectroscopy indicated the presence of unreacted 4-toluic acid, which was confirmed by co-addition of 4-toluic acid into the NMR sample.

2.1.10 Synthesis of polymer-supported benzylaminotriphenylphosphonium trifluoromethanesulfonate 166

Polymer-supported triphenylphosphine oxide 158 (0.3 g, 0.9 mmol, 3 mmol/g) was swollen in DCM (10 mL) under an atmosphere of nitrogen. Triflic anhydride (0.17 mL, 1 mmol) was added and the slurry stirred for 1 hour at room temperature. Following treatment with benzylamine (0.13 mL, 1.2 mmol) and diisopropylethylamine (0.4 mL, 2.3 mmol), the mixture was stirred at room temperature overnight. The beads were collected by filtration, washed with DCM (60 mL) and dried under high vacuum. The resulting dark brown beads (0.35 g) were shown to contain a mixture of polymer-supported benzylaminotriphenylphosphonium trifluoromethanesulfonate 166 and polymer-supported triphenylphosphine oxide 158 in a 9 : 1 ratio by $^{31}$P NMR spectroscopy. $^{31}$P NMR (162 MHz, CDCl$_3$, gelphase) δ 30.0 (br s), 39.9 (br s), ratio 1:9.
2.2 Reactions using polymer-supported triphenylphosphine ditriflate 157

2.2.1 Synthesis of 4-nitrobenzyl 4-nitrobenzoate 61
Polymer-supported triphenylphosphine oxide 158 (0.3 g, 0.9 mmol, 3 mmol/g) was swollen in dry DCM (10 mL) under an atmosphere of nitrogen. Triflic anhydride (0.12 mL, 0.66 mmol) was added and the dark mixture stirred 1 hour. 4-Nitrobenzyl alcohol (0.1 g, 0.66 mmol) was added and the slurry stirred for a further hour at room temperature. 4-Nitrobenzoic acid (0.11 g, 0.66 mmol) and diisopropylethylamine (0.4 mL, 2.3 mmol) were added and the slurry stirred at room temperature for 2 hours. The reaction mixture was worked up according to procedure 1.3.1 to yield 4-nitrobenzyl 4-nitrobenzoate 61 as a yellow solid (0.19 g, 95%). Mp 165-167°C (Lit. 275 168°C). 1H NMR (200 MHz, CDCl3) δ 5.51 (s, 2H, CH2), 7.63 (d, J = 8.8 Hz, 1H, H2', H6'), 8.22-8.4 (m, 6H, H2, H3, H5, H6, H3', H5'). ESMS (+ve mode) MH+ , 302 (15%).

2.2.2 Synthesis of N-benzyl-4-nitrobenzamide 112
Polymer-supported triphenylphosphine ditriflate 157 (0.66 mmol) was prepared according to procedure 2.2.1 from polymer-supported triphenylphosphine oxide 158 (0.3 g, 0.9 mmol, 3 mmol/g) and triflic anhydride (0.12 mL, 0.66 mmol). 4-Nitrobenzoic acid (0.11 g, 0.66 mmol) was added and the solution stirred at room temperature for 2 hours. Consecutive addition of benzylamine (72 µL, 0.66 mmol) and diisopropylethylamine (0.4 mL, 2.3 mmol) produced a light brown slurry which was stirred at room temperature for 2 hours. The reaction mixture was worked up according to procedure 1.3.2 to yield N-benzyl-4-nitrobenzamide 112 as a light yellow solid (0.15 g, 90%). Mp 140-143°C (Lit. 284 141.5-143°C). 1H NMR (200 MHz, CDCl3) δ 4.57 (d, J = 5.9 Hz, 2H, CH2), 6.55-6.65 (br s, 1H, NH), 7.18-7.35 (m, 5H, H2'-H5'), 7.86 (d, J =
8.8 Hz, 2H, H2, H6), 8.18 (d, \( J = 8.8 \) Hz, 2H, H3, H5). ESMS (+ve mode) MNa\(^+\), 279 (25%); MLi\(^+\), 263 (50%).

2.2.3 Synthesis of \( N \)-benzyl-4-methoxybenzamide 167

\( N \)-Benzyl-4-methoxybenzamide 167 was prepared according to procedure 2.2.2 using anisic acid (0.102 g, 0.66 mmol) and benzylamine (72 µL, 0.66 mmol) and obtained as a beige solid (0.14 g, 88%). Mp 124-126°C (Lit.\(^{284}\) 127-129°C). \(^1\)H NMR (200 MHz, CDCl\(_3\)) \( \delta \) 3.86 (s, 3H, OCH\(_3\)), 4.65 (d, \( J = 5.9 \) Hz, 2H, CH\(_2\)), 6.25-6.45 (br s, 1H, NH), 6.93 (d, \( J = 8.8 \) Hz, 2H, H3, H5), 7.18-7.35 (m, 5H, H2'-H5'), 7.77 (d, \( J = 8.8 \) Hz, 2H, H2, H6). ESMS (+ve mode) MLi\(^+\), 264 (100%).

2.2.4 Synthesis of \( N \)-benzyl-\( N \)-(4-nitrobenzoyl)-4-nitrobenzamide 168

Polymer-supported triphenylphosphine ditriflate 157 (0.66 mmol) was prepared according to procedure 2.2.1 from polymer-supported triphenylphosphate oxide 158 (0.3 g, 0.9 mmol, 3 mmol/g) and triflic anhydride (0.12 mL, 0.66 mmol). 4-Nitrobenzoic acid (0.11 g, 0.66 mmol) was added to 157 and the solution stirred at room temperature for 2 hours. Consecutive addition of benzylamine (72 µL, 0.66 mmol) and diisopropylethylamine (0.4 mL, 2.3 mmol) produced a light brown slurry which was stirred at room temperature overnight. The reaction mixture was worked up according to procedure 1.3.2. Purification by flash chromatography (DCM/hexane, 3:1) yielded \( N \)-benzyl-\( N \)-(4-nitrobenzoyl)-4-nitrobenzamide 168 as a pale yellow solid (0.12 g, 90%). Mp 165-167°C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 5.23 (s, 2H, CH\(_2\)), 7.2-7.4 (m, 5H, H2'-H6'), 7.57 (d, \( J = 9.0 \) Hz, 4H, 2 × H2, 2 × H6), 8.07 (d, \( J = 9.0 \) Hz, 4H, 2 × H3, 2 × H5). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 50.6 (CH\(_2\)), 123.8, 128.3, 128.5, 128.9, 129.5 (2 × o-C\(_6\)H\(_5\), 2 × m-C\(_6\)H\(_5\), p-C\(_6\)H\(_5\), 4 × o-C\(_6\)H\(_4\), 4 × m-C\(_6\)H\(_4\)), 136.0, 141.1, 149.5 (i-C\(_6\)H\(_5\), 2 × i-C\(_6\)H\(_4\)), 171.6 (C=O). IR (KBr disk) 1350 (s, NO\(_2\)), 1526 (s, NO\(_2\)), 1603 (m,
C(O)N), 1691 cm\(^{-1}\) (s, C(O)N). ESMS (-ve mode) M\(^{-}\), 404 (10%); M-(C(O)-C\(_6\)H\(_4\)-NO\(_2\)), 255 (30%); M-(NC(O)-C\(_6\)H\(_4\)-NO\(_2\)), 166 (100%). Anal. Calcd for C\(_{21}\)H\(_{15}\)N\(_3\)O\(_6\): C, 62.22; H, 3.73; N, 10.37. Found: C, 62.23; H, 3.80; N, 10.21.

2.2.5 Synthesis of N-(4-nitrophenyl)-4-methoxybenzamide 169

N-(4-Nitrophenyl)-4-methoxybenzamide 169 was prepared according to procedure 2.2.2 using anisic acid (0.102 g, 0.66 mmol) and 4-nitroaniline (0.092 g, 0.66 mmol). After stirring at room temperature overnight, N-(4-nitrophenyl)-4-methoxybenzamide 169 was obtained as a pale yellow solid (0.15 g, 83%). Mp 178-180\(^\circ\)C (Lit.\(^\text{295}\) 184-185\(^\circ\)C). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.90 (s, 3H, OCH\(_3\)), 7.02 (d, \(J = 8.8\) Hz, 2H, H3, H5), 7.84 (d, \(J = 8.8\) Hz, 2H, H2, H6), 7.87 (d, \(J = 9.5\) Hz, 2H, H2', H6'), 8.05 (br s, 1H, NH), 8.27 (d, \(J = 9.5\) Hz, 2H, H3', H5'). ESMS (+ve mode) MH\(^+\), 273 (95%); (-ve mode) M\(^-\), 271 (100%).

2.2.6 Synthesis of N-(4-methoxyphenyl)-4-nitrobenzamide 170

N-(4-Methoxyphenyl)-4-nitrobenzamide 170 was prepared according to procedure 2.2.2 using 4-nitrobenzoic acid (0.11 g, 0.66 mmol) and 4-anisidine (0.082 g, 0.66 mmol). After stirring at room temperature overnight, N-(4-methoxyphenyl)-4-nitrobenzamide 170 was obtained as a pale yellow solid (0.13 g, 72%). Mp 193-196\(^\circ\)C (Lit.\(^\text{296}\) 199-202\(^\circ\)C). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.83 (s, 3H, OCH\(_3\)), 6.93 (d, \(J = 8.1\) Hz, 2H, H3', H5'), 7.55 (d, \(J = 7.3\) Hz, 2H, H2', H6'), 7.82 (br s, 1H, NH), 8.04 (d, \(J = 7.5\) Hz, 2H, H2, H6), 8.33 (d, \(J = 7.7\) Hz, 2H, H3, H5). ESMS (+ve mode) MH\(^+\), 273 (100%); (-ve mode) M\(^-\), 271 (100%).

2.2.7 Synthesis of N-(4-methoxyphenyl)-4-methoxybenzamide 171

N-(4-Methoxyphenyl)-4-methoxybenzamide 171 was prepared according to procedure 2.2.2 using anisic acid (0.102 g, 0.66 mmol) and 4-anisidine (0.082 g, 0.66 mmol).
After stirring at room temperature overnight, \( N-(4\text{-methoxyphenyl})\)-4-methoxybenzamide 171 was obtained as a white solid (0.12 g, 71%). Mp 206-208°C (Lit.\(^{297}\) 202-203°C). \(^1\text{H NMR (400 MHz, CDCl}_3\) \(\delta 3.82 (s, 3\text{H, OCH}_3), 3.88 (s, 3\text{H, OCH}_3), 6.91 (d, J = 8.1 \text{ Hz, 2H, H3', H5'}), 6.98 (d, J = 7.8 \text{ Hz, 2H, H3, H5}), 7.53 (d, J = 7.8 \text{ Hz, 2H, H2', H6'}), 7.65 (br s, 1\text{H, NH}), 7.84 (d, J = 7.8 \text{ Hz, 2H, H2, H6}).\) ESMS (+ve mode) \(\text{MH}^+, 258 (100\%); \text{MLi}^+, 264 (100\%); (-\text{ve mode}) \text{M}^-, 256 (65\%).\)

2.2.8 Synthesis of \( N-(4\text{-nitrobenzoyl})\)-piperidine 172

\(N-(4\text{-Nitrobenzoyl})\)-piperidine 172 was prepared according to procedure 2.2.2 using 4-nitrobenzoic acid (0.11 g, 0.66 mmol) and piperidine (65.4 µL, 0.66 mmol). After stirring at room temperature overnight, \(N-(4\text{-nitrobenzoyl})\)-piperidine 172 was obtained as a beige solid (0.14 g, 84%). Mp 114-116°C (Lit.\(^{298}\) 120°C). \(^1\text{H NMR (200 MHz, CDCl}_3\) \(\delta 2.4-2.8 (m, 6\text{H, 2 × CH}_2), 3.2-3.4 (m, 2\text{H, 2 × CH}_{2\text{(ax)}}), 3.6-3.8 (m, 2\text{H, 2 × CH}_{2\text{(eq)}}), 7.56 (d, J = 8.8 \text{ Hz, 2H, H2, H6}), 8.28 (d, J = 8.8 \text{ Hz, 2H, H3, H5}).\) ESMS (+ve mode) \(\text{MLi}^+, 241 (100\%); \text{MNa}^+, 257 (50\%).\)

2.2.9 Synthesis of \( N-(4\text{-methoxybenzoyl})\)-piperidine 173

\(N-(4\text{-Methoxybenzoyl})\)-piperidine 173 was prepared according to procedure 2.2.2 using anisic acid (0.102 g, 0.66 mmol) and piperidine (65.4 µL, 0.66 mmol). After stirring at room temperature overnight, \(N-(4\text{-methoxybenzoyl})\)-piperidine 173 was obtained as an orange oil (0.13 g, 90%). \(^1\text{H NMR (200 MHz, CDCl}_3\) \(\delta 1.5-1.8 (m, 6\text{H, 3 × CH}_2), 3.4-3.7 (m, 4\text{H, 2 × CH}_2), 3.83 (s, 3\text{H, OCH}_3), 6.9 (d, J = 8.8 \text{ Hz, 2H, H3, H5}), 7.37 (d, J = 8.8 \text{ Hz, 2H, H2, H6}).\) ESMS (+ve mode) \(\text{MH}^+, 220 (20\%); \text{MNa}^+, 242 (80\%); \text{MLi}^+, 226 (70\%).\) The \(^1\text{H NMR data obtained for 173 was consistent with that previously reported in the literature.}\(^{299}\)
2.2.10 Synthesis of \(N,N\)-diisopropyl-4-nitrobenzamide 174

\(N,N\)-Diisopropyl-4-nitrobenzamide 174 was prepared according to procedure 2.2.2 using 4-nitrobenzoic acid (0.11 g, 0.66 mmol) and diisopropylamine (45.8 µL, 0.66 mmol). After stirring at room temperature overnight, \(N,N\)-diisopropyl-4-nitrobenzamide 174 was obtained as an orange solid (0.142 g, 86%). Mp 136-138°C (Lit.\(^{300} \) 141.5-142°C). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 1.0-1.6\) (m, 12H, 4 × CH\(_3\)), 3.5-3.7 (m, 2H, 2 × CH), 7.46 (d, \(J = 8.8\) Hz, 2H, H2, H6), 8.24 (d, \(J = 9.0\) Hz, 2H, H3, H5). ESMS (+ve mode) MH\(^+\), 251 (100%); MLI\(^+\), 257 (20%).

2.2.11 Synthesis of \(N,N\)-diisopropyl-4-methoxybenzamide 175

\(N,N\)-Diisopropyl-4-methoxybenzamide 175 was prepared according to procedure 2.2.2 using anisic acid (0.102 g, 0.66 mmol) and diisopropylamine (45.8 µL, 0.66 mmol). After stirring at room temperature overnight, \(N,N\)-diisopropyl-4-methoxybenzamide 175 was obtained as an orange oil (0.12 g, 77%). \(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta 1.1-1.5\) (m, 12H, 4 × CH\(_3\)), 3.6-3.9 (m, 2H, 2 × CH), 3.82 (s, 3H, OCH\(_3\)), 6.88 (d, \(J = 8.8\) Hz, 2H, H3, H5), 7.27 (d, \(J = 8.8\) Hz, 2H, H2, H6). ESMS (+ve mode) MH\(^+\), 236 (100%); MLI\(^+\), 242 (60%). The \(^1\)H NMR data obtained for 175 was consistent with that previously reported in the literature.\(^{301}\)

2.2.12 Synthesis of \(N\)-(4-nitrophenyl)-4-nitrobenzamide 176

\(N\)-(4-nitrophenyl)-4-nitrobenzamide 176 was prepared according to procedure 2.2.2 using 4-nitrobenzoic acid (0.11 g, 0.66 mmol) and 4-nitroaniline (0.092 g, 0.66 mmol). After stirring at room temperature for 1 week, \(N\)-(4-nitrophenyl)-4-nitrobenzamide 176 was obtained as a dark orange solid (0.12 g, 63%). Mp 264-266°C (Lit.\(^{302} \) 260-262°C). \(^1\)H NMR (200 MHz, d\(_6\)-DMSO) \(\delta 8.07\) (d, \(J = 9.5\) Hz, 2H, H2', H6'), 8.21 (d, \(J = 8.8\) Hz, 2H, H3', H5').
Hz, 2H, H3', H5'), 8.3 (d, J = 8.8 Hz, 2H, H2, H6), 8.4 (d, J = 8.1 Hz, 2H, H3, H5), NH not observed. ESMS (-ve mode) $M^-$, 286 (100%).

### 2.2.13 Preparation of benzenesulfonamide 179

Benzenesulfonamide 179 was prepared according to Vogel.\textsuperscript{303} Benzenesulfonyl chloride (2 g, 14.2 mmol) was heated with concentrated ammonia (15 mL, 28%) until boiling. The solution was then cooled and the resulting white solid isolated by filtration. Recrystallisation from boiling water yielded benzenesulfonamide 179 as a white crystalline solid (2 g, 90%). Mp 148-149\textdegree C (Lit.\textsuperscript{303} 150-152\textdegree C). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) $\delta$ 4.87 (br s, 2H, NH\textsubscript{2}), 7.51-7.63 (m, 3H, Ar-H), 7.95 (dd, J = 7.1, 1.4Hz, 2H, Ar-H). ESMS (+ve mode) MLi\textsuperscript{+}, 164 (100%); (-ve mode) $M^-$, 156 (20%).

### 2.2.14 Synthesis of N-benzoyl-benzenesulfonamide 178

N-Benzoyl-benzenesulfonamide 178 was prepared according to procedure 2.2.2 using benzoic acid (0.081g, 0.66 mmol) and benzenesulfonamide 179 (0.104 g, 0.66 mmol). After stirring at room temperature overnight, N-benzoyl-benzenesulfonamide 178 was obtained as a white solid (0.11 g, 71%). Mp 145-146\textdegree C (Lit.\textsuperscript{304} 148-149\textdegree C). \textsuperscript{1}H NMR (200 MHz, CDCl\textsubscript{3}) $\delta$ 7.25-7.9 (m, 8H, Ar-H), 8.1-8.3 (m, 3H, Ar-H, NH). ESMS (+ve mode) MLi\textsuperscript{+}, 268 (10%); (-ve mode) M\textsuperscript{-}, 260 (10%).

### 2.2.15 Synthesis of Z-Gly-Phe-Val-OMe 180

#### 2.2.15.1 Room temperature overnight

Polymer-bound triphenylphosphine oxide 158 (0.15 g, 0.45 mmol, ~3 mmol/g) was dried by azeotropic distillation of water using dry toluene. The dry polymer was stirred gently in dry DCM (10 mL) for 30 minutes under a nitrogen atmosphere. Addition of triflic anhydride (57.5 µL, 0.33 mmol) generated a dark brown slurry which was left to stir for
1 hour. Diisopropylethylamine (0.32 mL, 1.82 mmol) and Z-Gly-Phe-OH (0.118 g, 0.33 mmol) were then added and the solution stirred at room temperature for 2.5 hours. Addition of H-Val-OMe.HCl (0.0435 g, 0.33 mmol) produced a yellow slurry which was stirred at room temperature overnight. The polymer beads were collected on a filter and washed with DCM (3 × 30mL). The yellow filtrate was washed with sodium hydrogen carbonate (5% aqueous solution, 3 × 50mL) and water (3 × 50mL). The combined DCM layers were dried (anhydrous MgSO₄) and concentrated in vacuo. The resulting residue was dried under high vacuum to remove the remaining traces of diisopropylethylamine. Z-Gly-Phe-Val-OMe 180 was obtained as a sticky light orange residue. ¹H NMR analysis revealed the ratio of L,L and D,L epimers to be 1:1. ¹H NMR (400 MHz, CDCl₃) δ 0.74 (d, J = 6.6 Hz, 6H, (CH₃)₂CH, D,L epimer), 0.82 + 0.85 (2 × d, J = 6.6 Hz, 6H, (CH₃)₂CH, L,L epimer), 2.05 (m, 1H, CH(CH₃)₂), 3.05 (m, 2H,CH₂Ph), 3.64 (s, 3H, CH₃O, D,L epimer), 3.65 (s, 3H, CH₃O, L,L epimer), 3.84 (m, 2H, HNC₂H₂CO), 4.4 (dd, J = 7.2 Hz, 1H, HNCH₂-iPr), 4.85 (m, 1H, CH-Bn), 5.1 (s, 2H, CH₂OCONH), 5.85 (dd, J = 5.3 Hz, NHCH₂), 7.0 (t, J = 8.8Hz, 1H, NHCH₂-iPr), 7.12-7.38 (m, 10H, 9 × Ar-H, NH).

2.2.15.2 Room temperature overnight with HOBT

Procedure 2.2.15.1 was repeated with the addition of 1-hydroxybenzotriazole (0.045 g, 0.33 mmol) prior to the addition of diisopropylethylamine. After stirring at room temperature overnight, the single isomer of L,L-Z-Gly-Phe-Val-OMe 180 was obtained as a light orange solid (0.1 g, 65%). Mp 95-97°C (Lit.²⁴⁹ 98°C). ¹H NMR (400 MHz, CDCl₃) δ 0.81 + 0.85 (2 × d, J = 6.9 Hz, 6H, (CH₃)₂CH), 2.0-2.15 (m, 1H, CH(CH₃)₂), 3.0-3.1 (m, 2H, CH₂Ph), 3.69 (s, 3H, OCH₃), 3.84-3.88 (m, 2H, HNCH₂CO), 4.42 (dd, J = 5.1, 8.5 Hz, 1H, HNCH₂-iPr), 4.74 (m, 1H, CH-Bn), 5.11 (s, 2H, CH₂OCONH), 5.53 (t, 1H, NHCH₂), 6.51 (d, J = 7.8 Hz, 1H, NH), 6.85 (d, J = 7.0 Hz, 1H, NH), 7.16-7.29 (m, 5H, Ar-H), 7.32-7.37 (m, 5H, Ar-H). ESMS (+ve mode) MH⁺, 470 (15%); MNa⁺, 492 (70%); MLi⁺, 476 (80%); (-ve mode) M⁻, 468 (5%).
2.2.16 Synthesis of benzonitrile 182

Polymer-supported triphenylphosphine ditriflate 157 (0.66 mmol) was prepared according to procedure 2.2.2. Benzamide (0.08 g, 0.66 mmol) and diisopropylethylamine (0.4 mL, 2.3 mmol) were then added to produce a yellow slurry which was heated at reflux overnight. The reaction mixture was worked up according to procedure 1.3.2 to give benzonitrile 182 as a colourless oil (0.06 g, 88%). $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 7.4-7.7 (m, 5H, Ar-H). IR (KBr disk) 2230 cm$^{-1}$ (C≡N). GC/MS m/z (relative intensity) 103 (M, 100%). The $^1$H NMR data obtained for 182 was in agreement with that previously reported.288

2.2.17 Synthesis of (E)-Stilbene oxide 30

(E)-Stilbene oxide 30 was prepared according to procedure 2.2.2 using meso-hydrobenzoin (0.14 g, 0.66 mmol). After stirring at room temperature overnight, (E)-stilbene oxide 30 was obtained as a white solid (0.12 g, 85%). Mp 64-66°C (Lit.305 69°C). $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 3.9 (s, 2H, trans epoxide H), 7.35-7.5 (m, 10H, Ar-H). GC/MS m/z (relative intensity) 196 (M-(C$_6$H$_4$)$_2$, 5%), 167 ((C$_6$H$_4$)$_2$-CH-, 100%).

2.2.18 Synthesis of dibenzyl ether 145

Dibenzyl ether 145 was prepared according to procedure 2.2.2 using benzyl alcohol (0.135 mL, 1.3 mmol). After stirring at room temperature overnight, dibenzyl ether 145 was isolated as a colourless oil (0.095 g, 73%). $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 4.57 (s, 4H, 2 × CH$_2$), 7.3-7.4 (m, 10H, Ar-H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 72.1 (CH$_2$), 127.6 (C4), 127.8 (C2, C6), 128.4 (C3, C5), 138.8 (C1). GC/MS m/z (relative intensity) 107 (C$_6$H$_5$-CH$_2$-O-, 15%), 92 (C$_6$H$_5$-CH$_2$-, 100%). The $^1$H and $^{13}$C NMR data obtained for 145 were in agreement with that previous reported.292
2.2.19 Synthesis of bis(4-nitrobenzyl)ether 142

Bis(4-nitrobenzyl)ether 142 was prepared according to procedure 2.2.2 using 4-nitrobenzyl alcohol (0.2 g, 1.3 mmol). After stirring at room temperature for 1 week, analysis by $^1$H NMR spectroscopy revealed only 45% conversion of the alcohol to the desired ether 142. The insolubility of the product in chloroform allowed the separation of bis(4-nitrobenzyl)ether 142 from the reaction mixture as a yellow crystalline solid (0.1 g, 42%). Mp 94-96°C (Lit. 97-98°C). $^1$H NMR (200 MHz, CDCl$_3$) δ 4.72 (s, 4H, 2 × CH$_2$), 7.56 (d, $J$ = 8.8 Hz, 4H, H2, H6), 8.25 (d, $J$ = 8.8 Hz, 4H, H3, H5). GC/MS m/z (relative intensity) 107 (C$_6$H$_5$-CH$_2$-O-, 45%), 92 (C$_6$H$_5$-CH$_2$-, 100%).

2.2.20 Synthesis of O-(4-nitrobenzyl)-4-methoxyphenol 66

O-(4-Nitrobenzyl)-4-methoxyphenol 66 was prepared according to procedure 2.2.2 using 4-nitrobenzyl alcohol (0.1 g, 0.66 mmol) and 4-methoxyphenol (0.083 g, 0.66 mmol). After stirring at room temperature overnight, analysis by $^1$H NMR spectroscopy revealed 85% conversion of the phenol to the desired ether 66. O-(4-Nitrobenzyl)-4-methoxyphenol 66 was separated by flash chromatography (DCM) as a yellow crystalline solid (0.15 g, 88%). Mp 88-90°C (Lit. 85-87°C). $^1$H NMR (200 MHz, CDCl$_3$) δ 3.78 (s, 3H, OMe), 6.8-6.95 (m, 4H, H2-H6), 7.6 (d, $J$ = 8.8 Hz, 2H, H2', H6'), 8.24 (d, $J$ = 8.8 Hz, 2H, H2', H6'). GC/MS m/z (relative intensity) 259 (M, 7%); 123 (O-C$_6$H$_4$-OCH$_3$, 100%).

2.2.21 Synthesis of 4-toluic anhydride 164

4-Toluic anhydride 164 was prepared according to procedure 2.2.2 using 4-toluic acid (0.12 g, 0.66 mmol). After stirring at room temperature overnight, 4-toluic anhydride 164 was obtained as a white solid (0.1 g, 95%). Mp 87-89°C (Lit. 89-93°C). $^1$H NMR (200 MHz, CDCl$_3$) δ 2.45 (s, 6H, 2 × CH$_3$), 7.32 (d, $J$ = 8.1 Hz, 4H, H3, H5), 8.04 (d, $J$
= 8.1 Hz, 4H, H2, H6). GC/MS m/z (relative intensity) 254 (M, 25%), 119 (CH₃-C₆H₄-CO-, 100%).

2.2.22 Synthesis of 4-chlorobenzyl azide 65

4-Chlorobenzyl azide 65 was prepared according to procedure 2.2.2 using 4-chlorobenzyl alcohol (0.094 g, 0.66 mmol) and sodium azide (0.043 g, 0.66 mmol, as a suspension in DMF). After stirring at room temperature overnight, 4-chlorobenzyl azide 65 was obtained as a clear yellow oil (0.095 g, 89%). ¹H NMR (200 MHz, CDCl₃) δ 4.33 (s, 2H, CH₂), 7.26 (d, J = 8.5 Hz, 2H, H2, H6), 7.37 (d, J = 8.5 Hz, 2H, H3, H5). The ¹H NMR data obtained was consistent with that of 65 prepared using the Hendrickson reagent 27 (Chapter One experimental, section 1.4).

2.2.23 Synthesis of 4-chlorobenzyl thioacetate 64

4-Chlorobenzyl thioacetate 64 was prepared according to procedure 2.2.2 using 4-chlorobenzyl alcohol (0.094 g, 0.66 mmol) and thiolacetic acid (59 µL, 0.66 mmol). After stirring at room temperature overnight, 4-chlorobenzyl thioacetate 64 was obtained as a yellow oil (0.12 g, 91%). ¹H NMR (200 MHz, CDCl₃) δ 2.36 (s, 3H, CH₃), 4.08 (s, 2H, CH₂), 7.17 (d, J = 8.7 Hz, 2H, H2, H6), 7.27 (d, J = 8.7 Hz, 2H, H3, H5). ESMS (+ve mode) M⁺(³⁵Cl) 199 (10%), M⁺(³⁷Cl) 201 (3%). The ¹H NMR data obtained was in agreement with that obtained for 64 prepared using the Hendrickson reagent 27 (Chapter One experimental, section 1.3).

2.2.24 Attempted formation of (4-methoxyphenyl)(4-nitrophenyl)-methanone 183

2.2.24.1 Room temperature overnight

Polymer-supported triphenylphosphine ditriflate 157 (0.66 mmol) was prepared according to procedure 2.2.2. 4-Nitrobenzoic acid (0.11 g, 0.66 mmol) was added and
the solution stirred at room temperature for 2 hours. Consecutive addition of anisole (0.071 g, 0.072 mL, 0.66 mmol) and diisopropylethylamine (0.4 mL, 2.3 mmol) produced a light brown slurry which was stirred at room temperature overnight. The polymer beads were collected on a filter and washed with DCM (3 × 30 mL). The yellow filtrate was washed with sodium hydrogen carbonate (5% aqueous solution, 3 × 50 mL) and the combined DCM layers dried (anhydrous MgSO₄) and concentrated in vacuo. Analysis of the crude residue by ¹H NMR spectroscopy indicated the presence of unreacted anisole, which was confirmed by addition of an aliquot of anisole into the NMR sample.

2.2.24.2 Reflux for 2 days

Procedure 2.2.24.1 was repeated and heated at reflux for 2 days. Again, the resulting residue was shown to contain unreacted anisole following analysis by ¹H NMR spectroscopy.

2.2.25 Synthesis of oxacycloundecan-2-one 186

Polymer-supported triphenylphosphine oxide 158 (0.3 g, 0.9 mmol) was swollen in dry DCM (10 mL) under nitrogen. Triflic anhydride (0.12 mL, 0.66 mmol) was added and the resulting slurry stirred for 1 hour at room temperature. 10-Hydroxydecanoic acid (0.112 g, 0.66 mmol) and diisopropylethylamine (0.4 mL, 2.3 mmol) were then added and the solution left to stir overnight at room temperature. The reaction mixture was worked up according to procedure 1.3.2. The resulting residue was passed through a short silica column (DCM/hexane, 1:1) to yield oxacycloundecan-2-one 186 as a pale yellow sticky solid (0.04 g, 36%). ¹H NMR (200 MHz, CDCl₃) δ 1.2-1.5 (m, 10H), 1.55-1.8 (m, 4H), 2.2-2.5 (m, 2H), 4.0-4.2 (m, 2H). ESMS (+ve mode) MLI⁺, 177
(25%). The $^1$H NMR data obtained for 186 was consistent with that previously reported.306

2.2.26 Synthesis of $O$-(4-nitrobenzoyl)-cyclohexanol 76

Polymer-supported triphenylphosphine ditriflate 157 (0.66 mmol) was prepared according to procedure 2.2.2. 4-Nitrobenzoic acid (0.11 g, 0.66 mmol) and diisopropylethylamine (0.4 mL, 2.3 mmol) were added at the solution stirred at room temperature for 15 minutes. The slurry was treated with DMAP (0.08 g, 0.66 mmol) and after 5 minutes, cyclohexanol (70 µL, 0.66 mmol) added. The resulting mixture was stirred at room temperature overnight. The reaction mixture was worked up according to procedure 1.3.1 to afford $O$-(4-nitrobenzoyl)-cyclohexanol 76 as a pale yellow solid (0.14 g, 85%). Mp 49-51°C (Lit.279 47-48°C). $^1$H NMR (400 MHz, CDCl3) $\delta$ 1.3-2.1 (m, 5H, H2-H6), 5.04-5.1 (m, 1H, H1), 8.21 (d, $J$ = 9.2 Hz, 2H, H3', H5'), 8.29 (d, $J$ = 9.2 Hz, 2H, H2', H6'). ESMS (+ve mode) MH$^+$, 250 (25%).

2.2.27 Attempted synthesis of $O$-(4-nitrobenzoyl)-cyclohexanol 76 using catalytic DMAP

Polymer-supported triphenylphosphine ditriflate 157 (0.66 mmol) was prepared according to procedure 2.2.2. 4-Nitrobenzoic acid (0.11 g, 0.66 mmol) was added and the solution stirred for 15 minutes at room temperature. The slurry was then treated with DMAP (8 mg, 0.066 mmol) and after 5 minutes, cyclohexanol (70 µL, 0.66 mmol) and diisopropylethylamine (0.4 mL, 2.3 mmol) added. After stirring at room temperature overnight, analysis of the reaction mixture by GC/MS showed cyclohexene 75 : $O$-(4-nitrobenzoyl)-cyclohexanol 76 : cyclohexanol = 68:18:14. The identity of the products generated was confirmed by $^1$H NMR spectroscopy.
2.2.27 Attempted preparation of neomenthyl 4-nitrobenzoate 67 [(1S,2S,5R)-5-methyl-2-(1-methylethyl)cyclohexyl 4-nitrobenzoate]

Polymer-supported triphenylphosphine ditriflate 157 (0.66 mmol) was prepared according to procedure 2.2.2. (1R,2S,5R)-(-)-Menthol (0.103 g, 0.66 mmol), 4-nitrobenzoic acid (0.11 g, 0.66 mmol) and diisopropylethylamine (0.4 mL, 2.3 mmol) were added and the mixture heated to reflux overnight. The polymer beads were removed by filtration. Analysis of an aliquot of the crude reaction mixture by GC/MS indicated the presence of 2- and 3-menthene 36 and 37, (1R,2S,5R)-(-)-menthol and neomenthyl 4-nitrobenzoate 67, in a ratio of 70 : 16 : 5. The remaining solution was worked up according to procedure 1.3.1. Analysis of the resulting residue by $^1$H NMR spectroscopy confirmed the presence of 2- and 3-menthene 36 and 37 (ratio 1 : 2), (1R,2S,5R)-(-)-menthol and neomenthyl 4-nitrobenzoate 67.

2.2.28 Synthesis of $O$-(4-nitrobenzoyl)-(–)-menthol 69 [(1R,2S,5R)-5-methyl-2-(1-methylethyl)cyclohexyl 4-nitrobenzoate]

Polymer-supported triphenylphosphine ditriflate 157 (0.66 mmol) was prepared according to procedure 2.2.2. 4-Nitrobenzoic acid (0.13 g, 0.8 mmol) and diisopropylethylamine (0.4 mL, 2.3 mmol) were added and the solution stirred for 15 minutes at room temperature. The slurry was treated with DMAP (0.1 g, 0.8 mmol) and after 5 minutes, (1R,2S,5R)-(-)-menthol (0.104g, 0.66 mmol) added. After stirring at room temperature for 15 minutes, analysis of the reaction mixture by GC/MS revealed the presence of $O$-(4-nitrobenzoyl)-(–)-menthol 69 and 2- and 3-menthene 36 and 37, in a ratio of 97 : 3. The reaction mixture was worked up according to procedure 1.3.1 to afford $O$-(4-nitrobenzoyl)-(–)-menthol 69 as a pale yellow oil which solidified upon standing (0.17 g, 84%). Mp 60-62°C. $^1$H NMR (200 MHz, CDCl$_3$) δ 0.76-2.2 (m, 18H, H2-H6, 5-CH$_3$, H1', 6 × H2'), 4.98 (ddd, $J$ = 11, 11, 4 Hz, 1H, H1), 8.21 (d, $J$ = 9.1 Hz,
2H, H2", H6"), 8.3 (d, J = 9.1 Hz, 2H, H3", H5""). GC/MS m/z (relative intensity) 138 (2- and 3-menthene 36 and 37, 50%). The ^1^H NMR data obtained for 69 was identical to that previously reported.\textsuperscript{224}
CHAPTER FIVE

Further considerations of the Mitsunobu and Hendrickson reagents

1.0 Phosphitylation via the Hendrickson reagent 27

1.1 Formation of dimethyl-4-nitrobenzyl phosphite 189

Triflic anhydride (0.5 mL, 3 mmol) was added to triphenylphosphine oxide (2 g, 7.2 mmol) in DCM (10 mL) at 0°C under a nitrogen atmosphere. After stirring at 0°C for 30 minutes, dimethyl phosphite 187 (0.29 g, 0.24 mL, 2.64 mmol) was added. When a clear solution resulted (~ 15 seconds), 4-nitrobenzyl alcohol (0.4 g, 2.64 mmol) and diisopropylethylamine (1.15 mL, 6.6 mmol) were added. The reaction was stirred at room temperature overnight, the solvent removed in vacuo and the crude residue analysed by $^{31}$P NMR spectroscopy. $^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ 9.7 (s, methyl-4-nitrobenzyl phosphite 190), 10.9 (s, dimethyl phosphite 187), 29.8 (s, triphenylphosphine oxide), 140.8 (s, methyl-bis(4-dinitrobenzyl) phosphite 191), 141.2 (s, dimethyl-4-nitrobenzyl phosphite 189) and 141.2 (s, trimethyl phosphite 192, Lit.$^{260}$ $\delta$ 141-139.6 ppm); ratio 6 : 6 : 75 : 2 : 8 : 1.

1.2 $^{31}$P NMR spectroscopy study of the formation of benzyldimethyl phosphite 193

A solution of the Hendrickson reagent 27 (0.2 mmol) in CD$_2$Cl$_2$ (0.75 mL) in a 5 mm NMR tube was prepared as described in procedure 1.1. A pre-addition $^{31}$P NMR spectrum recorded at 25°C indicated the presence of the Hendrickson reagent 27 ($\delta$ 76 ppm, br s) and protonated triphenylphosphine oxide ($\delta$ 53 ppm, br s) in a ratio of 17 : 3 respectively. Dimethyl phosphite 187 (15.3 µL, 0.17 mmol), benzyl alcohol (18 µL, 0.17 mmol) and diisopropylethylamine (87 µL, 0.5 mmol) were added and the tube mixed briefly by vortex. $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$) $\delta$ 9.5 (s, benzylmethyl
phosphite 194), 10.9 (s, dimethyl phosphite 189), 29.3 (s, triphenylphosphine oxide), 140.3 (s, methylidibenzyl phosphite 195), 140.7 (s, benzyldimethyl phosphite 193) and 141.1 (s, trimethyl phosphite 192, Lit. 260 δ 141-139.6 ppm); ratio 2 : 4 : 73 : 2 : 17 : 2.

1.3 $^{31}$P NMR spectroscopy study of the attempted synthesis of benzylidimethyl phosphite 193 with a change in the order of addition

The Hendrickson reagent 27 (0.2 mmol) was prepared in a 5 mm NMR tube as described in procedure 1.2. A pre-addition $^{31}$P NMR spectrum recorded at 25°C indicated the presence of the Hendrickson reagent 27 (δ 76 ppm, br s) and protonated triphenylphosphine oxide (δ 53 ppm, br s) in a 9 : 1 ratio respectively. Benzyl alcohol (19 µL, 0.18 mmol) was added and the tube vortexed until a clear solution resulted. Analysis by $^{31}$P NMR spectroscopy indicated the formation of benzyloxytriphenylphosphonium trifluoromethanesulfonate 196 (δ 63 ppm, s) and protonated triphenylphosphine oxide (δ 53 ppm, br s) in a ratio 2 : 3 respectively. Subsequent addition of dimethyl phosphate 187 (16 µL, 0.18 mmol) and diisopropylethylamine (87 µL, 0.5 mmol) generated a clear yellow solution. $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$) δ 10.8 (s, dimethyl phosphate 187), 29.0 (s, triphenylphosphine oxide) and 63.0 (s, benzyloxytriphenylphosphonium trifluoromethanesulfonate 196); ratio 44 : 29 : 27.

1.4 $^{31}$P NMR spectroscopy study of the formation of dimethyl N,N-diethylphosphoramidite 198

The Hendrickson reagent 27 (0.2 mmol) was prepared in a 5 mm NMR tube as described in procedure 1.2. A pre-addition $^{31}$P NMR spectrum recorded at 25°C indicated the presence of the Hendrickson reagent 27 (δ 76 ppm, br s) and protonated triphenylphosphine oxide (δ 53.0 ppm, br s) in a 3 : 1 ratio respectively. Addition of
dimethyl phosphite \textbf{187} (13.5 \, \mu\text{L}, 0.15 \, \text{mmol}) and diethyleamine (0.2 \, \text{mL}, 2 \, \text{mmol}) formed a clear solution after mixing by vortex briefly. \[^{31}\text{P} \text{NMR (162 MHz, CD}_2\text{Cl}_2\] \(\delta = 29.0\) (s, triphenylphosphine oxide) and 149.9 (s, dimethyl \(N,N\)-diethylphosphoramidite \textbf{198}, Lit.\[^{262}\] \(\delta = 151.02\) ppm); ratio 17 : 3.

\section*{1.5 Attempted formation of benzyldimethyl phosphite 193 through the dimethyl \(N,N\)-diethylphosphoramidite 198 intermediate}

The Hendrickson reagent \textbf{27} (3 \, \text{mmol}) was prepared according to procedure 1.1. Dimethyl phosphite \textbf{187} (0.24 \, \text{mL}, 2.64 \, \text{mmol}) was added and when a clear solution formed, diethyleamine (0.24 \, \text{mL}, 2.64 \, \text{mmol}) was added. After 5 minutes, the addition of benzyl alcohol (0.27 \, \text{mL}, 2.64 \, \text{mmol}) and diisopropylethylamine (1.15 \, \text{mL}, 6.6 \, \text{mmol}) produced a clear yellow solution which was stirred at room temperature overnight. The crude reaction mixture was concentrated \textit{in vacuo} and analysed by \[^{31}\text{P} \text{NMR spectroscopy. \[^{31}\text{P} \text{NMR (162 MHz, CDCl}_3\] \(\delta = 9.4\) (s, benzylmethyl phosphite \textbf{194}), 10.8 (s, dimethyl phosphite \textbf{187}), 30.1 (s, triphenylphosphine oxide), 140.4 (s, methyldibenzyl phosphite \textbf{195}), 140.9 (s, benzyldimethyl phosphite \textbf{193}, Lit.\[^{261}\] \(\delta = 141.28\) ppm) and 141.4 (s, trimethyl phosphite \textbf{192}, Lit.\[^{260}\] \(\delta = 141-139.6\) ppm); ratio 6 : 9 : 79 : 1 : 4 : 1.

\section*{2.0 Methylenation of catechols using the Mitsunobu reaction}

\subsection*{2.1 Attempted synthesis of 1,3-benzodioxole 199}

\subsection*{2.1.1 Room temperature overnight}

A solution of triphenylphosphine (1.31 g, 5 \, \text{mmol}) in dry THF (15 \, \text{mL}) under a nitrogen atmosphere was cooled on ice. Slow addition of DIAD (1 \, \text{mL}, 5 \, \text{mmol}) generated a
pale yellow precipitate almost immediately. After 10 minutes, catechol (0.5 g, 4.5 mmol) was added and the light brown mixture was warmed to room temperature over 15 minutes. Formaldehyde (generated from heating paraformaldehyde at 150°C) was bubbled through the solution for 30 minutes and the solution stirred at room temperature overnight. The solvent was removed in vacuo and the resulting residue dried under high vacuum. Analysis of the residue by 1H NMR spectroscopy and HPLC/MS revealed a complex mixture of products.

2.1.2 Room temperature overnight, portion-wise addition of formaldehyde

Procedure 2.1.1 was repeated with the bubbling of formaldehyde through the solution for 4 × 10 minute portions (with 30 minutes between additions). After stirring at room temperature overnight, the solvent was removed in vacuo and the resulting residue dried under high vacuum. Analysis of the residue by 1H NMR spectroscopy and HPLC/MS revealed a complex mixture of products.

2.2 Synthesis of 4-methoxy-1,3-benzodioxole 200

2.2.1 Room temperature overnight

A solution of triphenylphosphine (0.56 g, 2.14 mmol) in dry THF (15 mL) under a nitrogen atmosphere was cooled to 0°C. Slow addition of DIAD (0.42 mL, 2.14 mmol) generated a yellow precipitate almost immediately. After 10 minutes, a solution of 3-methoxycatechol (0.3 g, 2.14 mmol) in THF (2 mL) was added. After stirring for 20 minutes, the solution was warmed to room temperature and formaldehyde (generated from heating paraformaldehyde to 150°C) was bubbled into the solution for 1 hour. The resulting dark red solution was stirred at room temperature overnight. The solvent was removed at reduced pressure to yield a red residue which was dried under high vacuum.
Analysis by $^1$H NMR spectroscopy showed 60% conversion of 3-methoxycatechol (δ 3.8, s, 3H, OCH$_3$) to 4-methoxy-1,3-benzodioxole 202 (δ 3.9, s, OCH$_3$).

**2.2.2 Room temperature overnight, portion-wise addition of formaldehyde**

Procedure 2.2.1 was repeated with the bubbling of formaldehyde through the solution for $4 \times 10$ minute portions (with 30 minutes between additions). After stirring at room temperature overnight, ethyl acetate (20 mL) was added and the solution extracted with 2M NaOH (3 × 30 mL) to remove excess 3-methoxycatechol. The solvent was then removed at reduced pressure to yield a red residue which was dried under high vacuum.

Analysis of the crude mixture by $^1$H NMR spectroscopy indicated 80% conversion of 3-methoxycatechol (δ 3.8, s, 3H, OMe) to 4-methoxy-1,3-benzodioxole 200 (δ 3.9, s, OMe). The mixture was subjected to column chromatography (2% ether/chloroform). 4-Methoxy-1,3-benzodioxole 200 was obtained as white crystals (0.29g, 76%). Mp 42-44°C (Lit. 268 39-41°C). $^1$H NMR (200 MHz, CDCl$_3$) δ 3.91 (s, 3H, OCH$_3$), 5.97 (s, 2H, CH$_2$), 6.5-6.8 (m, 3H, 3 × Ar-H). $^{13}$C NMR (50 MHz, CDCl$_3$) δ 56.5 (CH$_3$), 101.1, 102.3, 107.4, 121.9 (3 × CH, CH$_2$), 135.2 (C), 144.1 (C), 148.7 (C). GC/MS m/z (relative intensity) 152 (M, 100%).

**2.3 Attempted synthesis of 4-methoxy-2-phenyl-1,3-benzodioxole 201**

A solution of triphenylphosphine (0.56 g, 2.14 mmol) and 3-methoxycatechol (0.3 g, 2.14 mmol) was prepared in dry THF (15 mL) under a nitrogen atmosphere. The solution was cooled to 0°C and DIAD (0.42 mL, 2.14 mmol) added slowly. Addition of benzaldehyde (0.22 mL, 2.14 mmol) formed a clear yellow solution which was heated at reflux for 2 days. The solvent was removed in vacuo and the resulting residue dried under high vacuum. Analysis of the crude mixture by $^1$H NMR spectroscopy revealed unreacted 3-methoxycatechol (δ 3.8, s, 3H, OCH$_3$).
2.4 $^{31}$P NMR spectroscopy study of 2,2-dihydro-2,2,2-triphenyl-4-methoxy-1,3,2-benzodioxaphosphole 204 formation

A solution of triphenylphosphine (0.093 g, 0.356 mmol) and 3-methoxycatechol (0.05 g, 0.356 mmol) in CDCl$_3$ (0.5 mL) was prepared in a 5 mm NMR tube under argon. A $^{31}$P NMR spectrum was obtained at 25°C. The tube was cooled to 0°C and DIAD (0.073 mL, 0.375 mmol) added. After brief vortexing, another $^{31}$P NMR spectrum was obtained at 25°C. With 0 equiv. DIAD: $^{31}$P NMR (162 MHz, CDCl$_3$) δ -5.2 (s); With 1.05 equiv. DIAD: $^{31}$P NMR (162 MHz, CDCl$_3$) δ -17.9 (s, 2,2-dihydro-2,2,2-triphenyl-4-methoxy-1,3,2-benzodioxaphosphole 204), 29.8 (s, triphenylphosphine oxide), 44.5 (s, betaine 83), ratio 8 : 1 : 1.

3.0 Alternatives to azodicarboxylates in the Mitsunobu reaction

3.1 Attempted synthesis of 4-nitrobenzyl 4-nitrobenzoate 61 using fumaronitrile and tributylphosphine

3.1.1 Room temperature in benzene overnight

A solution of 4-nitrobenzyl alcohol (0.46 g, 3 mmol) and 4-nitrobenzoic acid (0.5 g, 3 mmol) in dry benzene (15 mL) was prepared under nitrogen. Consecutive addition of tributylphosphine (0.75 mL, 3 mmol) and fumaronitrile (0.235 g, 3 mmol) produced an orange solution which was stirred at room temperature overnight. The mixture was concentrated in vacuo and dried briefly under high vacuum. Analysis by $^1$H NMR spectroscopy indicated 55% conversion of the alcohol to its corresponding ester 61.

3.1.2 Room temperature in toluene for 1 week

Procedure 3.1.1 was repeated using toluene and stirred at room temperature for 1 week. Analysis by $^1$H NMR spectroscopy revealed 57% conversion of the alcohol to its corresponding ester 61.
3.1.3 Reflux in toluene for 3 hours

Procedure 3.1.1 was repeated in toluene and heated to reflux for 3 hours. Analysis by \(^1\)H NMR spectroscopy revealed 73% conversion of the alcohol to its corresponding ester 61. The crude mixture was submitted to flash chromatography (DCM/hexane, 1:1) to yield 4-nitrobenzyl 4-nitrobenzoate 61 as a yellow solid (1.3 g, 72%). Mp 165-167\(^\circ\)C (Lit.\(^2\)168\(^\circ\)C). \(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta\) 5.51 (s, 2H, CH\(_2\)), 7.63 (d, \(J = 8.8\) Hz, 1H, H2', H6'), 8.22-8.4 (m, 6H, H2, H3, H5, H6, H3', H5'). ESMS (+ve mode) M+H, 302 (15%).

3.1.4 \(^{31}\)P NMR spectroscopy study of attempted formation of intermediate 207

A solution of tributylphosphine (0.095 mL, 0.38 mmol) in d\(_6\)-benzene was place in a 5 mm NMR tube under nitrogen. A \(^{31}\)P NMR spectrum was recorded at 25\(^\circ\)C. Fumaronitrile (0.03 g, 0.38 mmol) was added, the tube briefly mixed by vortex and another \(^{31}\)P NMR spectrum obtained at 25\(^\circ\)C. With 0 equiv. fumaronitrile: \(^{31}\)P NMR (162 MHz, CDCl\(_3\)) \(\delta\) -31.8 (s); With 1.0 equiv. fumaronitrile: \(^{31}\)P NMR (162 MHz, CDCl\(_3\)) \(\delta\) -31.7 (s).

3.2 Attempted synthesis of 4-nitrobenzyl 4-nitrobenzoate 61 using \(N\)-phenylmaleimide and tributylphosphine

3.2.1 Room temperature overnight

A solution of 4-nitrobenzyl alcohol (0.46 g, 3 mmol) and 4-nitrobenzoic acid (0.5 g, 3 mmol) in dry benzene (15 mL) was prepared under nitrogen. Consecutive addition of tributylphosphine (0.75 mL, 3 mmol) and \(N\)-phenylmaleimide (0.52 g, 3 mmol) produced an orange solution which was stirred at room temperature overnight. The mixture was then concentrated \textit{in vacuo} (a colour change to black was observed) and
dried briefly under high vacuum. Analysis by $^1$H NMR spectroscopy revealed unreacted 4-nitrobenzyl alcohol.

3.2.2 Room temperature for 1 week

The above method was repeated at room temperature for 1 week. Analysis by $^1$H NMR spectroscopy indicated ~1% conversion of the 4-nitrobenzyl alcohol to its corresponding ester 61.

3.3 Attempted synthesis of 4-nitrobenzyl 4-nitrobenzoate 61 using $N$-phenylmaleimide and tributylphosphine

3.3.1 Synthesis of 3-phenylsydnone 209

$N$-Phenylglycine (15 g, 0.1 mol) was placed in water (180 mL) and cooled to 0°C. A solution of sodium nitrite (7.5 g, 0.11 mol) in water (45 mL) was added dropwise over 40 minutes such that the temperature remained at 0°C. The resulting dark red solution was filtered by suction. Activated carbon (Norit) (0.5 g) was added to the filtrate and the solution stirred for a few minutes. The mixture was filtered by suction. Addition of concentrated hydrochloric acid (15 mL) to the filtrate gave a slurry of crystals which was stirred for 10 minutes. The crystals were collected on a filter and washed with ice-cold water. After drying under high vacuum, $N$-nitroso-$N$-phenylglycine 210 was obtained as tan coloured crystals (14 g, 78%). Mp 103-105°C (Lit. 103-104°C). $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 4.7 (s, 2H, CH$_2$), 7.36-7.58 (m, 5H, Ar-H), 7.85-8.1 (br s, 1H, COOH). ESMS (-ve mode) M$^-$, 179 (100%).

$N$-Nitroso-$N$-phenylglycine 210 (7 g, 0.039 mol) was dissolved in acetic anhydride (500 mL) and the solution heated at 100°C for 2 hours. After cooling, the mixture was
poured into cold water (250 mL). The solution was stirred for 5 minutes and crystals began to separate. The solid was collected on a filter, washed with ice-cold water and dried under high vacuum. 3-Phenylsydnone 209 was obtained as pale yellow crystals (5.5 g, 87%). Mp 138-140°C (Lit. 136-137°C). $^1$H NMR (200 MHz, CDCl$_3$) δ 6.75 (s, 1H, CH), 7.55-7.8 (m, 5H, Ar-H). ESMS (+ve mode) MH$^+$, 163 (20%); MLi$^+$, 169 (100%).

3.3.2 Reflux for 3 hours
Tributylphosphine (0.75 mL, 3 mmol) and 3-phenylsydnone (0.49 g, 3 mmol) were added consecutively to a stirred solution of 4-nitrobenzyl alcohol (0.46 g, 3 mmol) and 4-nitrobenzoic acid (0.5 g, 3 mmol) in dry toluene (15 mL) under nitrogen. The yellow solution was then heated at reflux for 3 hours, after which point a black mixture resulted. The solution was cooled and solvent removed by rotary evaporation. Analysis by $^1$H NMR showed ~ 7% conversion to the desired ester 61.

3.3.2 Room temperature for 1 week
Procedure 3.3.2 was carried out and allowed to stir at room temperature for 1 week. Removal of the solvent and brief drying under high vacuum yielded a yellow residue. Analysis by $^1$H NMR showed ~ 5% conversion to the desired ester 61.

3.4 Control reaction
4-Nitrobenzoic acid (0.5 g, 3 mmol) and 4-nitrobenzyl alcohol (0.46 g, 3 mmol) were stirred in dry toluene (15 mL) under a nitrogen atmosphere for 1 week at room temperature. Removal of the solvent at reduced pressure and brief drying under high vacuum yielded a pale yellow residue which was shown to contain unreacted 4-nitrobenzyl alcohol but no ester 61 following analysis by $^1$H NMR spectroscopy.
REFERENCES


33. Watanabe, T., Gridnev, I. D., and Imamoto, T. Chirality 2000, 12, 346.
41. Harvey, P. J. *PhD Thesis*; Griffith University: Brisbane, Australia, **1996**.


APPENDIX ONE

DATA AND CALCULATIONS FOR KINETIC STUDY OF 4-NITROBENZYL 4-NITROBENZOATE 61 FORMATION USING 27, 90-92.
Table 12. Data for Figure 3.

<table>
<thead>
<tr>
<th>Entry (^a)</th>
<th>Hendrickson reagent 27 (equiv.)</th>
<th>Conversion to 4-nitrobenzyl 4-nitrobenzoate 61 (%) (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>74.8</td>
</tr>
<tr>
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<td>1.0</td>
<td>97.5</td>
</tr>
<tr>
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<td>92.4</td>
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<td>4</td>
<td>1.2</td>
<td>63.8</td>
</tr>
<tr>
<td>5</td>
<td>1.4</td>
<td>45.4</td>
</tr>
<tr>
<td>6</td>
<td>1.6</td>
<td>38.2</td>
</tr>
<tr>
<td>7</td>
<td>1.8</td>
<td>33.5</td>
</tr>
<tr>
<td>8</td>
<td>2.0</td>
<td>22.3</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: 4-nitrobenzyl alcohol (1.0 equiv.), 4-nitrobenzoic acid (1.0 equiv.) and diisopropylethylamine (2.2 equiv.) were employed in DCM (10 mL) for 2 hours at room temperature.

\(^b\) Percentage conversion to 61 determined by \(^1\)H NMR spectroscopy.

**Calculations for the kinetic study of 4-nitrobenzyl 4-nitrobenzoate 61 formation using 27, 90-92.**

Total volume = 150 mL (solvent) + diisopropylethylamine (1.74 mL) + triflic anhydride (0.34 mL) = 152.08 mL = 0.15208 L

\([A]_o = \text{[initial 4-nitrobenzyl alcohol]} = \text{moles / vol (L)} = 0.002 / 0.15208 = 0.01315 \text{ M}\)

\([A] = \text{[4-nitrobenzyl alcohol]} \text{ at time } t = (\% \text{ 4-nitrobenzyl alcohol at time } t / 100) * \text{[initial 4-nitrobenzyl alcohol]}\)

Pseudo-first-order conditions were achieved using 5 equiv. 4-nitrobenzoic acid in 150 mL solvent at 0°C.

Rate constant (k) = - gradient (m).

\(T_{1/2} = \ln 2 / k\)
Table 13. Data for Figure 12 for Hendrickson reagent 27 in DCM/toluene 1 : 1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time (sec)</th>
<th>Conversion to 4-nitrobenzyl 4-nitrobenzoate 61 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>47.6</td>
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<td>3</td>
<td>180</td>
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<td>5</td>
<td>600</td>
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<td>900</td>
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<tr>
<td>7</td>
<td>1800</td>
<td>99.2</td>
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<sup>a</sup>Reaction conditions: Hendrickson reagent 27 (1.0 equiv.), 4-nitrobenzyl alcohol (1.0 equiv.), 4-nitrobenzoic acid (5.0 equiv.), diisopropylethylamine (5.0 equiv.), solutions 0.013 M in 27, 0°C.

<sup>b</sup>Percentage conversion to 4-nitrobenzyl 4-nitrobenzoate 61 determined by <sup>1</sup>H NMR integration, as described in Chapter Two experimental, section 3.1.

Table 14. Data for Figure 12 for Hendrickson reagent 27 in DCM.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time (sec)</th>
<th>Conversion to 4-nitrobenzyl 4-nitrobenzoate 61 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
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<tr>
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</table>

<sup>a</sup>Reaction conditions: Hendrickson reagent 27 (1.0 equiv.), 4-nitrobenzyl alcohol (1.0 equiv.), 4-nitrobenzoic acid (5.0 equiv.), diisopropylethylamine (5.0 equiv.), solutions 0.013 M in 27, 0°C.

<sup>b</sup>Percentage conversion to 4-nitrobenzyl 4-nitrobenzoate 61 determined by <sup>1</sup>H NMR integration, as described in Chapter Two experimental, section 3.1.
Table 15. Data for Figure 12 for Hendrickson reagent 27 in DCM/CH₂CN 1 : 1.

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Time (sec)</th>
<th>Conversion to 4-nitrobenzyl 4-nitrobenzoate 61 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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</thead>
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<tr>
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<td>83.3</td>
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<td>9</td>
<td>10800</td>
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</table>

<sup>a</sup>Reaction conditions: Hendrickson reagent 27 (1.0 equiv.), 4-nitrobenzyl alcohol (1.0 equiv.), 4-nitrobenzoic acid (5.0 equiv.), diisopropylethylamine (5.0 equiv.), solutions 0.013 M in 27, 0°C.

<sup>b</sup>Percentage conversion to 4-nitrobenzyl 4-nitrobenzoate 61 determined by ¹H NMR integration, as described in Chapter Two experimental, section 3.1.

Table 16. Data for Figure 13 for five-membered cyclic analogue 90 in DCM.

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Time (sec)</th>
<th>Conversion to 4-nitrobenzyl 4-nitrobenzoate 61 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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</thead>
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<td>98.0</td>
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</table>

<sup>a</sup>Reaction conditions: reagent 90 (1.0 equiv.), 4-nitrobenzyl alcohol (1.0 equiv.), 4-nitrobenzoic acid (5.0 equiv.), diisopropylethylamine (5.0 equiv.), solutions 0.013 M in 27, 0°C.

<sup>b</sup>Percentage conversion to 4-nitrobenzyl 4-nitrobenzoate 61 determined by ¹H NMR integration, as described in Chapter Two experimental, section 3.2.
Table 17. Data for Figure 13 for six-membered cyclic analogue 91 in DCM.

<table>
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<tr>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Time (sec)</th>
<th>Conversion to 4-nitrobenzyl 4-nitrobenzoate 61 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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<sup>a</sup>Reaction conditions: reagent 91 (1.0 equiv.), 4-nitrobenzyl alcohol (1.0 equiv.), 4-nitrobenzoic acid (5.0 equiv.), diisopropylethylamine (5.0 equiv.), solutions 0.013 M in 27, 0°C.  
<sup>b</sup>Percentage conversion to 4-nitrobenzyl 4-nitrobenzoate 61 determined by <sup>1</sup>H NMR integration, as described in Chapter Two experimental, section 3.2.

Table 18. Data for Figure 13 for seven-membered cyclic analogue 92 in DCM.

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Time (sec)</th>
<th>Conversion to 4-nitrobenzyl 4-nitrobenzoate 61 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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<tr>
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<td>10800</td>
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</tr>
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<sup>a</sup>Reaction conditions: reagent 92 (1.0 equiv.), 4-nitrobenzyl alcohol (1.0 equiv.), 4-nitrobenzoic acid (5.0 equiv.), diisopropylethylamine (5.0 equiv.), solutions 0.013 M in 27, 0°C.  
<sup>b</sup>Percentage conversion to 4-nitrobenzyl 4-nitrobenzoate 61 determined by <sup>1</sup>H NMR integration, as described in Chapter Two experimental, section 3.2.
Figure 22. Pseudo-first-order plot of the Hendrickson reagent 27 in DCM/toluene 1:1.

Table 19. Data for Figure 22.

<table>
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<th>[A](_o)</th>
<th>[A]/[A](_o)</th>
<th>Ln [A]/[A](_o)</th>
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</thead>
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\(^a\)4-Nitrobenzyl alcohol (%) = 100% - 4-nitrobenzyl 4-nitrobenzoate 61 (%)
Figure 23. First-order plot for Hendrickson reagent 27 in DCM.

Table 20. Data for Figure 23.

<table>
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<th>[A]₀</th>
<th>[A]/[A]₀</th>
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$^a$4-Nitrobenzyl alcohol (%) = 100% - 4-nitrobenzyl 4-nitrobenzoate 61 (%)
Figure 24. First-order plot of the Hendrickson reagent 27 in DCM/CH$_3$CN 1:1.

Table 21. Data for Figure 24.

<table>
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<th>[A]$_0$</th>
<th>[A]/[A]$_0$</th>
<th>Ln [A]/[A]$_0$</th>
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$^a$4-Nitrobenzyl alcohol (%) = 100% - 4-nitrobenzyl 4-nitrobenzoate 61 (%)
Figure 25. First-order plot of five-membered cyclic analogue 90 in DCM.

Table 22. Data for Figure 25.

<table>
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<th>Time (sec)</th>
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<th>[A]&lt;sub&gt;o&lt;/sub&gt;</th>
<th>[A]/[A]&lt;sub&gt;o&lt;/sub&gt;</th>
<th>Ln [A]/[A]&lt;sub&gt;o&lt;/sub&gt;</th>
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<sup>a</sup>4-Nitrobenzyl alcohol (%) = 100% - 4-nitrobenzyl 4-nitrobenzoate 61 (%)
Figure 26. First-order plot of six-membered cyclic analogue 91 in DCM.

Table 23. Data for Figure 26.

<table>
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<th>[A]/[A](_o)</th>
<th>Ln ([\text{A}/\text{[A]}_o])</th>
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\(^a\)4-Nitrobenzyl alcohol (%) = 100% - 4-nitrobenzyl 4-nitrobenzoate 61 (%)
**Figure 27.** First-order plot of seven-membered cyclic analogue 92 in DCM.

**Table 24.** Data for Figure 27.

<table>
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<th>Ln [A]/[A]&lt;sub&gt;0&lt;/sub&gt;</th>
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<sup>a</sup>4-Nitrobenzyl alcohol (%) = 100% - 4-nitrobenzyl 4-nitrobenzoate 61 (%)
APPENDIX TWO

PUBLICATIONS
NOTE

Refereed journal publications resulting from the work detailed in this thesis have been deposited as separate PDF files. The references to these publications are as follows:

‘The Hendrickson reagent and the Mitsunobu reaction : a mechanistic study’

‘Cyclic analogues of the Hendrickson ‘POP’ reagent’

‘Polymer-supported triphenylphosphine ditriflate : a novel dehydrating reagent’

‘Novel polymer-supported coupling/dehydrating reagents for use in organic synthesis’