Synthesis and Applications

Thesis submitted for the Degree of

Doctor of Philosophy

By

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in the Department of Chemistry

at the

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Statement

This thesis is based on work conducted by the author, in the Department of Chemistry at the University of Leicester, during the period October 2000 to September 2003.

All the work described in this thesis is original, unless otherwise acknowledged in the text or in the references. None of this work has been submitted for another degree in this or any other University.

Signed:_____ Date:_____

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Signed: T. Reeve Date: 15/5/04

Toby Benjamin Reeve

Abstract

Title: Diol-Functionalised Polystyrene Resins: Synthesis and Applications

Author: Toby Benjamin Reeve

This thesis describes the preparation of diol-functionalised polystyrene-divinylbenzene (PS-DVB) resins and preliminary investigations into their application for the heterogenisation of Lewis acid catalysts in carbon-carbon bond-forming reactions.

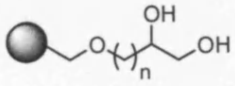
Chapter 1 introduces the motivation behind and the methods for the use of insoluble polymers for the heterogenisation of well-defined homogenous catalysts.

In chapter 2 a variety of routes to spacer-modified hydroxy-functionalised diols suitable for grafting onto PS-DVB resins are discussed. The grafting step was problematic, the ease with which the alcohol substrates were bound to the support being shown to be related to their steric bulk. A range of diol-functionalised resins **136-140** of consistent polymer morphology was obtained.

In chapter 3 this methodology is extended to scalemic diols derived either from olefins by asymmetric dihydroxylation (AD) (**168**, **173** and **191**) or from tartaric acid (**217**). Resins **207** and **208**, with the same immobilised diol unit as for **168** and **173**, respectively, were also prepared by solid-phase AD of polymer-bound olefins, although with lower conversion and poorer enantioselectivity.

Chapter 4 investigates the use of titanium species derived from **136-140** as Lewis acids and probes the effect of alkyl spacer length on their activity in the Diels-Alder reaction of methyl acrylate and cyclopentadiene. The incorporation of a nine-carbon methylene spacer (**138**) led to an improvement in catalyst activity relative to catalysts derived from **136** and **137**. A significant drop in reactivity was seen in reactions employing catalysts derived from **139** and **140**, when compared to those generated from **136-137** despite the presence of the spacer (in **139** and **140**).

The application of titanium-based Lewis acids prepared from (**168**, **173**, **191** and **217**) in the asymmetric Diels-Alder reaction of methacrolein and cyclopentadiene and diethylzinc addition to benzaldehyde is also reported with enantioselectivities of up to 39 % obtained.



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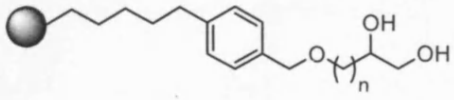
137 n = 4
138 n = 9



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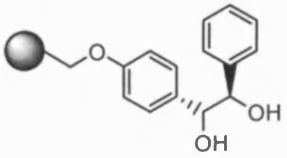
140 n = 4



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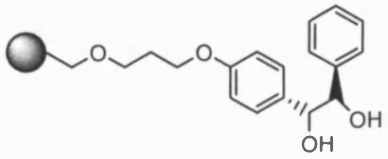

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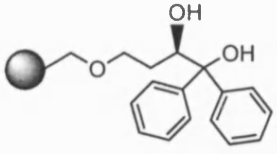

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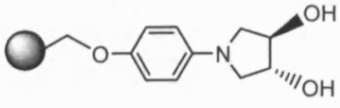

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Most of all I thank my family for their endless support in every way possible.

Contents

Abbreviations and Symbols

General and Physical:

AES	=	atomic emission spectroscopy
ATR	=	attenuated total internal reflectance
br s	=	broad singlet
CP	=	cross-polarisation
d	=	doublet
dd	=	doublet of doublets
dt	=	doublet of triplets
δ	=	chemical shift
°	=	degrees
EI	=	electron impact
GC	=	gas chromatography
HOMO	=	highest occupied molecular orbital
ICP	=	inductively coupled plasma
IR	=	infra-red
h	=	hour
LUMO	=	lowest unoccupied molecular orbital
m	=	multiplet
MAS	=	magic angle spinning
M.p.	=	melting point
MS	=	mass spectrometry
m/z	=	mass / charge ratio
NMR	=	nuclear magnetic resonance
ppm	=	parts per million
q	=	quartet
quint	=	quintet
rt	=	room temperature
s	=	singlet
sept	=	septet
t	=	triplet
TLC	=	thin layer chromatography

Chemical:

	=	lightly cross-linked (1-2 %) PS-DVB resin (unless where otherwise stated)
AD	=	asymmetric dihydroxylation
AIBN	=	α,α'-azoisobutyronitrile
Bn	=	benzyl
Boc	=	*N-tert*-butoxycarbonyl
^{n}Bu	=	*n*-butyl
^{t}Bu	=	*tert*-butyl
COD	=	cyclooctadiene
Cp	=	cyclopentadienyl
CpH	=	cyclopentadiene
15-crown-5	=	1,4,7,10,13-pentaoxacyclopentadecane
18-crown-6	=	1,4,7,10,13,16-hexaoxacyclooctadecane
DAIB	=	3-*exo*-dimethylaminoisoborneol
DCC	=	1,3-dicyclohexylcarbodiimide
DCM	=	dichloromethane
de	=	diastereomeric excess
DHQ	=	dihydroquinine
DHQD	=	dihydroquinidine
DMAP	=	*N*-dimethyl-4-amino-pyridine
DMF	=	N,N-dimethylformamide
DMP	=	2,2-dimethoxypropane
DMSO	=	dimethyl sulphoxide
DVB	=	divinylbenzene
ee	=	enantiomeric excess
Et	=	ethyl
hfc	=	3-(heptafluoropropylhydroxymethylene)-(-)-camphorate
IND	=	indoline
Me	=	methyl
MeCN	=	acetonitrile

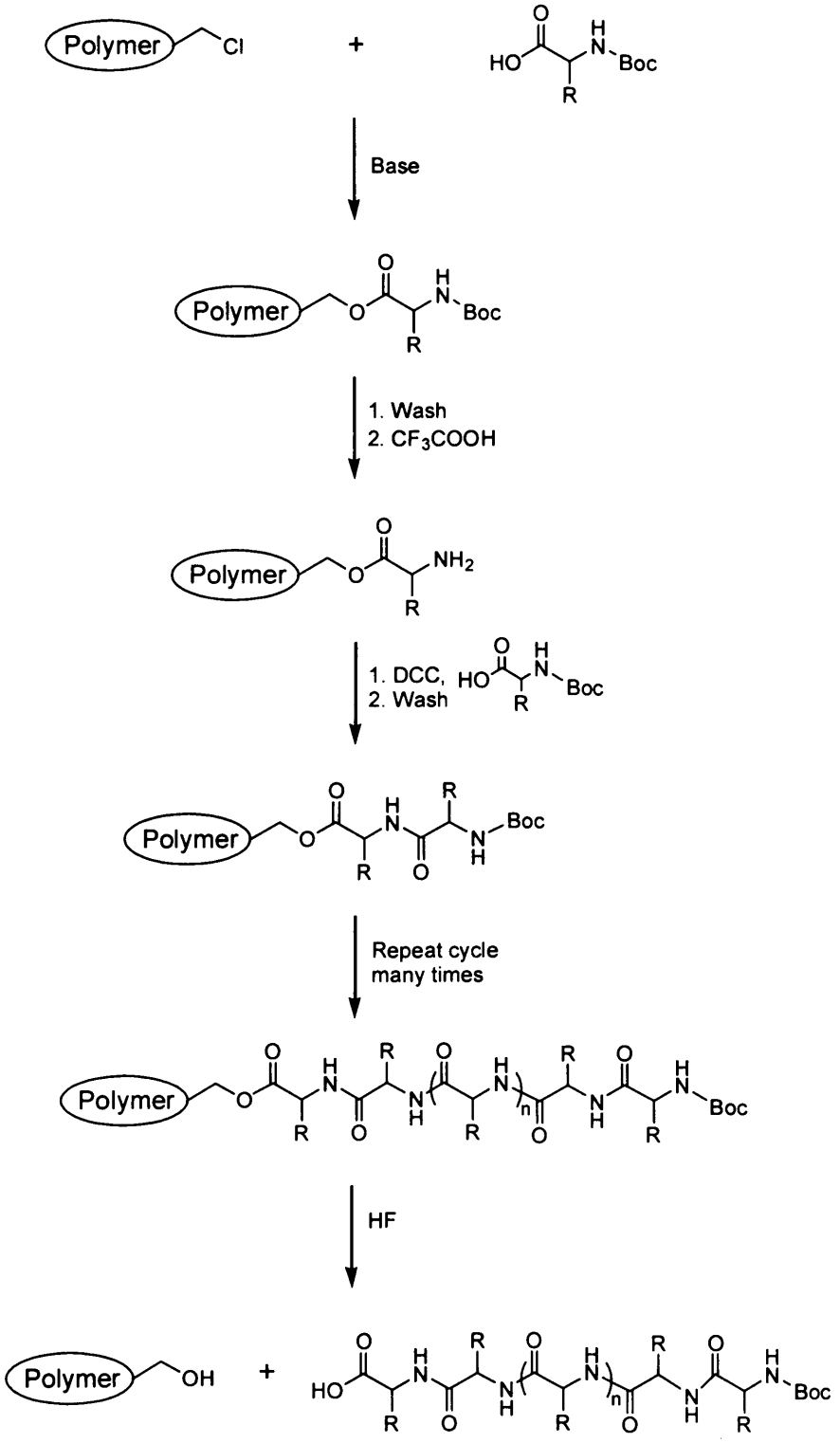
MeOH	=	methanol
NMO	=	*N*-methylmorpholine *N*-oxide
OAc	=	acetate
PCC	=	pyridinium chlorochromate
PEG	=	polyethylene glycol
Ph	=	phenyl
PHAL	=	phthalazine
PPTS	=	pyridinium *p*-toluene sulfonate
^{i}Pr	=	isopropyl
^{n}Pr	=	*n*-propyl
PS	=	polystyrene
py	=	pyridine
PYR	=	pyrimidine
SPOS	=	solid phase organic synthesis
TADDOL	=	α, α, α', α'-tetraaryl-1,3-dioxolane-4,5-dimethanol
TBDMS	=	*tert*-butyldimethylsilyl
THF	=	tetrahydrofuran
TMS	=	trimethylsilyl
tol	=	toluene
Ts	=	toluenesulphonyl

Chapter 1

Introduction

1.1 Merrifield peptide synthesis and SPOS

In 1963, the pioneering work of Merrifield introduced a method for the rapid and high-yielding synthesis of polypeptide chains (scheme 1).[1] The process utilized a strategy of immobilizing an amino acid-derived substrate on an insoluble polymeric support, thus enabling ease of product separation and purification at each step of the multi-stage

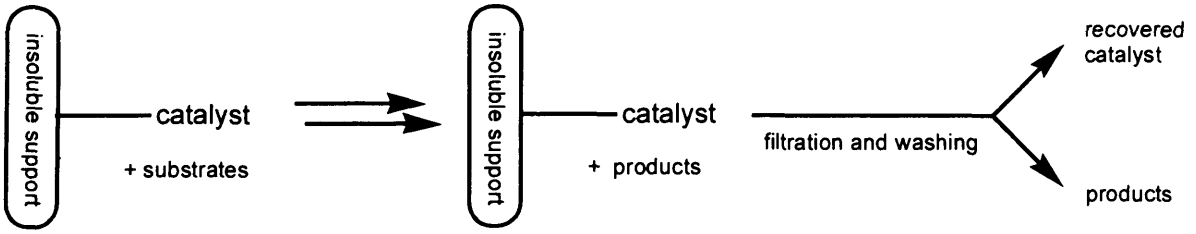


Scheme 1. Merrifield solid-phase peptide synthesis.

synthesis, by simple filtration and washing of the insoluble polymer. Since then this 'Solid-Phase Organic Synthesis' (SPOS) approach has been developed for the routine, automated synthesis of polypeptides,[2] oligo- and poly-nucleotides[3] and oligosaccharides.[4] More recently, research has focused on the application of solid-supports in the automated, simultaneous synthesis of libraries of small molecules in combinatorial chemistry.[5-7]

1.2 Heterogenising homogenous catalysts

The beneficial properties of homogenous catalysts – generally having high activity and selectivity, whilst operating under mild conditions – are often offset by difficulties associated with their separation, recovery and subsequent recycling. There has therefore been great interest in methods of "heterogenising" highly tuned, metal/ligand homogenous catalytic systems. The aim is to retain the solution phase behaviour of the catalyst in a biphasic system that allows easy separation of the metal-containing species from reactants and products. One such method, which arose following Merrifield's work, involves the attachment of a reagent or catalyst to an 'inert', insoluble support.[8-14] The basic principle is shown in scheme 2 and can be considered the inverse of SPOS. The catalyst is immobilized on a support, allowed to react with substrates and, once the reaction is complete, recovered from the reaction mixture by filtration.



Scheme 2

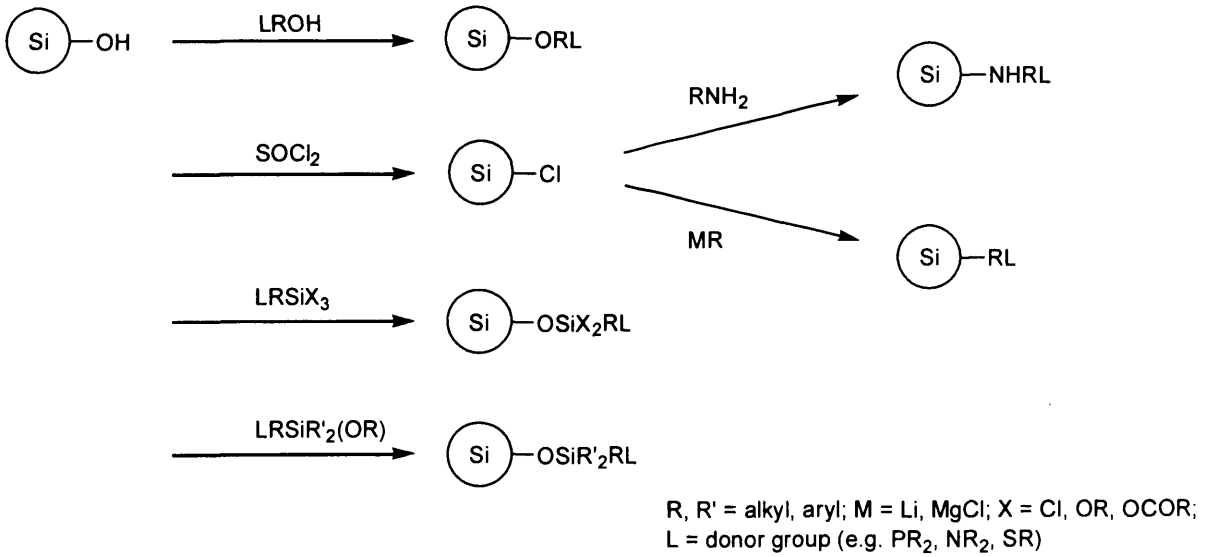
The immobilization of a catalyst (or reagent) on an insoluble support and the subsequent ease of catalyst/product separation this can engender, offers a number of potential advantages. From an economic point of view, reaction work-up is simplified and the loss of expensive metal species or, in the case of asymmetric catalysis, expensive and difficult to prepare chiral ligands, is prevented. The methodology can also help limit metal contamination of reaction waste and products, alleviating toxicological and ecological concerns. Furthermore, supported catalysts can be employed in flow reactors, providing reactions proceed quickly enough, or in automated processes (*e.g.* combinatorial chemistry and parallel synthesis).[15]

There are two broad classes of supports that have been used for the heterogenisation of optimised homogeneous catalysts – inorganic oxides and organic polymer supports. These two types of support will now be outlined, with a comparison of their relative merits being presented in section **1.5**.

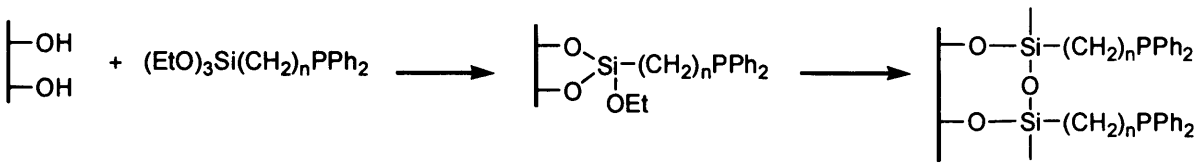
1.3 Inorganic oxide supports[8]

Inorganic oxide supports, such as silica, have traditionally been used to prepare 'classical' heterogenous catalysts with direct attachment of metal species to surface silanol units (*e.g. via* Si—O—M linkages).[16] Discussion in this chapter (sections **1.3** and **1.4**), however, is focussed on the application of these solids for the purpose outlined in section **1.2**, *i.e.* immobilisation of well-defined homogenous catalysts.

Silica, alumina and silica-alumina mixtures are examples of inorganic solids that have been used as supports.[16-19] The most widely used is silica, with general formula $SiO_2.xH_2O$, which can be thought of as the polycondensation product of orthosilicic acid $Si(OH)_4$. In order to obtain a porous support material with a large surface area and, therefore, potentially high numbers of surface hydroxyl (or more specifically silanol, Si-OH) groups available for functionalisation (and hence of use in catalyst grafting), the desired silicas can be prepared by a variety of specialised techniques. These include acid precipitation from silicate solutions, hydrolysis of silicon halides, SiX_4, or alkoxides, $Si(OR)_4$, and pyrogenic methods using simultaneous hydrolysis of silicon halides. The physical properties of the porous silicas obtained using these methods are very different to



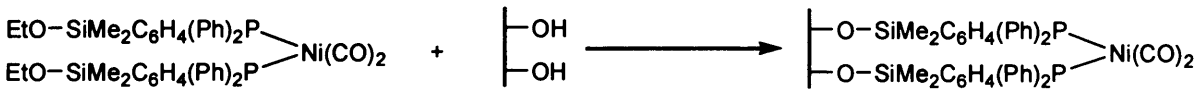
Scheme 3. Methods of functionalising silica.



Scheme 4. Example of possible cross-linking in grafting of silyl ethers to silica.

the glassy solid obtained from the cooling of liquid state silica.

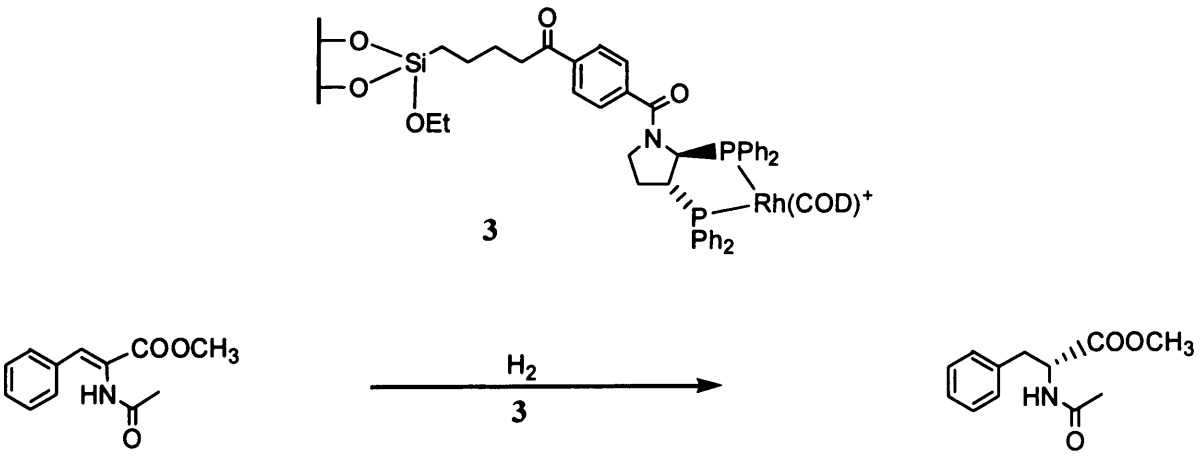
Functionalisation of silica can be achieved *via* conversion of surface hydroxyl groups to a variety of different functional groups suitable for either further modification or direct co-ordination to a metal centre. The metal is then bound to the support by coordination to ligand L, often a phosphine. The grafting of ligand-functionalised alcohols, LROH, or alkoxy silanes, $LRSiR'_2(OR)$, has been shown to proceed more cleanly, with reduced undesirable cross-linking reactions (*e.g.* scheme 4).[20]



1 **2**

Scheme 5

A less common approach, due to the problematic synthesis of such compounds, is to graft a complex functionalised with a leaving group X (remote from the metal centre) directly onto silica. An example is the synthesis of di-anchored complex **2** (scheme 5, X = EtO).[20] The dropwise addition of a solution of **1** to silica is necessary to give the di-anchored, chelated (and hence more strongly bound) product rather than the mono-tethered complex, which is favoured under direct addition conditions.



3

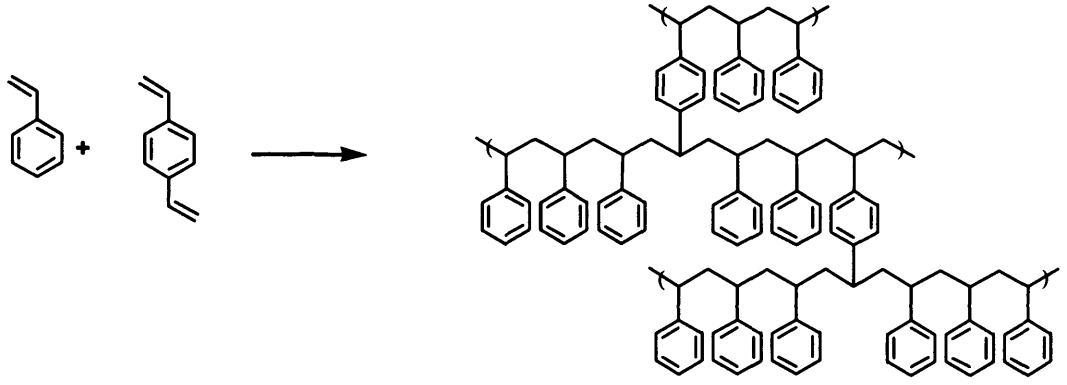
100 % ee

Scheme 6

An example of the application of a functionalised silica as a support for a previously prepared homogenous catalyst involves the asymmetric hydrogenation catalyst **3**, which gave 100 % ee in the hydrogenation of methyl acetamidecinnamate (scheme 6).[21] Immobilised catalyst **3** was found to be as active as its homogenous counterpart.

1.4 Organic polymers as supports

A number of different organic polymers have been used as supports for immobilizing homogenous catalysts. By far the most commonly used, however, are cross-linked polystyrenes, synthesised *via* the free-radical-initiated polymerisation of styrene and divinylbenzene (DVB) (scheme 7). The result is a resin – a cross-linked polymeric network, or matrix – that is insoluble in all solvents. The physical properties of styrene/DVB copolymers depend on the method of polymerisation and the proportion of DVB (*i.e.* the degree of cross-linking) in the monomer mixture.



Scheme 7. Copolymerisation of styrene and DVB to form cross-linked polystyrene.

There are a number of different methods for the synthesis of these types of cross-linked polystyrene.[8] The first is bulk polymerisation, where polymerisation of a neat monomer mixture is initiated. The polymerisation proceeds very rapidly and is highly exothermic and difficult to control. The resulting polymer is a glassy material that is difficult to process into a workable form.

Alternatively, a second method is a solution polymerisation process. Here, the monomer mixture is dissolved in a suitable solvent, *e.g.* toluene, and polymerisation is initiated using a radical source (*e.g.* AIBN). This method is safer, with the solvent acting as a heat transfer agent. As polymerisation proceeds and the cross-linked network forms, the polymer precipitates. The disadvantage of solution polymerisation is again difficulty in

obtaining the polymer in a useful physical form, with irregularly shaped polymer particles being obtained. Irregularly shaped particles are more susceptible to mechanical attrition and breakdown to a powder, which can clog filtration apparatus.

The two methods of polymerisation that are most commonly used to give a polymer suitable for use as a support are "popcorn" and suspension polymerisation. "Popcorn" polymerisation is achieved by gently heating the neat monomer mixture, containing a low percentage of DVB, in the absence of initiators. Under the right conditions, over a long period, a white, fluffy opaque granular material, that is highly porous, is obtained. This popcorn-like product is easily separated from unreacted monomer and then mechanically broken into smaller particles suitable for subsequent use.

A more elegant method of polystyrene synthesis is suspension polymerisation.[22] This is usually the method of choice when synthesising a polymer suitable for use as a support, since spherical polymer particles (or beads) that have a relatively uniform size and shape, are produced. These beads are easy to handle and less susceptible to mechanical degradation, which can lead to formation of a powder. For most applications of supported catalysis, a uniform particle size and shape, and an easily reproducible structure of the polymer (and therefore reproducible physical properties) are essential. Physical robustness or resistance to mechanical degradation is also an important factor.

There are two basic methods of suspension polymerisation of styrene/DVB co-monomer mixtures, which lead to two different types of resin: *gel-type* and *macroporous* resins. Gel-type resins are so named because, although solid in the dry state, they interact with certain solvents to give a material that is between the solid and liquid states. Macroporous resins are those that have a permanent porous structure that changes little in the presence or absence of solvents. The synthesis and morphology of these two types of resin will be explained in the following section.

1.4.1 Synthesis of gel-type PS-DVB resins

To synthesise gel-type resin beads, the liquid monomer mixture of styrene / DVB is suspended in an excess of a non-solvent, usually water, containing a dissolved suspension stabilizer. The mixture is stirred so as to maintain a suspension of monomer droplets and a free radical initiator (*e.g.* AIBN) is added. The suspension stabilizer, usually a water-soluble polymer (such as polyvinyl alcohol), helps prevent the droplets from combining.

The mixture is typically heated to 80°C for 12 hours with the resulting polymer forming within the droplets as hard, glassy, transparent beads.

An important point regarding the polymerisation process, which helps account for the differences in polymer morphology resulting from variations in the method of synthesis, concerns the relative reactivity of the vinyl groups in styrene and DVB.[22] A vinyl group of DVB is more reactive towards free-radical polymerisation relative to the vinyl group of styrene. Therefore DVB monomer molecules are incorporated into the growing polymer chain at a statistically greater rate than styrene molecules (than would be expected from the proportion of DVB in the monomer feed), at the onset of polymerisation. Note, however, that after incorporation into the polymer chain the pendant vinyl group of DVB, which leads to cross-linking, essentially has the same reactivity as that of a free styrene monomer molecule. As polymerisation proceeds, the polymer chains that are formed become cross-linked as the second pendant vinyl group of DVB reacts. Due to the initial superior rate of incorporation of DVB over styrene, formation of small volumes of microgel, or nuclei, unconnected or interconnected by regions of low cross-linking density, occurs. As polymerisation proceeds further, the polymer molecules eventually become infinitely cross-linked and macrogelation occurs, to give a soft gel, with the polymer swollen by the unreacted comonomer mixture. The interaction between the polymer chains and comonomer mixture means that, although insoluble, the polymer chains can move apart as if solvated. As the remaining comonomer mixture is consumed, the nuclei aggregate together in a relatively slow process to give a spherical product with a smooth glass-like appearance.[22]

Another possible source of cross-linking that can arise during polymerisation is the introduction of irreversible chain entanglements (*e.g.* Fig.1). The occurrence of these "entanglement cross-links" generally increases as the rate of polymerisation is increased, for example, by increasing the temperature, or concentration of free-radical sources.

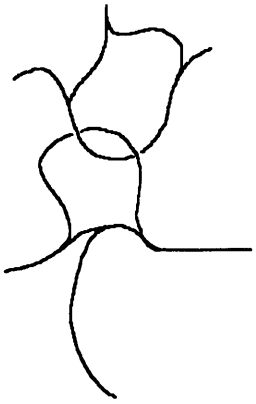


Fig. 1. Permanent entanglement cross-link.

Vigorous stirring however can help reduce the presence of these cross-links.

1.4.2 Solvent interaction and physical properties of gel-type PS-DVB resins[8,22]

In the dry state, gel-type resin beads have very low porosity and small surface area. With the addition of a suitable solvent the aggregation of nuclei that causes the bead formation is reversed, with the interconnected polymer chains separating and expanding to the maximum limit as defined by the cross-linking. This process, known as swelling, results in a highly porous gel network that consists predominantly of solvent. Solvents that cause the resin to swell, known as "good" solvents, are those solvents that would dissolve the uncross-linked polymer, *i.e.* polystyrene. So-called "good" solvents include aromatics, halogenated hydrocarbons and THF. Solvents in which linear polystyrene is insoluble cause no expansion of the polymer network and no swelling is observed. These "bad" solvents include water, methanol, other polar solvents and solvents of very low polarity such as aliphatic hydrocarbons and diethyl ether.

The degree of swelling of a gel-type resin is defined as the amount of solvent absorbed by the polymer beads, or the change in the volume of the beads that occurs upon solvation. The swelling of a gel-type resin is important in the context of solid-phase reactions as it allows free movement of solvent and, hence, dissolved substrates and reactants around the polymer matrix, enabling interactions with supported species to occur. The degree of swelling depends on many factors, the most important of which is the degree of cross-linking in the matrix, *i.e.* the proportion of DVB in the monomer mixture. If there is a low degree of cross-linking (< 2 % DVB) the resins show excellent swelling properties and every pendant aromatic ring can be considered accessible to substrates dissolved in the reaction medium. The volume of such resins can expand up to 10 times upon interaction with a good solvent. A resin with more than 20 % DVB will show little swelling and the polymer matrix will consist of highly cross-linked regions inaccessible to substrates.

An increase in cross-linking also correlates with an increase in the mechanical stability of the resin. Cross-linking of less than 1 % gives a resin that is very susceptible to mechanical damage and it is apparent that there is a balance between mechanical stability and swelling.[22] Gel-type resins with 1-4 % DVB are the most commonly used supports. Even with these resins care is required during their manipulation in a reaction to maintain their bead form and also to prevent the breakdown of the polymer into a fine powder. The use of overhead stirrers or shakers in reactions rather than a conventional stirrer bead is

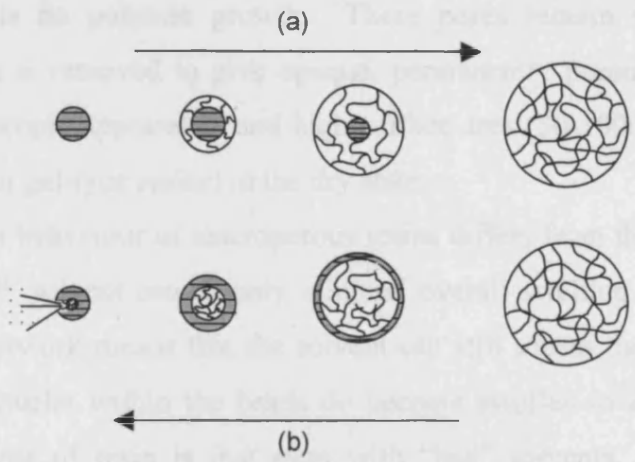


Fig. 2. Solvation behavior of PS-DVB beads; a) beads swell; b) contraction in a non solvent from the outside inwards can result in osmotic shock.

necessary to avoid physical damage. It is also important to avoid dramatic changes in solvent polarity (*e.g.* during washing of polymer beads) that can cause a rapid collapse of swollen beads, possibly resulting in their fracture or bursting, a process known as osmotic shock.[22] This phenomenon takes place due to the beads becoming swollen, or contracting, in a process that occurs from the outside of the beads to the inside (Fig.2). Gel-type resins are only useful as catalyst supports if repeated cycles of swelling and deswelling are possible without damage to the beads.

The swelling property of a particular gel-type resin is also affected by functionalisation. The introduction of functional groups onto the polymer can cause the matrix to swell better in different solvents. This effect is obviously greater when there is a high degree of loading onto the support (*i.e.* a high proportion of the pendant aromatic groups of the polystyrene are functionalised). Notably, introduction of a high loading of hydrophilic groups, for example, onto a resin will cause the beads to swell poorly in non-polar solvents yet swell considerably in water.

1.4.3 Synthesis and properties of macroporous PS-DVB resins[22]

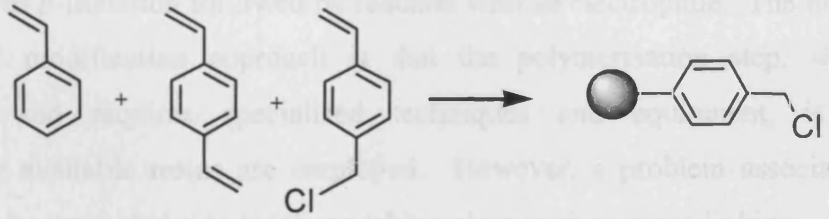
The key difference in the synthesis of macroporous compared with gel-type resins is the addition of a solvating diluent, such as toluene, into the monomer mixture prior to polymerisation. The diluent causes the phase separation of the growing polymer matrix and the comonomer/diluent mixture. This can occur either before or after the macrogelation stage, depending on the nature and quantity of the diluent. The result is that at full conversion, the beads have regions of highly cross-linked polymer and a network of

pores where there is no polymer growth. These pores remain when the remaining comonomer solution is removed to give opaque, permanently porous beads. The beads have a rough microscopic appearance and high surface area (50-1000 m^2 g^{-1} compared to less than 10 m^2 g^{-1} for gel-type resins) in the dry state.

The solvation behaviour of macroporous resins differs from that of gel-type resins. Addition of a "good" solvent causes only minimal overall swelling of the bead, but the permanent porous network means that the solvent can still access the matrix and that the highly cross-linked nuclei within the beads do become swollen to a certain extent. An advantage of this type of resin is that even with "bad" solvents, the porous structure remains and thus reactions can generally be carried out in any solvent.

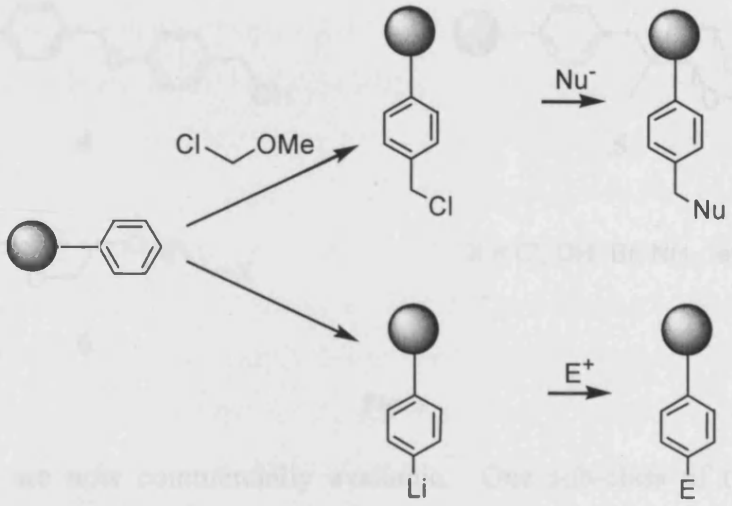
1.4.4 Functionalisation of cross-linked polystyrene

There are two basic methods for the incorporation of functional groups onto a polystyrene resin. The first method is to introduce a suitably functionalised styrene monomer into the styrene/DVB mixture prior to polymerisation. A simple example is the synthesis of chloromethylated polystyrene beads by polymerising styrene/DVB with *p*-vinyl benzyl chloride (scheme 8). The main benefits of this approach are that the loading



Scheme 8. Copolymerisation of styrene, DVB and *p*-vinyl benzyl chloride to form chloromethylated PS-DVB (Merrifield resin).

and distribution of functionalised aromatic rings can be closely controlled. In addition, if a more complicated monomer is used (*e.g.* a styrene functionalised metal complex), the supported species can be fully characterised prior to heterogenisation, avoiding the problems associated with characterising a supported species. However, it should be noted that the reactivity of the vinyl group of the functionalised styrene will vary according to the nature of the *p*-substituent, something that will make the rates of polymerisation of the three components potentially quite different. This will impact upon the final composition of the resin.

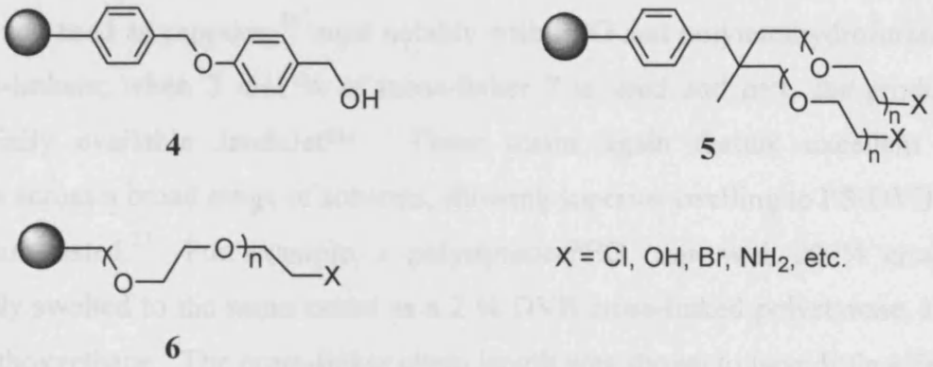


Scheme 9. Methods of chemical modification of PS-DVB beads; Nu = nucleophile, E = electrophile.

The second method of functionalisation is by chemical modification of a preformed styrene/DVB copolymer. For this approach the pendant aromatic rings can be considered as having the same intrinsic reactivity as isopropyl benzene. Two common methods for the introduction of functional "handles" are shown in scheme 9. The first involves reaction with, for example, chloromethyl ethyl ether to give chloromethylated polystyrene (Merrifield resin). This is commercially available and is a common starting resin, suitable for further functionalisation by, for example, nucleophilic attack. The second method shown involves *p*-lithiation followed by reaction with an electrophile. The main benefit of the chemical modification approach is that the polymerisation step, which can be troublesome and requires specialised techniques and equipment, is avoided if commercially available resins are employed. However, a problem associated with this approach can be unwanted side reactions taking place such as cross-linking.

1.4.5 Other organic polymers as supports

Although styrene/DVB copolymers are the most commonly used supports for the heterogenisation of homogenous catalysts, numerous other supports have also been used. In 1956 silk was used to immobilize metallic palladium for use in enantioselective hydrogenation reactions.[8] Another natural product, cellulose, has been modified with diphenylphosphino groups and used as a ligand in rhodium-catalysed hydrogenations.[8] In these two cases the materials were chosen for their inherent chirality. Numerous other supports based on polystyrene have been developed, usually for applications in SPOS,



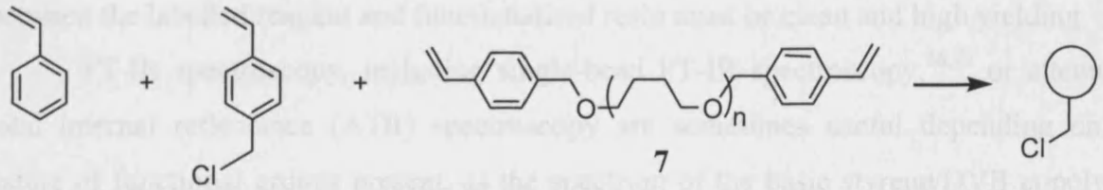
4 5 6

Fig. 3

many of which are now commercially available. One sub-class of these polystyrene-derived polymers are lightly cross-linked (1-2 %) PS-DVB resins modified with various pendant "linkers", which alter the physical properties of the polymer, for example to improve the swelling performance of the resins in different solvents. These supports include Wang (**4**), Tentagel™ (**5**) and ArgoGel™ (**6**) resins (Fig.3), which incorporate polar linkers (benzyloxybenzyl alcohol or polyethylene glycol {PEG}) in order to give a greater degree of swelling in more polar solvents. This is significant, since the swelling of a resin is necessary to allow the supported species to become more accessible to dissolved reagents. Thus, a resin that swells well in a variety of solvents can potentially be used in a wider range of reactions. The linker not only improves the resin's swelling in polar solvents, but also improves the flexibility and mobility of the functional end group. Resins **4-6** are available with a variety of functionalities at the termini of the linkers.

The swelling abilities of the Wang and Tentagel™ resins in various solvents has been compared to that of a standard Merrifield resin and it was shown that the former two resins had superior swelling in polar solvents (*e.g.* DMSO, MeCN), with the PEG linked resin **6** even showing a good degree of swelling in water (4 times its volume).[23] The Merrifield resin was found to perform better than the other two in less polar solvents however (*e.g.* THF, DCM, toluene).

Another class of polystyrene-based resin utilizes alternative cross-linking agents to



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Scheme 10. Synthesis of Polytetrahydrofuran cross-linked polystyrenes. (When 2 mol % of cross-linker is used and n=1, the product is commercially available as JandaJel™).

DVB. Various resins with more flexible cross-linkers, compared with DVB, have been prepared and used as supports,[24] most notably with PEG and polytetrahydrofuran (scheme 10) cross-linkers; when 2 mol % of cross-linker **7** is used and n=1, the product is the commercially available JandaJel™. These resins again feature excellent swelling properties across a broad range of solvents, showing superior swelling to PS-DVB resins in all solvents tested.[25] For example, a polystyrene-PEG resin with 20 % cross-linking remarkably swelled to the same extent as a 2 % DVB cross-linked polystyrene, in toluene and dimethoxyethane. The cross-linker chain length was shown to have little effect on the degree of swelling, except at high levels of incorporation of the cross-linker (>20 %), where an increase in spacer length led to an increase in the swelling ability.

1.4.6 Characterisation of polymer-supported species

Cross-linked polystyrene resins are insoluble macromolecules and, as a result, characterisation of supported species is non-trivial and a major disadvantage in both their synthesis and use. This is particularly the case when attempts are made to further functionalise a pre-formed resin and to subsequently characterise the new material or to quantify conversion.

Gravimetric analysis is one method of "following" such a reaction. If grafting or cleaving groups onto or from a polymer matrix results in a significant change in the mass of the supported group, then recovery and weighing of the beads can give an estimation of the extent to which a reaction has occurred.

In some instances elemental analysis can give information on the success of a reaction. Reactions involving changes in Cl, P or N loadings are all particularly suitable for monitoring *via* elemental analyses, *e.g.* reactions involving loss of chlorine from Merrifield resin following substitution. Another approach is to derivatise a supported species by reaction with a suitably "labelled" group (*e.g.* with a halogen or isocyanate). For this approach to be reliable, as with all reactions involving solid supports, the reaction between the labelled reagent and functionalised resin must be clean and high yielding.

FT-IR spectroscopy, including single-bead FT-IR spectroscopy,[26,27] or attenuated total internal reflectance (ATR) spectroscopy are sometimes useful depending on the nature of functional groups present, as the spectrum of the basic styrene/DVB copolymer has a large number of peaks and often interferes. Only reactions that produce supported species with easily detectable and identifiable IR absorption bands are usefully

identified/quantified using this technique. For example, carbonyl groups can usually be observed by IR spectroscopy and there are examples of quantitative analysis of the loss of the absorbance at 1250cm^{-1}, corresponding to the CH_2-Cl stretching frequency, in reactions involving Merrifield resin.[28]

NMR spectroscopy is an area where there have been a number of recent developments in improving the on-bead analysis of supported species.[7,29] ^{13}C NMR spectra can be obtained from gel-type resins that are lightly cross-linked and therefore have good swelling properties. This gel-phase approach is a cross between normal solution phase NMR and solid-state NMR spectroscopy. Research has been conducted in recent years to optimise data-processing parameters and acquisition/relaxation delays to allow reasonable spectra to be obtained from these gels using conventional solution phase spectrometers in short periods of time.[29] The spectra obtained vary in quality depending of the degree of swelling of the resin and the mobility of attached groups. Strong signals from the polymer backbone can dominate the spectra, which means that the loading of a supported species needs to be sufficiently high to compete with these peak intensities. Gel-phase ^{1}H NMR spectra obtained in a similar fashion are not useful due to severe line broadening of polymer backbone peaks. High resolution Magic Angle Spinning (HRMAS) NMR can be used to analyse functionalised PS resins swollen in solvents, although the quality of the spectra obtained have been shown to depend significantly on the nature of the support.[30] Resins with a very high degree of swelling, such as the PEG-funtionalised polystyrenes have been shown to give the best spectra. In one example, HRMAS was used to determine the enantiomeric excess of Wang resin-supported diols prepared by enantioselective dihydroxylation reactions.[31]

Chemical reactions involving polymer beads have been monitored using matrix-assisted laser desorption time-of-flight mass spectrometry (MALDI-TOF-MS).[32] Conventional electron-impact (EI) mass-spectrometry has also been used to detect fragments supported on polymer beads.[33] The latter method necessitates high temperatures (above 400°C) to depolymerise the resin prior to mass spectroscopic analysis.

1.5 Comparison of supports

The types of supports that have been described above (sections **1.3** and **1.4**) have various advantages and disadvantages associated with them and it is worth summarising these differences. Discussion will focus solely on their use as supports for catalysts rather

than in SPOS, as there are some differences between the requirements of each application. Most commercially available supports have been designed with SPOS in mind, with the focus often being on obtaining a high loading of grafted functionality, together with methods of linking and cleaving organic substrates to or from the support at the initial and final steps of a synthesis. It may also be desired that a support for SPOS is functional in a variety of reaction media, such as in a multi-step synthesis, hence the development of the PEG-functionalised resins described previously, which swell in a variety of solvents. These considerations are either not important or less significant when designing a support for a homogenous catalyst.

A property that is important, however, for the immobilisation of well-defined catalyst species is mechanical stability. Inorganic oxides, such as silica, are generally more robust, and are unaffected by sudden changes in solvent polarity. Macroporous PS resins, with a permanently porous structure are also resistant to sudden solvent polarity changes. In order to maintain the porous structure of macroporous resins, a high proportion of DVB is usually incorporated giving a high degree of cross-linking and therefore good mechanical strength. Gel-type resins are more fragile due to the low cross-linking levels used and are also susceptible to osmotic shock. Inorganic oxides are stable at far higher temperatures than organic polymers, the latter generally not being stable above 150°C. This has made inorganic oxides particularly attractive to industrial processes as supports for traditional heterogenous catalysts. However, organic polymers are more stable to changes in pH than inorganic oxides, which can dissolve in strong acid or basic conditions. Organic polymers have the advantage over inorganic oxides of being amenable to a wider range of methods of functionalisation and there are more convenient methods of chemical modification available than there are for inorganic oxides.

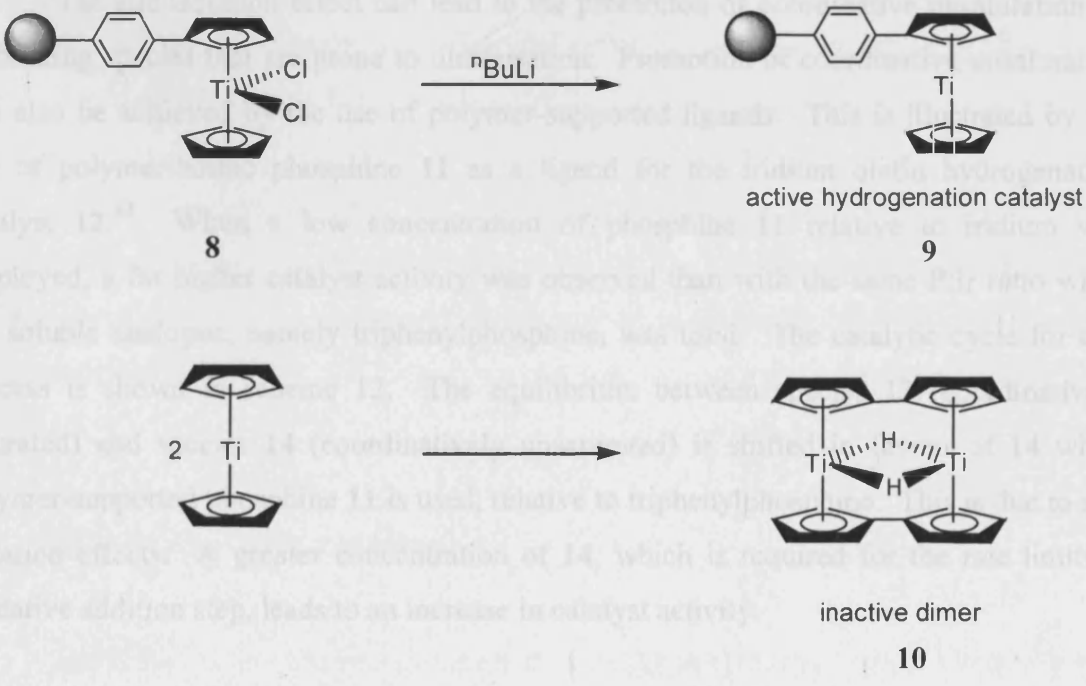
A final point to make about the inorganic oxides concerns difficulties arising from the poorly defined nature of the surface of these solids. It is difficult to functionalise every surface hydroxyl group and the ill-defined surfaces and interference from unreacted hydroxyl groups can lead to irregular catalyst active sites and also to reactions between the support and the supported metal's coordination sphere. For example, silica has generally rather reactive surface silanols (pKa values in the range 4-7, dependent upon the method of preparation of the silica), combined with well-documented proton surface mobility between oxygen centres,[34] which together can make this oxide incompatible with sensitive organometallic species. These problems mean that inorganic oxides, such as silica, are generally less suitable for the tethering of well-defined homogenous catalysts.

1.6 Effects of immobilizing a catalyst

Although one important aim when supporting an active homogenous catalyst on a solid support is to retain the behaviour and properties of its soluble analogue, there are inevitably other possible consequences arising from such immobilisation.[35]

One such effect is site isolation. By tethering a catalyst to a support it is usual to observe reduced interactions between supported species compared with the solution phase. This can lead to increased stability of reactive intermediates (which could be involved in a catalytic process) that are, for example, prone to dimerisation. This effect has been observed in the tethering of a number of species to solid supports. An example is the immobilization of titanocene residues by Grubbs *et al.* (scheme. 11).[36,37] Reduction of supported dichloride **8** gave the titanocene species **9**, which was found to have considerably higher activity in the hydrogenation of hex-1-ene than was observed for the equivalent homogenous system (Cp_2Ti). This was attributed to prevention of the active titanocene units dimerizing to give catalytically inactive species **10**.

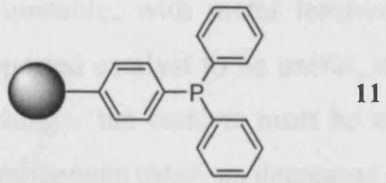
The site isolation effect depends heavily on the loading and the "mobility" of the supported species. Mobility is the movement of the tethered species in the solvated environment and is related to the rigidity of the support. In the case of gel-type polystyrene resins, mobility will be high with low cross-linking. Mobility also depends on the length and nature of the linker attaching the catalyst to the support. As the loading of a



Scheme 11

species is increased, and mobility of the species is raised, the interaction possible between supported species augmented and the species is less isolated. In practise, true site isolation is only achieved with a low loading of catalyst on a resin prepared with high DVB content (>20 %).

The effect can be exploited, however, using a highly swollen gel-type resin, both maximising accessibility of reagents to the supported species and reducing the concentration of active sites so as to ensure interaction between catalyst and substrate is favoured over site-site interactions (relative to the equivalent homogenous system).



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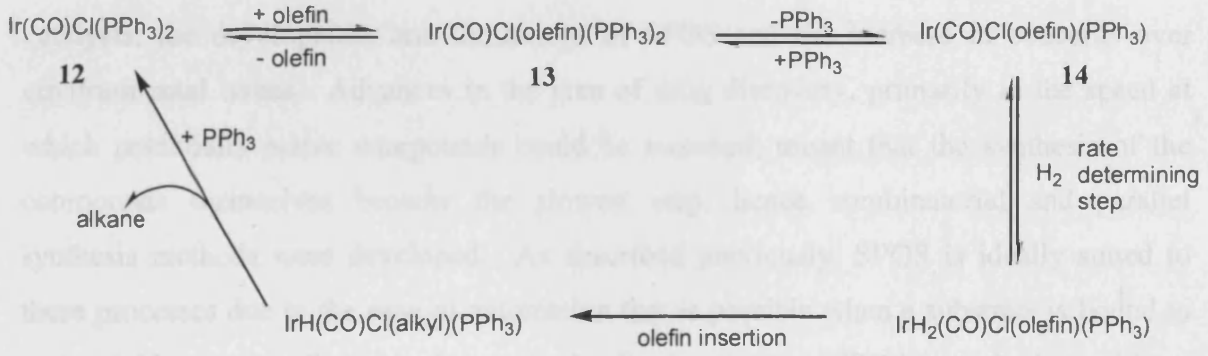


Scheme 12

The site isolation effect can lead to the promotion of coordinative unsaturation by stabilizing species that are prone to dimerisation. Promotion of coordinative unsaturation can also be achieved by the use of polymer-supported ligands. This is illustrated by the use of polymer-bound phosphine **11** as a ligand for the iridium olefin hydrogenation catalyst **12**.[38] When a low concentration of phosphine **11** relative to iridium was employed, a far higher catalyst activity was observed than with the same P:Ir ratio when the soluble analogue, namely triphenylphosphine, was used. The catalytic cycle for this process is shown in scheme 12. The equilibrium between species **13** (coordinatively saturated) and species **14** (coordinatively unsaturated) is shifted in favour of **14** when polymer-supported phosphine **11** is used, relative to triphenylphosphine. This is due to site isolation effects. A greater concentration of **14**, which is required for the rate limiting oxidative addition step, leads to an increase in catalyst activity.

1.7 Development of polymer-supported catalysis

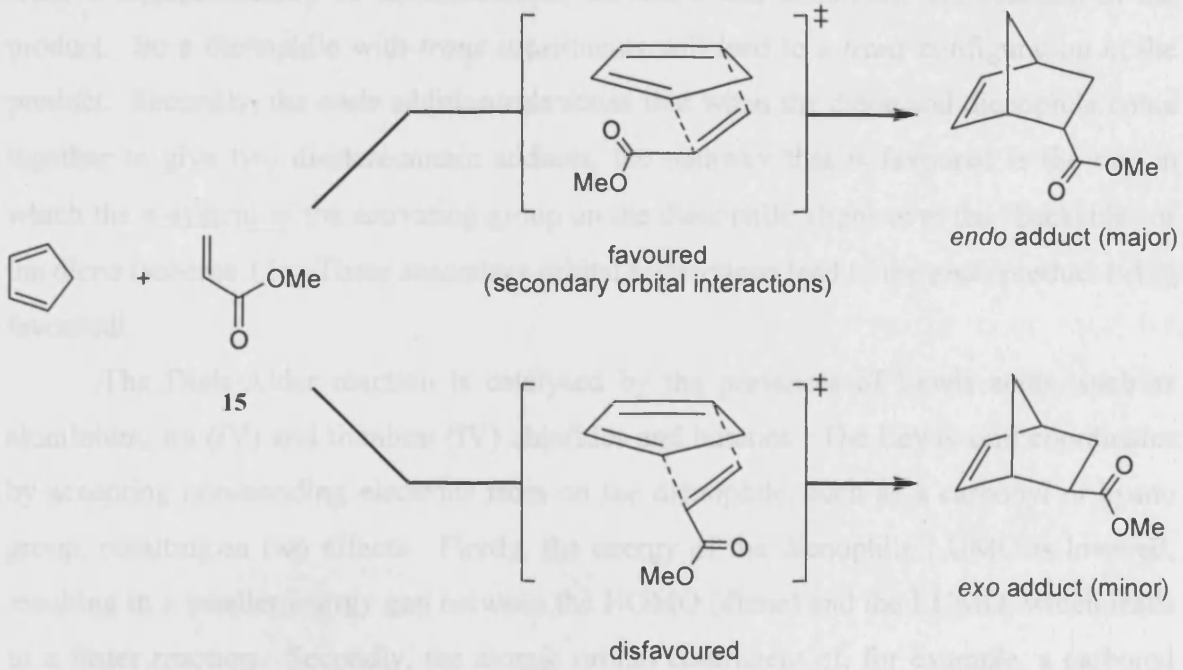
In the initial development of supported metal complex catalysts, through the 1970's, and early 80's, the emphasis was often placed on the activity of the catalyst sometimes at the expense of other important factors such as stability and recyclability. The focus was often on the use of low-valent metals as catalysts in reactions involving alkenes, such as hydrogenation, hydroformylation, hydrosilylation and isomerization.[8,9] As a result, when industrial researchers explored the commercial viability of these systems, they were often found to be unstable, with metal leaching from the support being a significant problem. For a supported catalyst to be useful, it is essential that it can be recovered and reused with no leaching – the catalyst must be truly heterogenised. Thus, interest in the use of supported homogenous catalysts decreased as a consequence.

Two factors have led to a recent resurgence in the interest in new supported catalysts: the development and limitations of SPOS and the increase in concerns over environmental issues. Advances in the area of drug discovery, primarily in the speed at which potentially active compounds could be screened, meant that the synthesis of the compounds themselves became the slowest step, hence combinatorial and parallel synthesis methods were developed. As described previously, SPOS is ideally suited to these processes due to the ease of automation that is possible when a substrate is bound to an insoluble support. Recently, however, the disadvantages of SPOS, namely the problems of characterisation and determination of purity of a product bound to a support, as well as the extra steps of attaching and cleaving the compound to and from the support, have led to a revival in the development of new supported catalysts, reagents and scavengers such that compound synthesis occurs in the solution phase, thereby overcoming some of the pitfalls of SPOS.

In the following sections, the application of polymer-supported catalysts in two classes of reactions will be reviewed. These are the Diels-Alder reaction and dialkylzinc addition to aldehydes. A summary of the use of homogenous diol ligands for these transformations is also included for reasons that will become apparent in section **1.10**.

1.8 The Diels-Alder reaction[39]

The Diels-Alder reaction is of great importance in synthetic organic chemistry as a method of constructing cyclohexene derivatives, for example. An electron-rich diene (*e.g.*



Scheme 13. Diels-Alder reaction of cyclopentadiene and methyl acrylate.

cyclopentadiene) undergoes a concerted [4 + 2] cycloaddition with an electron-poor dienophile {*e.g.* methyl acrylate (**15**)} forming two new carbon-carbon bonds (scheme 13). The reaction occurs *via* "head-on" overlap of the highest occupied molecular orbital (HOMO) of the diene and the lowest unoccupied molecular orbital (LUMO) of the dienophile in a pericyclic process (Fig. 4). The reaction is useful primarily because of the stereoselectivity that is observed. Firstly, due to the concerted nature of the reaction, the

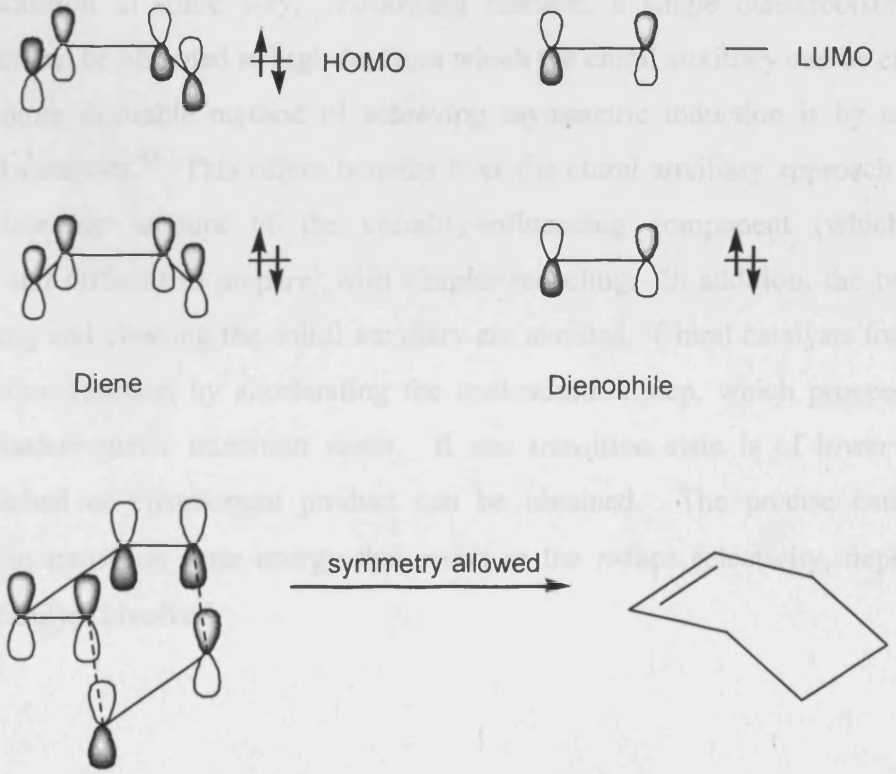


Fig. 4

relative stereochemistry of substituents of the diene and dienophile are retained in the product. So a dienophile with *trans* substituents will lead to a *trans* configuration in the product. Secondly, the *endo* addition rule states that when the diene and dienophile come together to give two diastereomeric adducts, the pathway that is favoured is the one in which the π-system of the activating group on the dienophile aligns over the "backside" of the diene (scheme 13). These secondary orbital interactions lead to the *endo* product being favoured.

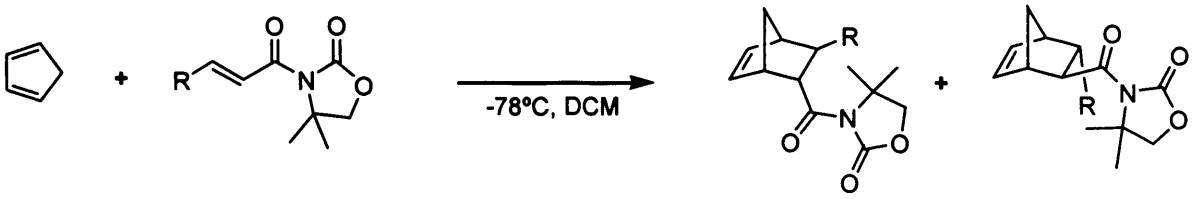
The Diels-Alder reaction is catalysed by the presences of Lewis acids, such as aluminium, tin (IV) and titanium (IV) chlorides and boranes. The Lewis acid coordinates by accepting non-bonding electrons from on the dienophile, such as a carbonyl or cyano group, resulting in two effects. Firstly, the energy of the dienophile LUMO is lowered, resulting in a smaller energy gap between the HOMO (diene) and the LUMO, which leads to a faster reaction. Secondly, the atomic orbital coefficient of, for example, a carbonyl carbon atom of the dienophile is increased, enhancing the secondary orbital interactions between the diene and dienophile. This improves the *endo*/*exo* selectivity of the reaction.

The control of absolute stereochemistry in the Diels-Alder reaction has attracted great interest in recent years due to the formation of up to 4 new chiral centres in one step.[40,41] One thoroughly researched method of achieving asymmetric induction in this step is through the use of chiral auxillaries.[42] Here, a chiral fragment, often an ester or amide, is incorporated into the dienophile and influences the stereochemical outcome of the cycloaddition in some way. Following reaction, a single diastereoisomer of the cycloadduct can be obtained in high de, from which the chiral auxiliary can be cleaved.

A more desirable method of achieving asymmetric induction is by using chiral Lewis acid catalysts.[43] This offers benefits over the chiral auxiliary approach of using a non-stoichiometric amount of the chirality-influencing component (which is often expensive and difficult to prepare) with simpler recycling. In addition, the two steps of incorporating and cleaving the chiral auxiliary are avoided. Chiral catalysts for the Diels-Alder reaction function by accelerating the cycloaddition step, which proceeds *via* two possible diastereomeric transition states. If one transition state is of lower energy an enantioenriched or enantiopure product can be obtained. The precise causes of the difference in transition state energy that result in the π-face selectivity, depend on the particular catalyst involved.

1.8.1 Asymmetric Diels-Alder cycloaddition catalysts featuring diol ligands

Numerous catalyst systems featuring chiral diolate ligands, with the aim of achieving asymmetric induction in the Diels-Alder reaction, have been reported. In all cases described, chiral diols were chosen as ligands due to their potential to form rigid cyclic dialkoxides upon coordination to Lewis acids. These lead to rigid conformations in transition states and hence can give good π-face selectivity. At the same time, the electron-withdrawing nature of the alkoxide ligands increases the Lewis acidity of the metal to which it is bound.

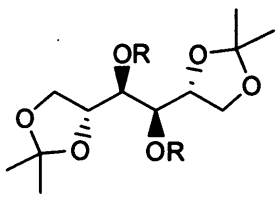


16 R = Me
17 R = H

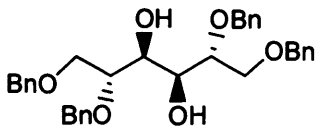
18a **18b**

Scheme 14

For example, Chapuis investigated the ability of various chelating chiral diol-derived ligands in combination with a range of Lewis acids to promote the asymmetric cycloaddition reaction of cyclopentadiene and 3-crotonoyl- (**16**) or 3-acryloyl- (**17**) 4,4-dimethyl-1,3-oxazolidin-2-one (scheme 14).[44] The dienophiles **16** and **17** were chosen due to their ability to chelate to the Lewis acid *via* the carbonyl oxygen atoms, restricting



19 R = H
20 R = $SiMe_3$



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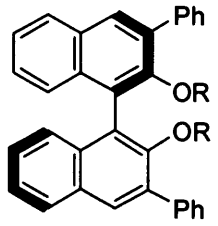
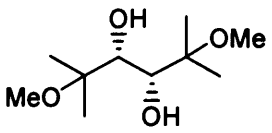


22 R = H
23 R = $SiMe_3$



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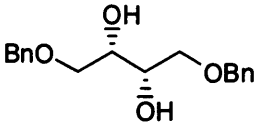

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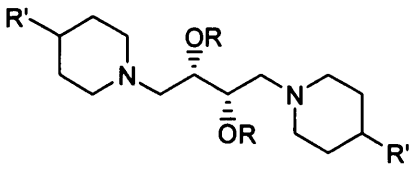


26 R = H, R' = H
27 R = $SiMe_3$, R' = H

Fig. 5

rotation about the C(O)-N bond. In addition, the methyl substituent of the ring helps to ensure the alkene adopts a *syn*-planar conformation relative to the chelated carbonyl groups. These factors help to form a rigid conformation in the transition state leading to good π-face selectivity. Thus, Lewis acids, including $EtAlCl_2$, Et_2AlCl and $TiCl_4$, were modified with chiral diols derived from D-mannitol (**19-21**), (*R*)-binaphthol (**22-23**) or L-tartaric acid (**24-27**) (Fig.5) and screened at stoichiometric levels, with one or two equivalents of Lewis acid relative to chiral diol (table 1).

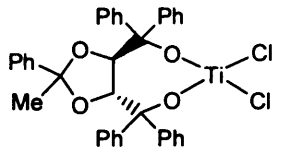
In the case of dienophile **16**, excellent π-face selectivity resulted with *endo* product **18a** being obtained with ee's ranging from 87 % to >98 %. Titanium catalysts were found to give a higher *endo/exo* selectivity ratio and asymmetric induction than their corresponding aluminium analogues. For dienophile **17**, lower selectivities were observed under the same conditions (17-36 % ee).

Dienophile	Ligand	Lewis Acid	Dienophile:Lewis Acid:Ligand	Yield (%)	*endo*:*exo* ratio	ee (%)
16	**19**	$EtAlCl_2$	1:2:1	89	75:25	94
16	**20**	$AlCl_3$	1:1:1	55	88:12	92
16	**20**	$TiCl_4$	1:1:1	86	93:7	96
16	**21**	Et_2AlCl	1:1:1	5	77:23	87
16	**21**	$EtAlCl_2$	1:2:1	73	73:27	92
16	**22**	Et_2AlCl	1:1:1	92	68:32	88
16	**22**	$EtAlCl_2$	1:2:1	92	76:24	95
16	**23**	$TiCl_4$	1:1:1	99	94:6	>98
16	**24**	$EtAlCl_2$	1:2:1	90	70:30	93
16	**25**	$EtAlCl_2$	1:2:1	71	73:27	91
16	**26**	$EtAlCl_2$	1:2:1	21	91:9	89
17	**27**	$EtAlCl_2$	1:2:1	29	77:23	36
17	**27**	$EtAlCl_2$	1:1:1	80	83:17	21
17	**27**	$EtAlCl_2$	1:0.5:0.25	96	81:19	17

Table 1. Diels-Alder reaction of cyclopentadiene and dienophiles **16** and **17**.

Narasaka was the first to report the use of chiral 1,4-diol ligands of general structure α, α, α', α'-tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL) in titanium-catalysed asymmetric Diels-Alder reactions.[45] Catalytic amounts of Ti (IV)-TADDOLates, such as **28**, were employed in the cycloaddition reaction between *N*-acrylyloxazolidinones and cyclopentadiene (scheme 15); some examples of the results obtained are summarised in table 2. In this system, the addition of 4Å molecular sieves gave the highest possible ee's. This was attributed to their dehydrating ability, since traces of water were found to

significantly decrease optical yields.[45] Solvent effects were also shown to be significant with aromatic solvents proving the most successful.



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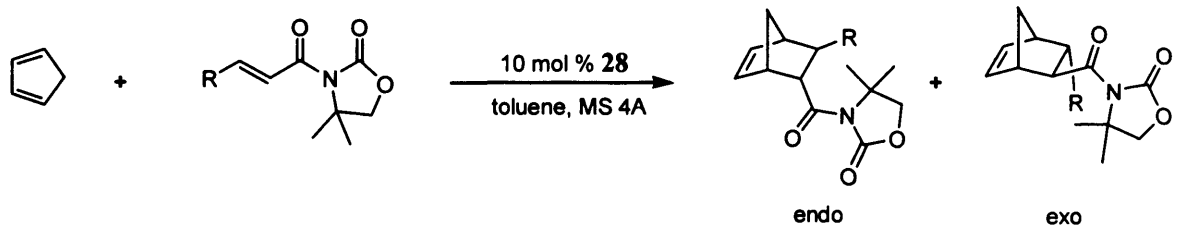
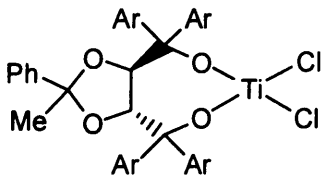


Scheme 15

R	Reaction Temp. °C	Yield (%)	*endo*:*exo* ratio	ee (%)
Me	0	87	92:8	91
Ph	rt	72	88:12	64
n-Pr	0	79	91:9	72
H	-40	93	96:4	64

Table 2. Diels-Alder reactions of cyclopentadiene and *N*-acrylyloxazolidinones with various subsitiuent R catalysed by 10 mol % **28**.

Corey varied the aryl and dioxolane-ring substituents of these TADDOL ligands, which resulted in the generation of the improved catalyst **29** (Fig. 6).[46] Replacement of the phenyl groups with 3,5-dimethylphenyl substituents, which are both bulkier and more π-basic, led to an improvement in enantioselectivities for the same reactions. By varying the aryl substituents further it was shown that there was a clear correlation between their π-basicity and enantioselectivity, as a result of stabilization of the transition state by π-electron rich substituents. In such Diels-Alder reactions, there was strong ^{1}H NMR



29 Ar = 3,5-dimethylphenyl

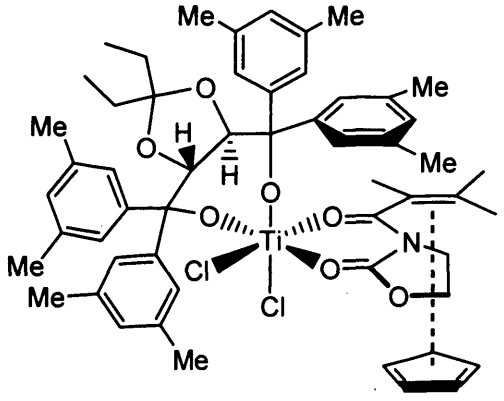
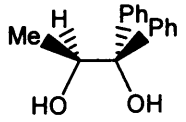


Fig. 6

spectroscopic and experimental evidence to suggest the catalytic process involves addition of the diene to an octahedral complex of the dienophile chelating to the Ti (IV)-TADDOLate (Fig. 6).[46]



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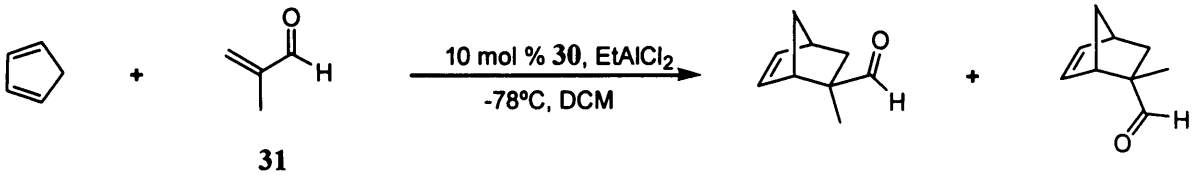


Scheme 16

Kagan reported investigations into asymmetric condensations of cyclopentadiene and more common dienophiles (such as methacrolein) using aluminium complexes combined with various chiral diol ligands.[47] When the catalysts were prepared *in situ* by addition of one equivalent of $EtAlCl_2$ to the diol at -78°C in DCM, high yields and *exo/endo* selectivities and moderate to good ee's were obtained following cycloaddition. The most successful catalyst was prepared from diol **30**, which gave an ee of up to 86 % in the Diels-Alder cycloaddition of cyclopentadiene with methacrolein (**31**) (scheme 16). The Lewis acid derived from **30** was shown to oligomerise over long periods of time or if allowed to warm, due to coordination of the second hydroxyl group (Fig. 7).[47] This resulted in loss of optical activity of the catalyst and loss of the reaction's enantioselectivity. The use of ligand **30** in the cycloaddition of cyclopentadiene with acrolein or methyl acrylate gave poorer *exo/endo* selectivity and enantioselectivity.[47] This

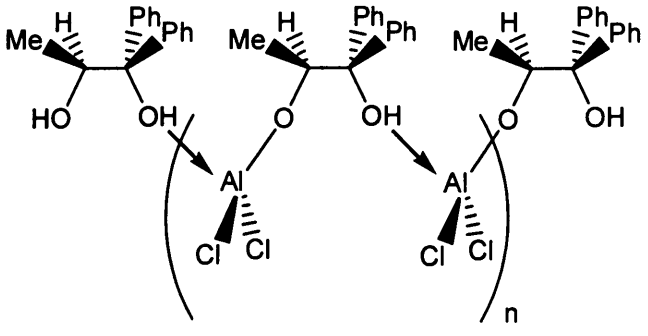
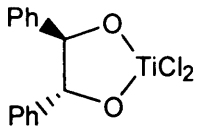


Fig. 7

trend is often observed for asymmetric Diels-Alder reaction catalysts

Oh used a similar chiral diol with C_2-symmetry as a precursor to titanium-based Lewis acid promoter **32** in the asymmetric Diels-Alder reactions of various combinations of dienes and carboxylic ester dienophiles (table 3).[48] Achieving high levels of asymmetric induction in the cycloadducts of these poorly reactive dienophiles is known to be more challenging.[43,47,49] Moderate to high ee's were observed, in some instances greater than 90 %, when stoichiometric quantities of the chirality-influencing component were used. Use of sub-stoichiometric amounts of **32** (0.25 equivalents) gave a 90 % yield, but just 16 % ee in the reaction between cyclopentadiene and dimethyl fumarate.



32

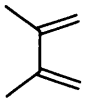
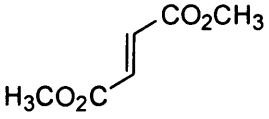
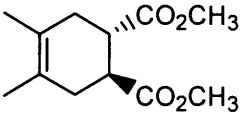
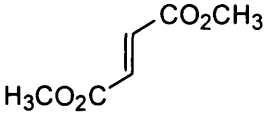
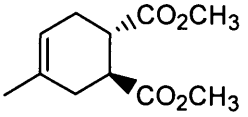
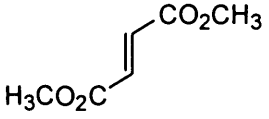
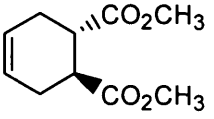
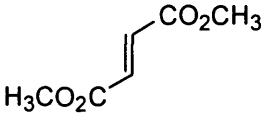
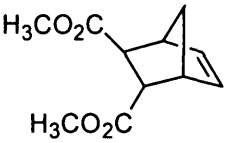
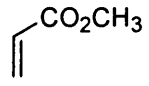
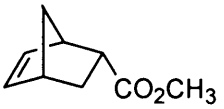
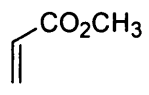
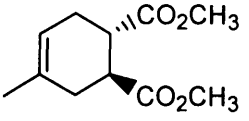
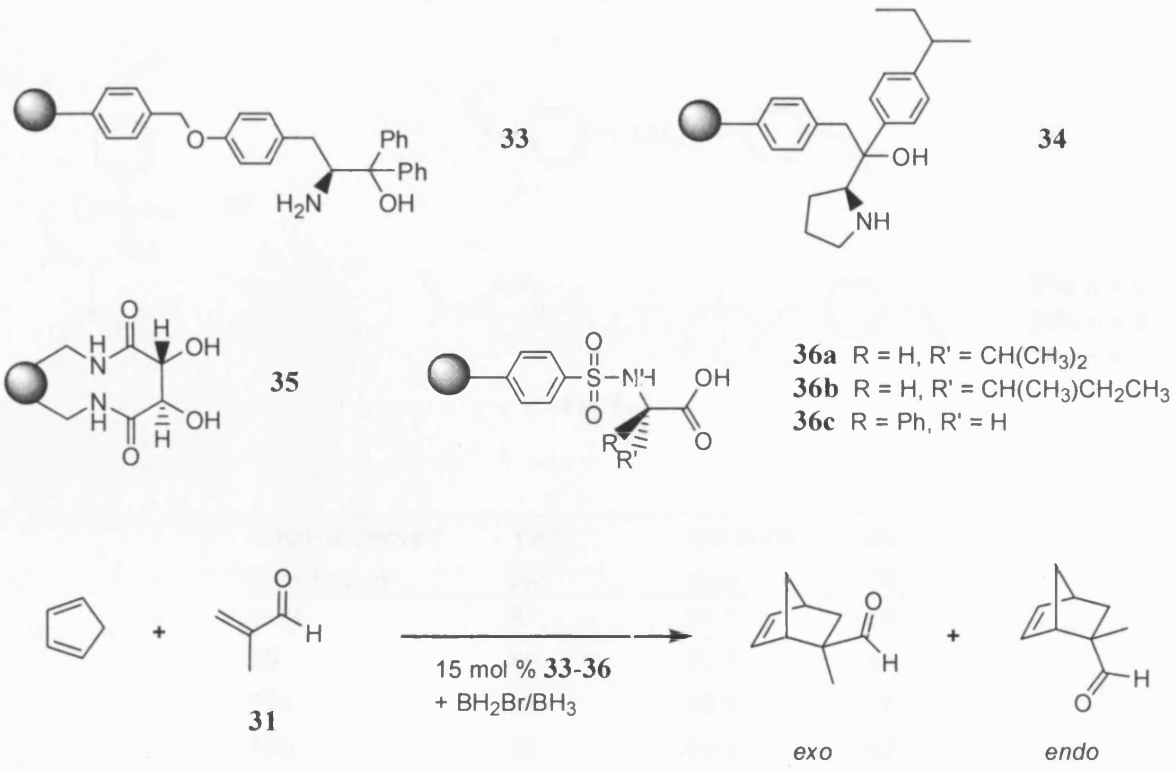
Diene	Dienophile	Major Product	Yield (%)	ee (%)
			79	92
			79	88
			79	60
			86	80
			85	36
			91	37

Table 3. Diels-Alder reactions promoted by 1 equivalent of **32**.

1.8.2 Polymer-supported Lewis acid catalysts for asymmetric Diels-Alder reactions

There have been several attempts to immobilize chiral Lewis acids on polymer supports for use as catalysts in asymmetric Diels-Alder reactions, with the hope of matching the high yields and ee's observed with certain homogenous analogues.



Scheme 17

Polymer	Borane	Solvent	Yield (%)	*exo*:*endo* ratio	ee(%)
33	BH_2Br	DCM	96	92:8	16
34	BH_2Br	DCM	98	96:4	25
35	BH_2Br	DCM	88	89:11	17
36a	BH_2Br	DCM	99	99:<1	44
36a	BH_3	DCM	95	99:<1	57
36a	BH_3	DCM/THF	89	99:<1	65
36a[a]	BH_3	DCM/THF	93	99:<1	65
36b	BH_3	DCM/THF	99	97:3	49
36c	BH_3	DCM/THF	99	96:4	49

Table 2. Diels-Alder reaction of cyclopentadiene and methacrolein using ligands **33-36**.

Itsuno reported the use of various polymer-supported boron-based Lewis acid catalysts in asymmetric Diels-Alder reactions.[50,51] PS-DVB resins featuring tethered chiral

amino alcohol (**33-34**), diol (**35**) and *N*-sulfonylamino (**36a-c**) moieties were prepared by copolymerisation and then functionalised with bromoborane or borane. The use of these catalysts in the cycloaddition of cyclopentadiene with methacrolein (scheme 17) gave mostly excellent yields, high *exo*/*endo* selectivity and low to moderate ee's (table 4). The most successful catalysts were **37a-c** featuring chiral oxazaborolidinones. Polymer **37a** was reused with no loss in activity or selectivity.[51]

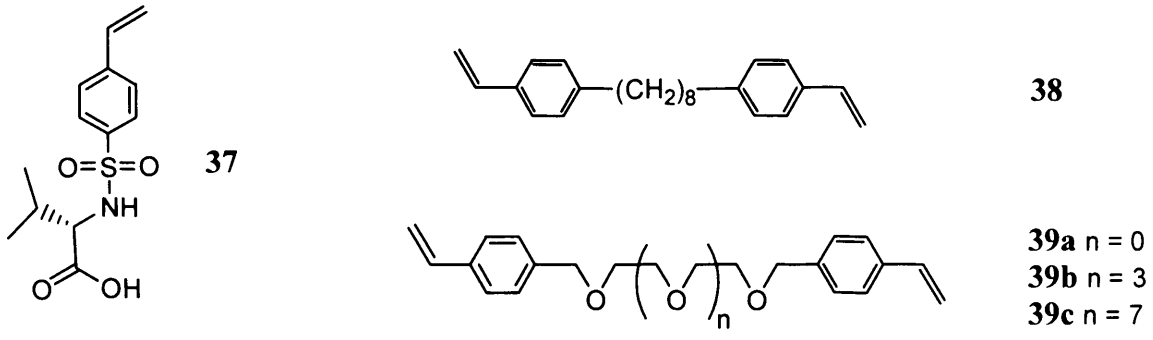


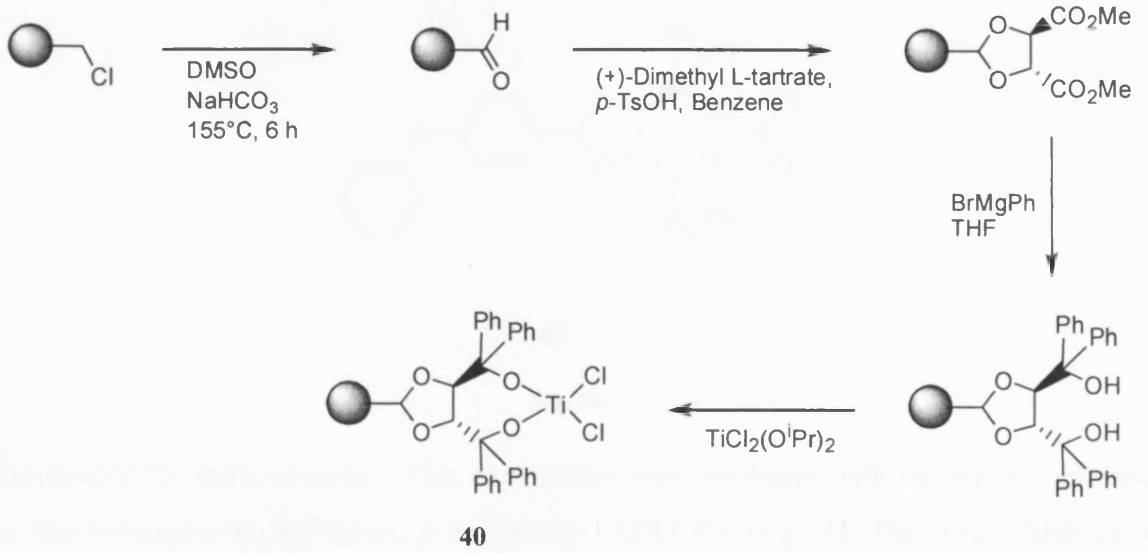
Fig. 8

Catalyst derived from **37** and	Yield (%)	*exo*:*endo* ratio	ee (%)
DVB	87	99:1	65
38	86	92:8	84
39a	85	95:5	77
39b	93	99:1	92
39c	88	96:4	95

Table 5. Diels-Alder reaction of cyclopentadiene and methacrolein using copolymers of **37**.

The study was extended by preparing oxazaborolidinone-functionalised PS resins, with more flexible cross-linkers than DVB, by copolymerising **37**, styrene and cross-linking agents **38** or **39a-c** (Fig. 8).[52] Higher ee's of up to 95 % were observed with the resins featuring these cross-linkers (table 5), which was attributed to the improved swelling abilities of these polymers.

The immobilization of TADDOL ligands, introduced in section **1.8.1**, has been reported and used in the titanium-catalysed Diels-Alder reaction of cyclopentadiene with 3-crotonoyl-1,3-oxazolidin-2-one **16**.[53] PS-DVB resin **40** was prepared in four steps from Merrifield resin (scheme 18). The loading of titanium onto the polymer beads by chelation to the 1,4-diol was monitored by ICP-AE analysis of polymer washings, after treatment with $TiCl_2(O^iPr)_2$ for 3 or 12 hours. The shorter reaction time proved sufficient for complete uptake of a sub-stoichiometric amount of metal. This was deemed to be adequate evidence that the titanium was heterogenised and that washing of the catalyst prior to use

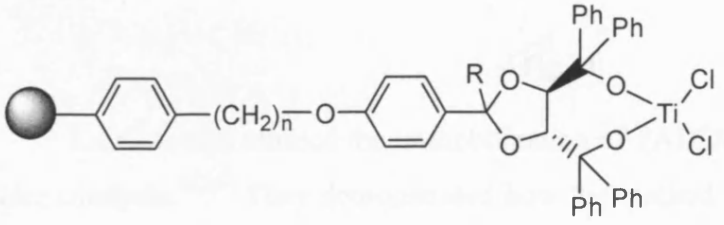


40

Scheme 18

was not necessary to avoid competing catalysis from achiral species in solution. This was supported by near identical results obtained when the supported catalyst was washed before use and when it wasn't.

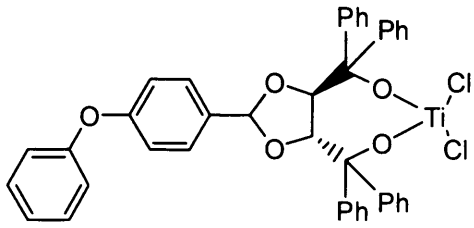
The reaction of **16** and cyclopentadiene in the presence of two equivalents of Lewis acid **40** relative to the dienophile, proceeded in quantitative yield with good *endo* selectivity (79-83 %) and moderate ee's (45-51 %). When a catalytic amount of **40** was used, the ee was seen to decrease to 24 %. Repeated recycling of the catalyst led to deterioration in the *endo*/*exo* selectivity and ee, attributed to leaching of titanium.



41a n = 1, R = H, Me, Ph
41b n = 6, R = H, Me, Ph
41c n = 9, R = H, Me, Ph

Fig. 8

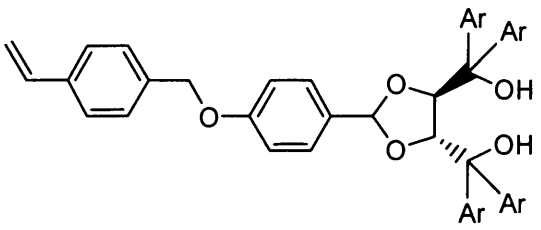
The same research group have also investigated the effect of inserting aliphatic spacer chains between the TADDOL unit and the polymer backbone.[54] When TADDOL-functionalised resins **41a-c** (Fig. 9) were used in the same reaction (namely **16** with cyclopentadiene), it was shown that a longer chain led to no improvement in the catalytic results obtained. They attributed this observation to the fact that there is a negative influence of the oxygen atom in the *para*-position of the phenyl substituent at position 2 of the dioxolanic ring on solvation, through coordination to the metal centre. It was proposed that this effect is not so important with the group close to the heterogenous backbone,



42

Fig. 10

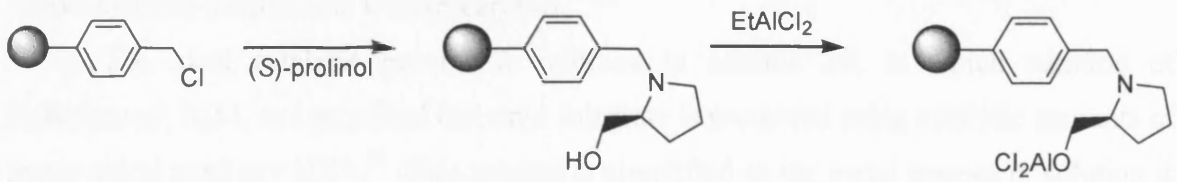
presumably for steric reasons. This explanation was consistent with the results obtained for the homogenous analogues, *p*-benzyloxy-TADDOLs (*e.g.* **42**, Fig. 10), which gave poorer yields and selectivities than the heterogenised catalyst **40** (scheme 18) with no spacer unit, and hence no oxygen atom in the tether.[54] It is important to note, however, that the synthesis of the spacer modified resins **41b** and **41c** from unfunctionalised polystyrene beads, was reported to be problematic. Yields and enantioselectivities were shown to be poorer than for the 'classical' homogenous TADDOL ligands described in section **1.8.1**.



43 Ar = 3,5-dimethylphenyl

Fig. 11

Luis has also studied the immobilization of TADDOL-type ligands for use in Diels-Alder catalysis.[55,56] They demonstrated how the method of immobilization can affect the activity, selectivity and stability of a supported species. Various polymer-supported Ti(IV)-TADDOL-functionalised polymers were prepared by grafting and/or copolymerisation methodologies, then the resulting catalysts compared with their homogenous counterparts in the Diels-Alder reaction between 3-crotonoyl-1,3-oxazolidin-2-one (**16**) and cyclopentadiene. An example of the differences in the results that were obtained from these catalysts was in the reactivity of a monolithic resin prepared by bulk copolymerisation of **43** (Fig. 11) with DVB (*i.e.* no styrene was included in the comonomer mix). The resulting resin, when functionalised with titanium, surprisingly gave the opposite sense of asymmetric induction to that observed for the same polymer-supported Ti(IV)-TADDOL species prepared by grafting.



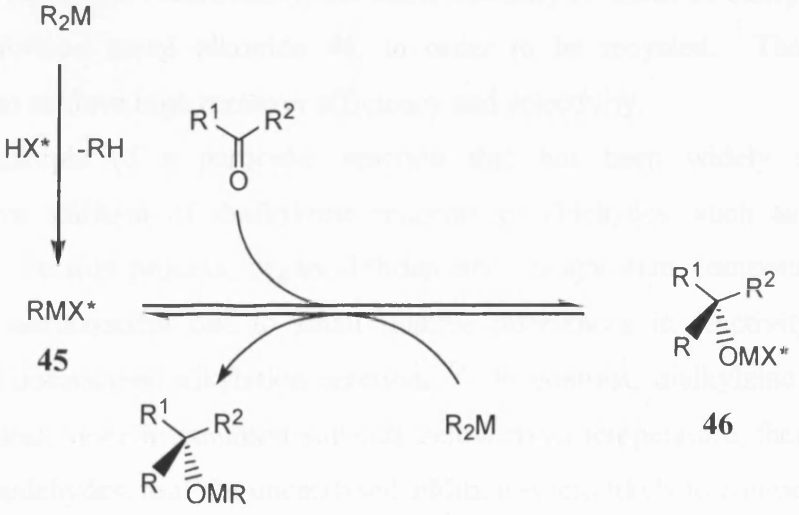
44

Scheme 19

The same research group also prepared other chiral aluminium and titanium polymer-supported Diels-Alder catalysts. A number of chiral amino alcohols were grafted onto polystyrene beads by reaction with chloromethylated polystyrene, and functionalised by reaction with $EtAlCl_2$ (*e.g.* scheme 19).[57] The resulting chiral Lewis acids were screened in the Diels-Alder reaction of methacrolein and cyclopentadiene. The homogenous analogues were also tested and it was found that the activity of the supported species was greater, something that was accounted for by site isolation, hindering formation of oligomers with the latter systems. Asymmetric induction was low for both supported and homogeneous catalysts with 14 % ee being the best result obtained, when (S)-prolinol was grafted onto the support and functionalised to give **44**.

1.9 Enantioselective addition of dialkylzinc reagents to aldehydes

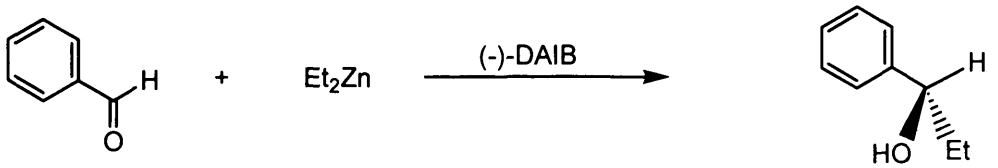
The use of chiral ligands to achieve enantioselective addition of organometallic reagents to carbonyl compounds, by both activating the metal species and controlling the



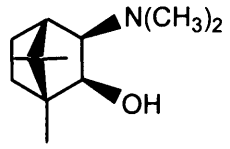
Scheme 20

steroechemical outcome, is well researched.[58,59]

The ideal catalytic process is outlined in scheme 20, in which addition of dialkylmetal, R_2M, to a prochiral carbonyl substrate is promoted using catalytic amounts of protic chiral auxiliary HX*.[59] This scheme is simplified as the metal species in solution is usually aggregated rather than a simple monomer. The reactivity of the R-M bond is enhanced by coordination of $[X^*]^-$, facilitating the alkyl transfer step from **45** to **46**, which proceeds *via* diastereomeric transition states, where the chirality of the anion X* ensures one face of the carbonyl group is susceptible to preferential attack. This allows the formation of enantio-enriched chiral secondary or tertiary alcohols, found in the structures of natural products and drug compounds, or used as important precursors to other functional groups.



(*S*)-**48**



47 (-)-DAIB

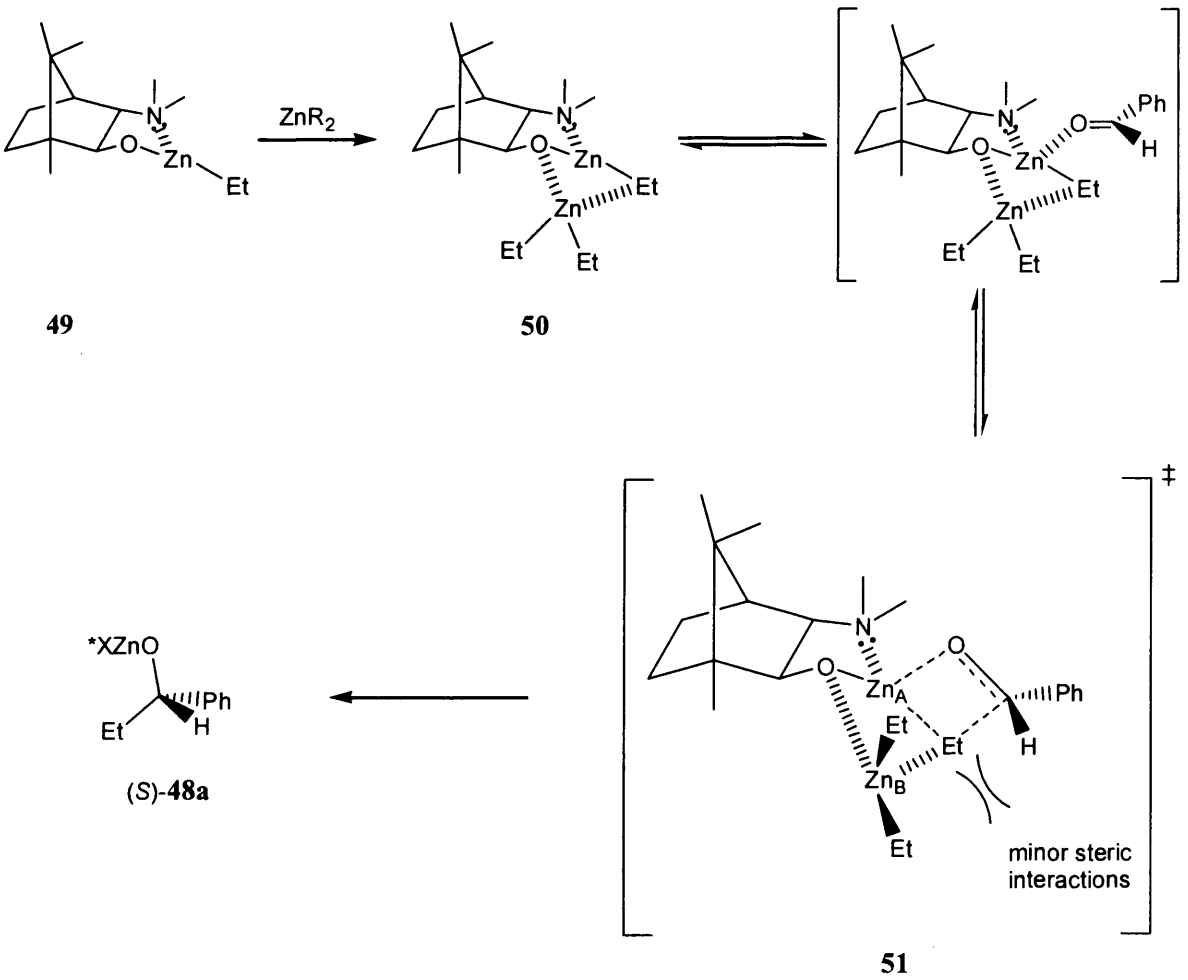
Scheme 21

For the catalytic process described in scheme 20 to be successful, there must be minimal non-competing achiral addition of the precursor organometallic compound R_2M directly to the carbonyl. Additionally, the chiral auxiliary X* must be easily detached from the initially formed metal alkoxide **46**, in order to be recycled. These factors are requirements to achieve high turnover efficiency and selectivity.

An example of a particular reaction that has been widely studied is the enantioselective addition of dialkylzinc reagents to aldehydes, such as benzaldehyde (scheme 21). In this process, organo-lithium and -magnesium compounds have been shown to be unsuccessful due to small relative differences in reactivity between the catalysed and uncatalysed alkylation reactions.[60] In contrast, dialkylzinc reagents were found to be ideal, since in common solvents below room temperature, there is almost no reaction with aldehydes, thus the uncatalysed addition is less likely to compete.

In 1984, Oguni and Omi observed a 49 % ee for the addition of diethylzinc to benzaldehyde when catalytic amounts of (S)-leucinol were present.[61] Since then a large number of chiral catalysts have been developed and high enantioselectivities achieved for this simple transformation, often used as a test reaction for new catalysts. The most widely studied class of ligands for this particular process are amino alcohols. Notably, (-)-3-*exo*-dimethylaminoisoborneol {(-)-DAIB, **47**} was the first ligand to give high ee's in this reaction. For example, the presence of 2 mol % of (-)-DAIB catalysed the addition of diethylzinc to benzaldehyde in toluene at 0°C, to give a 97 % yield of (*S*)-1-phenylpropan-1-ol (**48**) with 98 % ee (scheme 21).[62]

A summary of the mechanism for this reaction, with transition states accounting for the sense of observed selectivity, is given in scheme 22.[58] The protic amino alcohol reacts with diethylzinc to form alkoxide **49**, which combines with another equivalent of diethylzinc to form bridged dimer **50**. The aldehyde substrate then coordinates to the more Lewis acidic, DAIB-chelated, Zn_A, activating the carbonyl carbon atom towards nucleophillic attack. The bridging alkyl group then reacts *via* diastereomeric transition state **51**, in which the non-bonded repulsion between the Ph or H carbonyl substituents and



49 50 51

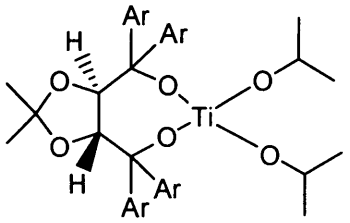
Scheme 22

the terminal R groups of Zn_B lead to preferential formation of the (*S*) enantiomer of alkoxide product **48a**.

The initially formed Zn alkoxide **49** acts both as a Lewis acid to activate the carbonyl group, and as a Lewis base to increase the nucleophillicity of R-Zn bond. The chiral environment of the ligand controls the stereoselectivity, with the sense of asymmetric induction determined by the configuration of the Zn_A and O-bridgehead atoms in the transition state, which in turn is controlled by the substituents at the α and β positions of the chelating amino alcohol.

1.9.1 Diol ligands in dialkylzinc additions to aldehydes

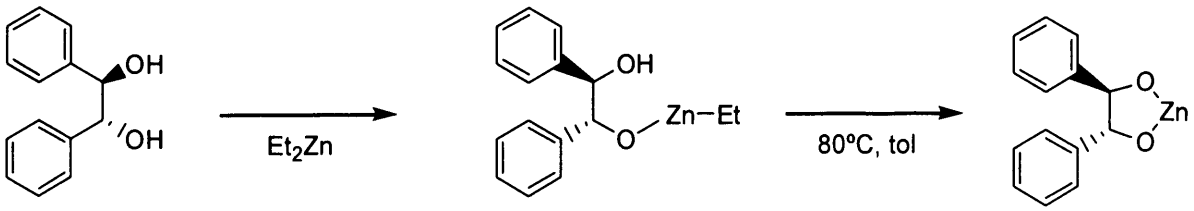
Whilst the majority of ligands reported for the catalytic asymmetric dialkylzinc addition to aldehydes are based on amino alcohols, chiral diols have also been applied. Indeed, a range of TADDOL ligands have been used in the titanium-catalysed asymmetric dialkylzinc addition to aldehydes. For example, 10-20 mol % of TADDOL complexes **51**, modified by addition of excess $Ti(O^iPr)_4$, led to high enantioselectivities (82-99 %) in diethylzinc additions to aromatic and aliphatic aldehydes.[63] Complex **51b** with bulkier 2-naphthyl substituents gave better results than those obtained using **51a**, especially in the alkylation of aliphatic, olefinic and acetylenic aldehydes.



51a Ar = Ph
51b Ar = 2-Naphthyl

Fig. 12

A range of further TADDOL complexes were synthesised with different dioxolane ring and aryl substituents.[64] Changing these groups had little effect on the



52 **53** **54**

Scheme 23

enantioselectivity of diethylzinc addition to benzaldehyde, which were consistently over 90 % when 20 mol % of titanium catalyst was used. However, the enantioselectivity was seen to decrease when lower loadings of catalyst were used, for example from 98 % with 20 mol % of catalyst to 68 % with 2 mol %.

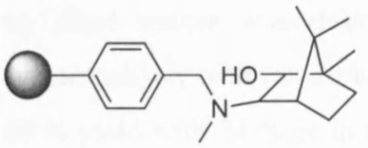
Joshi reported the use of a zinc-based catalyst bearing a C_2-symmetric dialkoxide ligand in the enantioselective addition of diethylzinc to a range of aryl aldehydes.[65] Complex **54** was prepared by heating diol **52** with diethylzinc to 80°C in toluene for 30 minutes (scheme 23). Heating was necessary to form the dialkoxide due to the slow reactivity of the monoalkoxide **53**, which is readily formed on reaction with alcohols. The use of 10 mol % of **54** in the reaction of diethylzinc with aryl aldehydes gave high yields of the alcohol products and good ee's (table 6). Reactions involving *ortho*-substituted aryl aldehydes were less successful, with yields of less than 50 % after 48 hours.

Aldehyde	Time (h)	Yield (%)	ee (%)
benzaldehyde	18	98	89
p-fluorobenzaldehyde	9	95	70
p-methylbenzaldehyde	14	98	82
p-chlorobenzaldehyde	24	85	69
β-naphthaldehyde	20	94	84

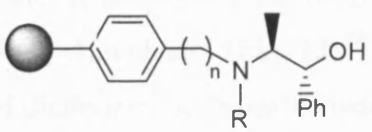
Table 6. Et_2Zn additions to various aldehydes catalysed by 10 mol % **54**.

1.9.2 Polymer-supported catalysts for the asymmetric addition of dialkylzinc reagents to aldehydes

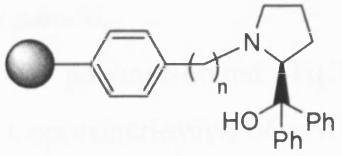
There has been great interest in the development of polymer-supported chiral diols and amino alcohols for use in the enantioselective addition of dialkylzinc reagents to aldehydes. Itsuno prepared various PS-DVB-supported β-amino alcohols, the N-O component bound to the resin *via* the amine group, including **55** and **56** (Fig. 13).[66] Resin



55



56 n = 1, R = Me
57 n = 1, R = Et
58 n = 1, R = ^{n}Pr
59 n = 1, R = ^{n}Bu
60 n = 6, R = ^{n}Bu



61 n = 1
62 n = 6

Figure 13

55 catalysed the addition of diethylzinc to benzaldehyde to give (*S*)-**48** in 91 % yield with 92 % ee. PS-DVB-supported (1*R*, 2*S*)-(–)-ephedrine (**56**) gave a 96 % yield and 80 % ee for the same reaction. Notably, catalyst **56** was reused once with no loss of activity or selectivity.

Soai also investigated the use of PS-DVB-bound *N*-alkylnorephedrines **56-59** (Fig. 13) in the addition of diethylzinc to various aldehydes.[67,68] In the alkylation of benzaldehyde, an increase in the size of *N*-alkyl substituent from methyl to butyl led to a decrease in the reactivity of the catalyst with poorer yields and ee's being determined (table 7, entries 1-4). The trends associated with the alkylation of aliphatic aldehydes were less clear, although catalyst **57** that bears an *N*-ethyl substituent, gave the best results (table 7, entries 5-8).

Entry	Catalyst	Aldehyde	Yield (%)	ee (%)
1	**56**	benzaldehyde	83	89
2	**57**	benzaldehyde	72	41
3	**58**	benzaldehyde	70	29
4	**59**	benzaldehyde	64	17
5	**56**	octanal	63	48
6	**57**	octanal	88	80
7	**58**	octanal	65	50
8	**59**	octanal	65	51

Table 7. Et_2Zn addition to aldehydes using catalysts **56-59**

The same research group extended the study and synthesised N-butylnorephedrine separated from a polystyrene resin by a six-carbon methylene spacer (**60**, Fig. 13).[69] This led to an improvement in the catalytic performance. For example, spacer-modified resin **60** catalysed the addition of diethylzinc to benzaldehyde in 80 % yield with 71 % ee compared to the 65 % yield with 51 % ee determined for the non-spacer-modified catalyst **59**. A clearer example of the improvement in reactivity that resulted from incorporation of an alkyl spacer was demonstrated in the reactivity of PS-DVB resins **61** and **62** functionalised with (*S*)-diphenyl(pyrrolidin-2-yl)methanol (Fig. 13).[69] Catalyst **61** gave a 68 % yield with 24 % ee in the addition of diethylzinc to benzaldehyde. Resin **62** with the amino alcohol separated from the polymer by a six-carbon chain gave a 91 % yield and 61 % ee in the same reaction.

The use of polymer-bound Ti(IV)-TADDOLate complexes has also been investigated.[70,71] Copolymerisation of TADDOL-functionalised cross-linkers **63-66** (Fig.

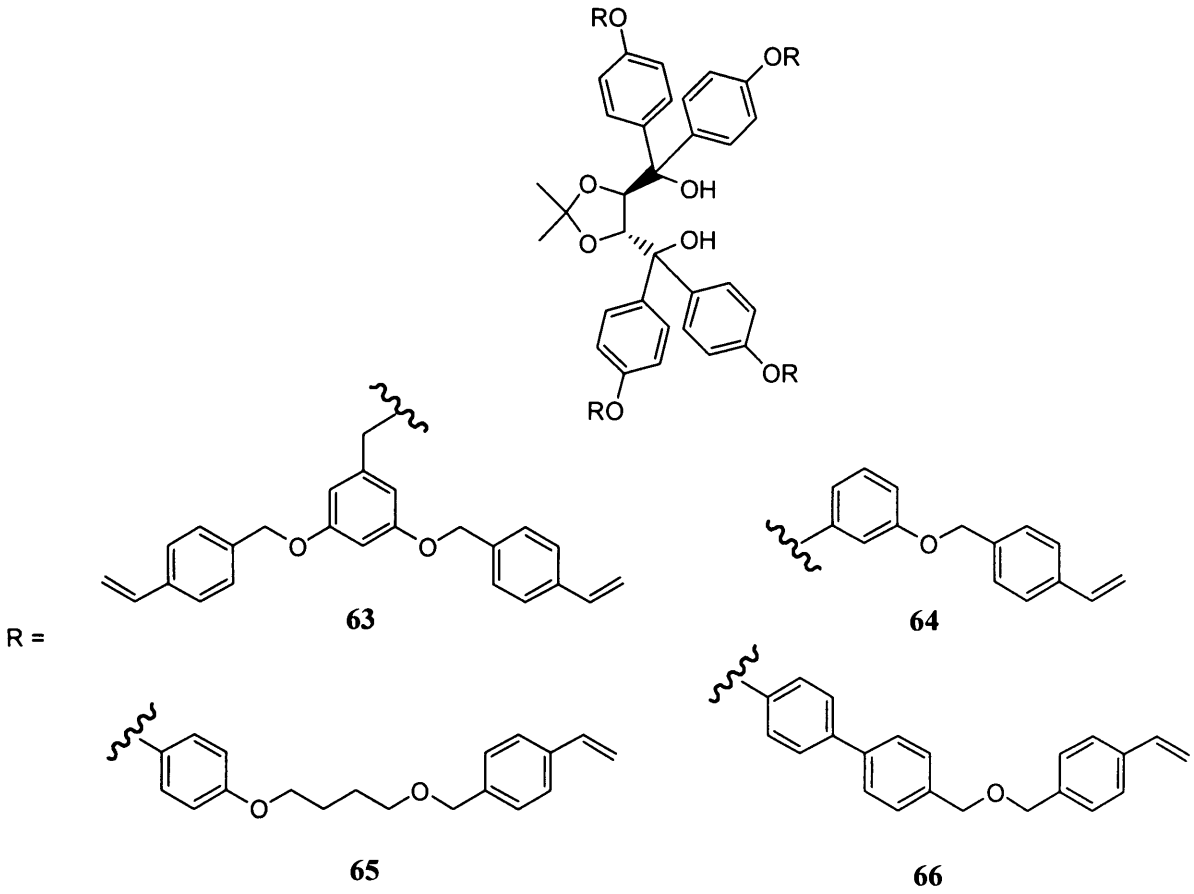


Fig. 14

14) followed by treatment with $Ti(O^iPr)_4$ gave the supported catalyst. The polymer prepared from cross-linker **63** gave the best results with a 96 % ee in the addition of diethylzinc to benzaldehyde. As the size of the cross-linker chain length was increased, the catalyst performance was seen to drop, presumably due to increased site-site interactions and therefore more interference from the oxygen donor atoms of the cross-linker. It is noteworthy that the catalyst prepared from **63** was reused 20 times with only a slight decrease in activity.

Hodge has carried out in-depth studies into the use of polymer-supported ephedrine **56** and camphor derivative **55** in the enantioselective addition of diethyl zinc to benzaldehyde.[72] PS-DVB supports with various morphologies were prepared. Resins with various degrees of cross-linking and various catalyst loadings were synthesised with the aim of investigating how the choice of support affected the selectivity obtained. The results showed that the most important factor in obtaining a successful catalyst, in terms of the nature of the support, was that there was good interaction between the polymer matrix and solvents, as increased swelling leads to easy access of reactants to catalyst sites. Thus, the best catalysts were lightly cross-linked (1 % DVB) and, since the ephedrine and camphor units caused decreased swelling of the resin, had a loading of less than 1 mmol g^{-1}

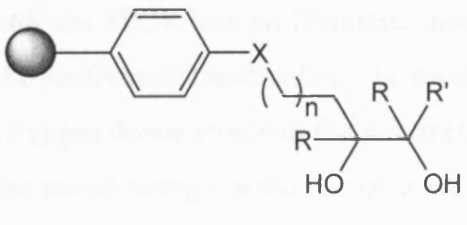
of the chiral component. Site-site interactions were shown to be of little importance for this system. Solvent effects were however shown to be important, with better results obtained in toluene than hexane, due to the poor swelling of PS-DVB resins in the latter solvent. Optimum ee's of 81 % and 97 % were obtained with the (*R*)-ephedrine and (*S*)-camphor-derived functionalised polymers, respectively.

The use of these catalysts in a continuous flow reactor was also investigated and found to be successful.[73] A mixture of diethylzinc and benzaldehyde was passed through a column of (*R*)-ephedrine-functionalised beads (**56**, Fig. 13). Using this method the addition product was obtained with an improved ee of 98 % (compared to 81 % for the non-flow system). The improvement was attributed to an increase in the effective concentration of the catalyst on the column and the continuous removal of the zinc alkoxide product, which is a mild, unselective competing catalyst for this reaction.

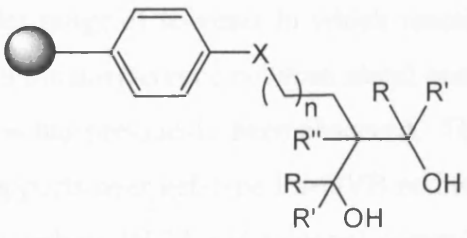
1.10 Aims of this work

The aim when incorporating a metal/ligand catalytic system onto a solid support is to have the benefits of a heterogenous catalyst whilst retaining the "tuned" properties of the homogenous catalyst. Ideally the environment surrounding the coordination sphere of the metal centre should be as close to that of the previously studied solution phase analogue as possible. The uniform, well-defined reactive centres of the homogenous catalyst, which generally show high activity and high, reproducible selectivity, would then be preserved.

There have been attempts to immobilize catalysts for all manner of applications on solid supports but, with some exceptions, the supported species have shown poorer performance (*e.g.* lower activity, yields or selectivity) than the corresponding homogenous system.[8-14] These differences have been attributed to interference at the metal centre



67



68

Fig. 15

caused by the solid support. Possible factors that have caused these problems include hindered diffusion of substrates through the polymer matrix to reach the catalyst and steric or electronic interference of reactive centres from the insoluble polymer backbone.

One method of achieving improved performance of supported catalysts is by the incorporation of spacer groups between the solid support and the tethered catalyst, such as alkyl chains, which both distance the metal's coordination sphere from the steric effects of the insoluble polymer backbone and create a more solution-like environment by increasing the mobility of the supported species. A good example of this is the addition of dialkylzinc to benzaldehyde promoted by chiral catalyst **62** above.[69]

The main aim of the work presented in this thesis is to synthesise a series of spacer-modified polystyrene-supported diols, with general structures **67** and **68** (Fig. 15), for potential study as ligands in a number of catalytic reactions including titanium and aluminium Lewis acid catalysts, reducing agents and olefin metathesis. There is also scope for the introduction of chirality for asymmetric induction. The combination of strong metal-oxygen bonds, which would form following deprotonation of **67** and **68**, and the chelate effect, should help to prevent leaching of the metal from the support. The strategy of using alkyl chain spacers of this type has not been extensively investigated, but has on occasion, been shown to improve the performance of supported species.[69,75-78] The pendant alkyl spacer group will be connected to the polymer *via* an ether or carbon-carbon bond due the relatively high stability, low reactivity and inert nature these afford.

Gel-type PS-DVB copolymer beads, with low cross-linking were chosen for use as the support. These resins have good swelling properties in a range of solvents and are convenient to manipulate and functionalise, in addition to being readily commercially available. It is also a relatively inert support material, with a purely hydrocarbon structure. As described earlier, a number of supports with superior all-round swelling abilities are available, such as polystyrene-PEG resins (TentaGel™, ArgoGel™ and JandaJel™). Although it is likely that the use of these supports would make the synthesis of resins **67** and **68** *via* SPOS less problematic, due to the wider range of solvents in which reactions can be performed, these will not be used due to possible interference between metal centres and oxygen donor atoms in the polymer structure, as has previously been observed. There is also no advantage in the use of some of these supports over gel-type PS-DVB resins, in terms of their swelling abilities in some solvents (such as DCM and toluene) commonly used in catalysis.[23]

The synthetic routes for the preparation of functional materials **67** and **68** will proceed *via* post-polymerisation modification of beads, rather than copolymerisation of

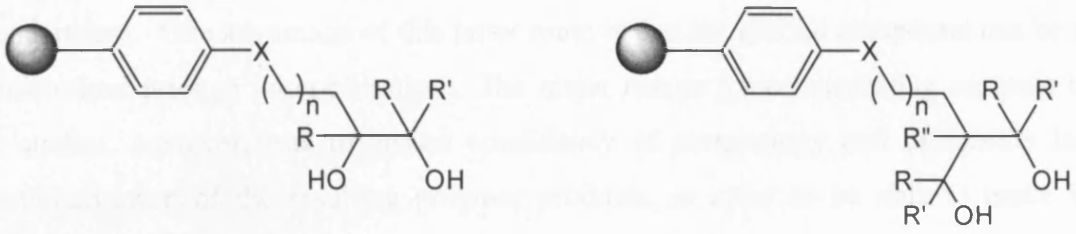
functionalised monomers. This approach was chosen for two reasons: Firstly, it was desired to follow synthetic routes that can be easily performed in a laboratory using standard equipment and techniques. More importantly, in order to assess the effect of the alkyl spacer on the activity of the supported species, it is necessary that the morphology of the polymer matrix remains constant. It is anticipated that the introduction of spacer-modified styrene-functionalised monomers at the polymerisation stage could lead to resins with significantly different morphologies. However, although there are likely to be small effects on the physical properties of the functional resins **67** and **68** following the introduction of the additional side chains, these are envisaged to be minimal compared to those resulting from co-polymerisation of suitable functionalised comonomers.

Chapter 2

Synthesis of spacer-modified diol-functionalised PS-DVB resins

2.1 Introduction

The synthesis of diol-functionalised polymers **67** and **68** (Fig. 16), incorporating alkyl spacers of varying length n, for use as supports for Lewis acid catalysts was desired. The aim was to probe the effect of the spacer on the reactivity of the tethered species, with the anticipation that it would be improved due to factors such as increased homogeneity, mobility and less steric interference from the insoluble polymer matrix. The use of simple

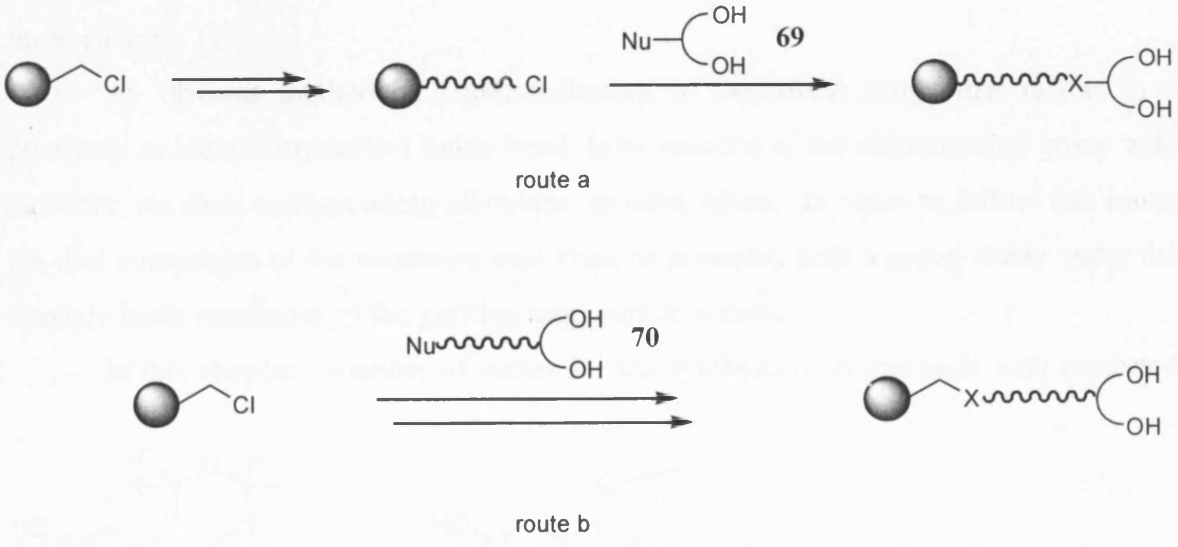


67 **68**

Fig. 16

diol-functionalised polymers as supports for catalysts has only rarely been investigated, but appears ideally suited for such an investigation due to the potentially high stability of supported metal complexes arising from the strong metal-oxygen bonds and chelate effect. This should result in minimal leaching of the metal species form the support.

For reasons outlined in section **1.10**, the strategy chosen for the synthesis of these functionalised polymers was by modification of previously prepared lightly DVB-cross-



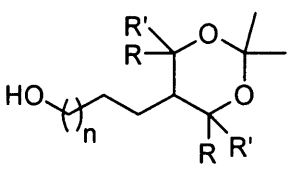
Scheme 24

linked gel-type chloromethylated polystyrene beads. Using this strategy, there are two general routes to the desired functionalised resins, which are broadly outlined in scheme 24. The first (route a) requires several steps of "solid-phase" modification of the polymer, by initially introducing the spacer unit and then grafting on a diol-functionalised compound (**69**). The main advantages of this route are the benefits of SPOS, *i.e.* simple reaction work-up and product purification at each step.

The second route (b) involves a minimal number of modification steps of the polymer resin, *i.e.* direct grafting of a suitably ω-functionalised, spacer-modified diol (**70**) is undertaken. One advantage of this latter route is that the grafted compound can be fully characterised prior to immobilisation. The major reason for concentrating on route b for our studies, however, was to ensure consistency of morphology and uniformity in the functionalisation of the resulting polymer products, in order to be able to make valid comparisons in their subsequent screening as supports for catalysts. Route a, in contrast, may lead to irregularities in the polymer products arising from, for example, incomplete reactions or occurrence of unwanted side-reactions at each modification step. In addition, there is the possibility that beads will suffer from "wear and tear" (something that can dramatically affect their swelling behaviour)[21] due to repeated reactions and washing sequences. These differences and uncertainties could make comparisons between spacer-modified resins and non-spacer-modified resins invalid, or at best complicated, if their respective syntheses differ. By following route b it can be ensured, as much as possible, that the only significant difference between resins is in the structure of the grafted groups and hence conclusions on the effect of these differences on catalysis can be rationalised more clearly.

An obvious method of functionalisation of Merrifield resins that results in a relatively stable and unreactive linker bond, is by reaction of the chloromethyl group with alcohols, *via* their corresponding alkoxides, to form ethers. In order to follow this route, the diol component of the necessary triol must be protected with a group stable under the strongly basic conditions of the grafting step, such as a ketal.

In this chapter a number of routes for the synthesis of compounds with protected



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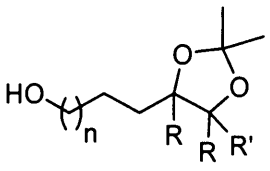


72

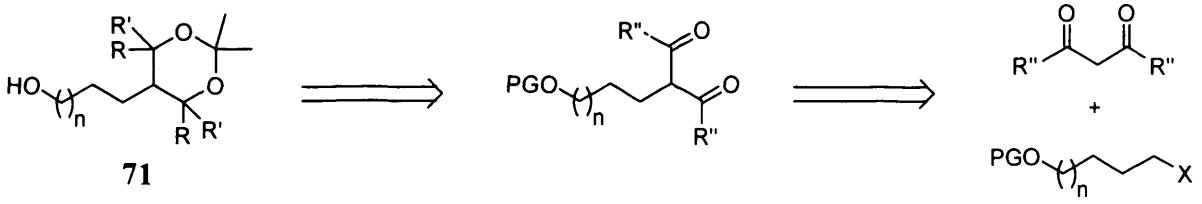
R, R' = H, Me, Ph, *etc.*

Fig. 17

1,3-diol (**71**) or 1,2-diol (**72**) (Fig. 17) units suitable for grafting to Merrifield resin are explored. The strategies used were chosen, for the most part, for their synthetic versatility in terms of being able to vary the length of spacer and the substituents α to the hydroxyl groups of the diol moiety. The reactivity of these compounds with Merrifield resin, in order to give the desired functionalised polymers, is also discussed.

2.2 Synthesis of ω-hydroxy-functionalised 1,3-diols

Retrosynthetic analysis of symmetrical ω-hydroxy-functionalised 1,3-diols **71** gives a possible route for the introduction of an alkyl spacer by alkylation of 1,3-dicarbonyl compounds (scheme 25). Alkylation performed so as to introduce a spacer group functionalised with a protected alcohol, followed by reduction of the carbonyl groups with hydride reducing agents, or alkylation with organometallic reagents would give ω-hydroxy-functionalised 1,3-diols suitable for grafting onto Merrifield resin.

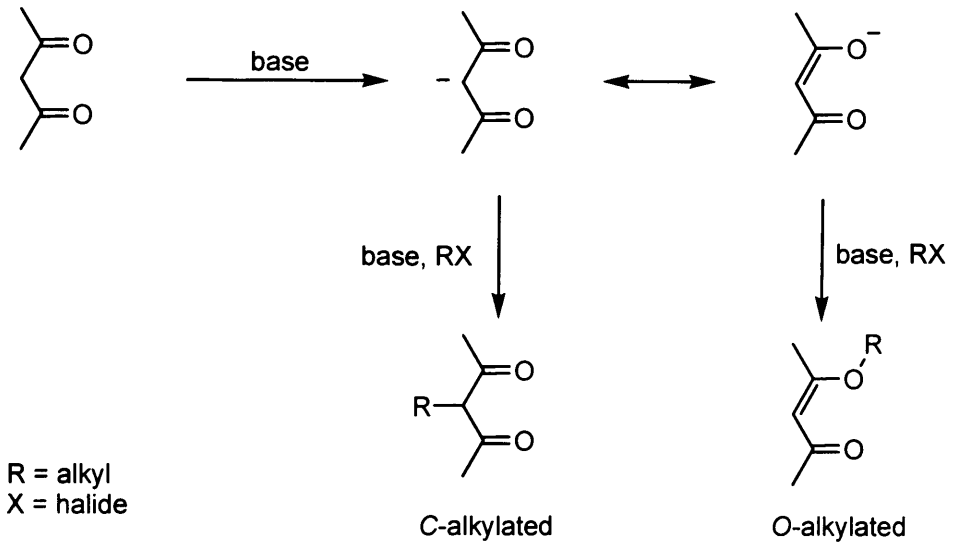


R" = OEt, Me; R, R' = H, Me, Ph, X = Cl, Br,
PG = protecting group

Scheme 25

2.2.1 Alkylation of 1,3-dicarbonyl compounds

To achieve this overall objective, an alkylation strategy is required in order to prepare the necessary alcohol-functionalised diketone. One method would involve deprotonation of an acidic α-hydrogen atom of a dicarbonyl group, followed by nucleophillic attack of the resulting carbanion on an aliphatic halide. In this way, a spacer with a remote hydroxyl functionality could be incorporated. However, the mono-alkylation of 1,3-dicarbonyl compounds selectively at the α-carbon position can be problematic due to the tautomeric keto-enol equilibrium that exists.[79] As a result, there is competition for *C*-alkylation and *O*-alkylation, the latter arising from reaction of the



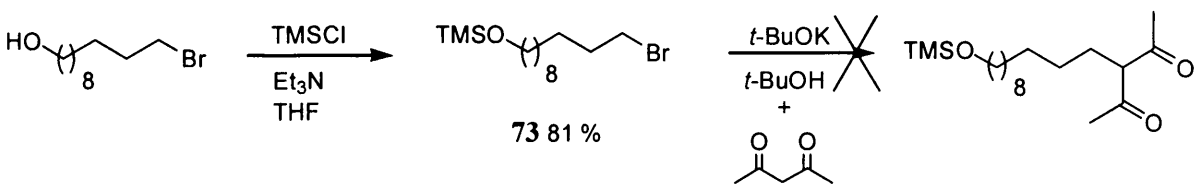
Scheme 26

enolate resonance form of the anion (scheme 26). Indeed, for 1,3-dicarbonyl compounds with a relatively high concentration of the enol tautomer, such as 1,3-diketones, the latter process is often favoured due to the higher electronegativity of the ambident oxygen atoms of the anion.[79]

However, under certain reaction conditions, selective *C*-alkylation can be achieved preferentially. For example, 1,3-dicarbonyl compounds can be mono-*C*-alkylated in high yield by simple alkyl iodides, such as iodomethane, in the presence of tetra-alkyl ammonium fluorides.[80] Nevertheless, under these conditions, longer chain or bulkier iodides do not give a high yield of the desired *C*-alkylated product.

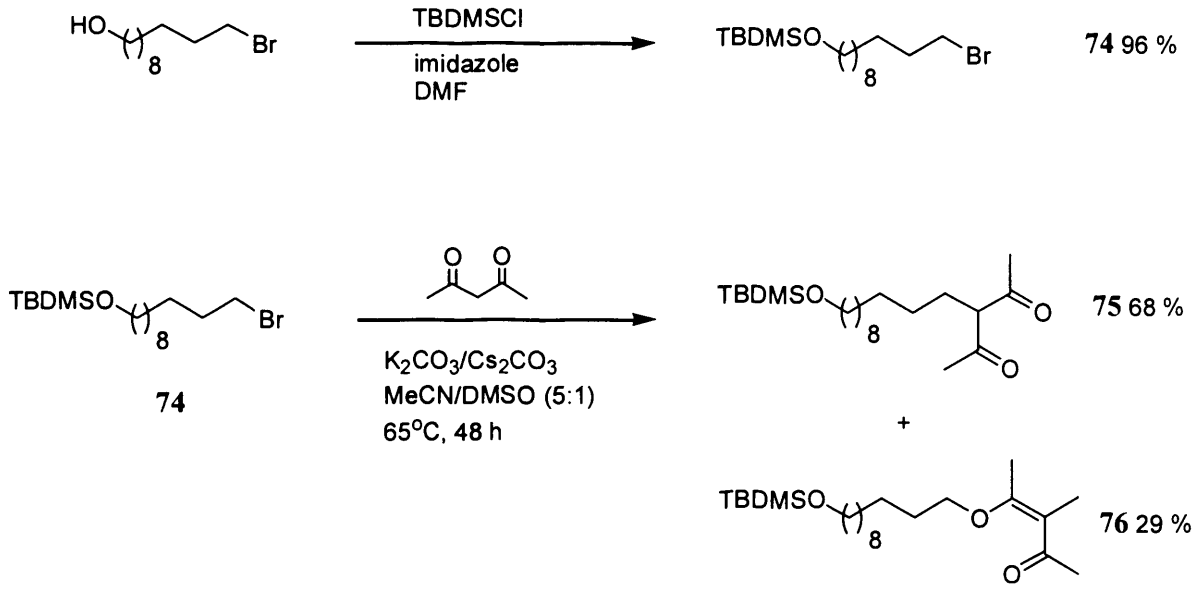
Another study highlighted how the choice of solvent can greatly affect the ratio of *C*- to *O*-alkylation. The mono *C*-alkylation of pentane-2,4-dione with ethyl bromoacetate was optimised by varying the reaction conditions and base used.[81] The yield improved from 40 % to 82 % on changing the reaction solvent from acetone to DCM, and by employing K_2CO_3 as base. For a longer chain ω-bromo ester, *C*-alkylation was most successful when the reaction was performed in a mixture of MeCN/DMSO, with a 72 % yield of the *C*-alkylated product being obtained. Reaction rates and yields were improved when a catalytic amount of Cs_2CO_3 was added, due to the improved solubility of Cs^+ over K^+ cations in the solvents used. This results in a phase transfer effect with the Cs^+ cations drawing the CO_3^{-2} base into solution.

Thus, the conditions described above for the optimal alkylation of diketones with



Scheme 27

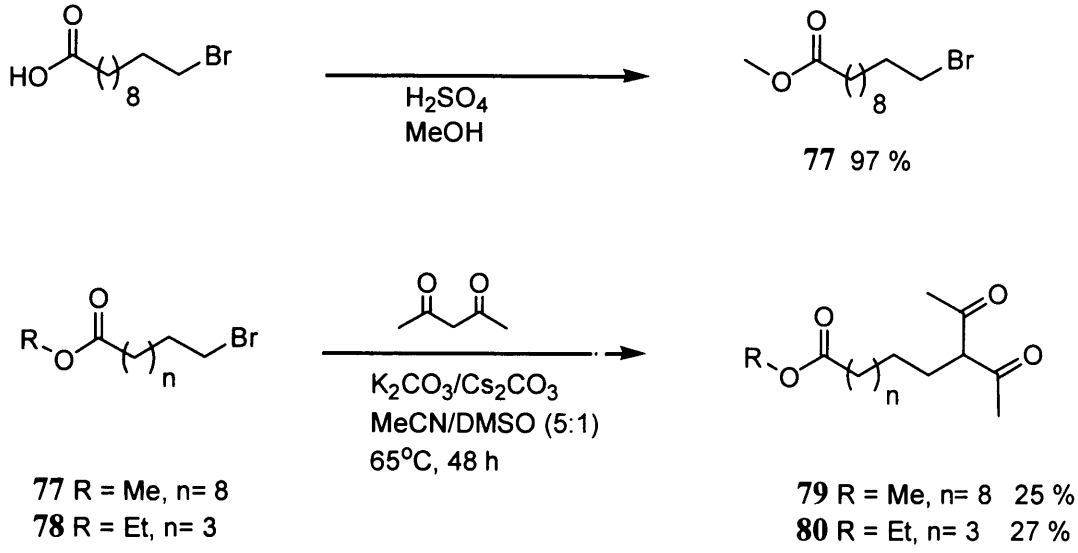
long chain alkyl halides were applied in a number of alkylation reactions of 1,3-dicarbonyl compounds with protected ω-hydroxy alkyl bromides. It was necessary to protect the alcohol functionality with a base-stable protecting group such as an ether, silyl ether or ester. The reaction of trimethylsilyl-protected alcohol **73** with pentane-2,4-dione using potassium t-butoxide base had already been attempted with no *C*-alkylated product being obtained, and cleavage of the TMS protecting group occurring during the aqueous reaction work-up (scheme 27).



Scheme 28

In order to try and overcome this problem, it was believed that the bulkier *tert*-butyldimethylsilyl (TBDMS) ether protecting group, which is more stable to acid hydrolysis, would be more suitable, particularly with regard to its stability in the subsequent reduction step of the alkylated dicarbonyl product. Hence, compound **74** was prepared by treatment of 11-bromoundecanol with *tert*-butyldimethylsilyl chloride in the presence of imidazole to give silyl ether **74** in 96 % yield (scheme 28). Reaction of **74** with pentane-2,4-dione in MeCN/DMSO using one equivalent of K_2CO_3 base, and a catalytic amount of Cs_2CO_3, gave a crude product that was shown by ^1H NMR spectroscopy and GC-MS analysis to contain the *C*-alkylated product **75** and *O*-alkylated product **76** in a ratio 68 % to 29 %, respectively. This is consistent with the alkylation ratio described previously for long chain alkyl bromides under these conditions.[81] Disappointingly, attempts to separate **75** and **76** by high-vacuum distillation failed with the products decomposing at elevated temperatures.

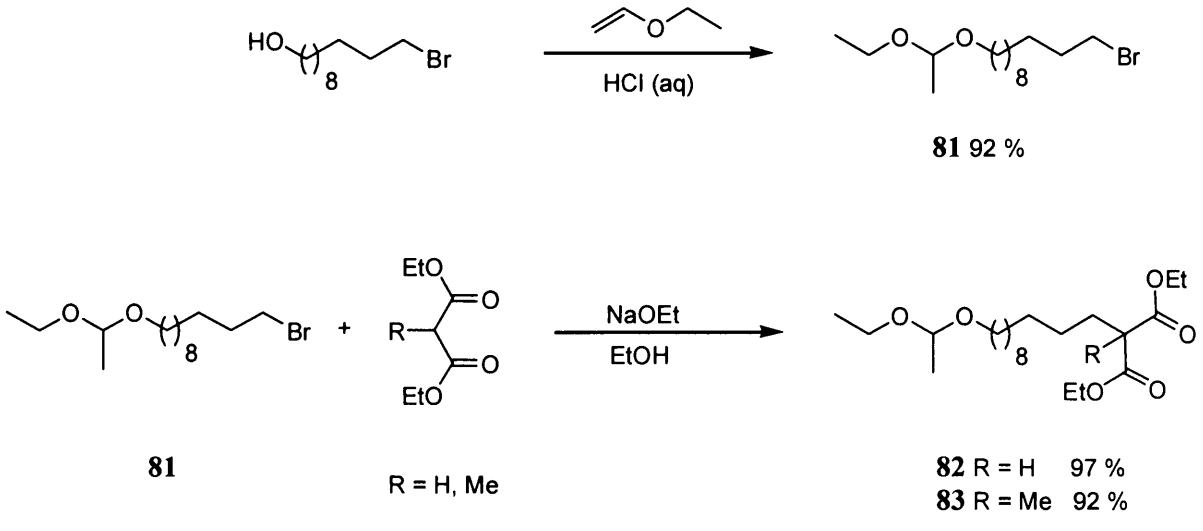
The separation of *C*- and *O*-alkylated products had previously been reported to be problematic due to them co-distilling. A method to remove the *O*-alkylated product from



Scheme 29

such reaction residues was described and involved heating the crude reaction products in a mixture of glacial acetic acid and sodium acetate, to reflux.[82] This method of separation would not be practical for a compound with a silyl ether-protected alcohol, however, as cleavage of the protecting group would result.

Therefore an alternative strategy was investigated, namely, the reaction between ω-bromoesters **77** and **78** with pentane-2,4-dione under the conditions described previously (scheme 29). Ethyl bromohexanoate **78** is commercially available, while methyl bromoundecanoate **77** was prepared from bromoundecanoic acid, by acid-catalysed esterification in methanol (scheme 29). In each case the *C*-alkylated diketone and *O*-alkylated product were obtained in a 7:3 ratio. Removal of the *O*-alkylated product was achieved by heating the mixture to reflux in glacial acetic acid in the presence of sodium



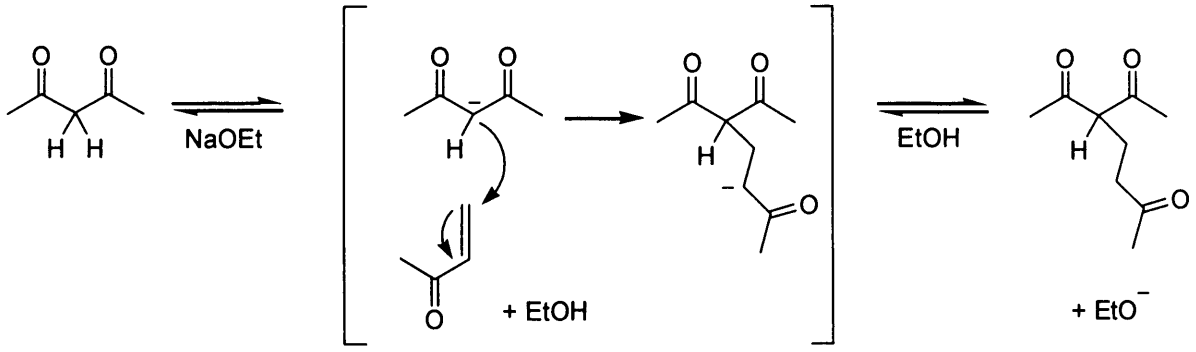
Scheme 30

acetate, followed by an organic / aqueous extraction. Removal of the *O*-alkylated product was confirmed by GC-MS. The mono-alkylated diketone products **79** and **80** could then be obtained in high purity, but low isolated yield, by vacuum distillation.

A second alternative route, which proceeds *via* alkylation of a 1,3-diester, is shown in scheme 30. An anomaly reported by Scharf *et al.* describes how ethoxyethyl-protected bromoundecanol reacts with diethyl malonate, to give solely the *C*-alkylated product in quantitative yield.[83] No explanation was offered for this result. In the same paper, the authors describe the reaction of t-butylether-protected bromoundecanol with diethyl malonate that afforded a 61 % yield of *C*-alkylated product, consistent with previous yields observed in the alkylation of β-dicarbonyl compounds.[81] Taking advantage of this result, and the fact that the ethoxyethyl protecting group is stable to both hydride reducing agents and organometallic reagents, **81** was prepared by reaction of bromoundecanol with ethyl vinyl ether. Subsequently, this was reacted with the sodium salts of diethyl malonate and methyl diethyl malonate, which were prepared by the reaction of the corresponding malonate with sodium ethoxide. The α-monosubstituted and α-disubstituted malonate derivatives **82** and **83** were obtained in 97 % and 92 % yields, respectively.

2.2.2 Michael additions of 1,3-dicarbonyl compounds

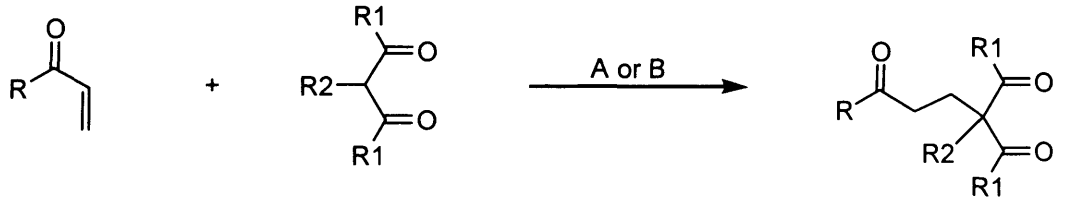
An alternative method of alkylation at the α-carbon atom of 1,3-dicarbonyl compounds is *via* the Michael reaction.[83,84] An example of the mechanism of a classic base-catalysed Michael addition is shown in scheme 31. Removal of an acidic α-hydrogen atom from the enolisable ketone, pentane-2,4-dione, gives a nucleophillic enolate anion which adds to the β-carbon of an α,β-unsaturated carbonyl compound to generate the 1,5-dicarbonyl product. It was thought that use of 1,3-dicarbonyl compounds as the Michael donor would provide a convenient route to 1,1',5-triols following reduction of the Michael



Scheme 31

addition product.

Recent investigations into the Michael reactions of 1,3-dicarbonyl compounds have led to the development of various methods that utilise mild and neutral conditions rather than the classical base-catalysed methodology.[85-88] The use of strong bases in such Michael additions can, in some cases, lead to unwanted side reactions such as aldol processes, rearrangements and ester solvolysis. Therefore, various other catalysts that function under neutral conditions have been reported, particularly lanthanide[85] and transition metal[86] compounds, where reactions proceed *via* the formation of 1,3-dionato complexes. In one example, iron (III) chloride hexahydrate was shown to be an efficient catalyst in Michael reactions between a number of 1,3-dicarbonyl compounds and enones.[87] Similarly, cerium (III) chloride heptahydrate in the presence of sodium iodide was reported as an efficient system for such reactions and is particularly useful, due to the mild conditions employed, in the reactions of Michael acceptors that have a high tendency to polymerise, such as acrolein.[88]



84 R = H
85 R = Me

86 - 90

A = 2 mol % $FeCl_3.6H_2O$, no solvent, rt
B = 20 mol% $CeCl_3.7H_2O$, 10 mol % NaI, no solvent, rt

Scheme 32

Product	R	R^1	R^2	Conditions	Yield (%)
86	Me	Ph	H	A	98
87	Me	Me	Me	A	66
88	Me	OEt	Et	A	25
89	H	Ph	H	B	48
90	H	Me	Me	B	25

Table 8. Synthesis of 1,1',5-tricrbonyl compounds by Michael reactions; A = 2 mol % $FeCl_3.6H_2O$, $CHCl_3$, rt; B = 20 mol% $CeCl_3.7H_2O$, 10 mol % NaI, MeCN, rt.

A number of symmetrical 1,3-dicarbonyl compounds were reacted with methyl vinyl ketone (**85**) or acrolein (**84**) in the presence of iron (III) chloride hexahydrate or cerium (III) chloride heptahydrate catalyst systems, respectively, to give 1,1',5-tricarbonyl

compounds **86-90** (Scheme 32). Reactions were performed at room temperature, in most cases in the absence of solvents, and gave α-alkylated 1,3-diketones or diesters in yields varying from excellent to moderate (table 8).

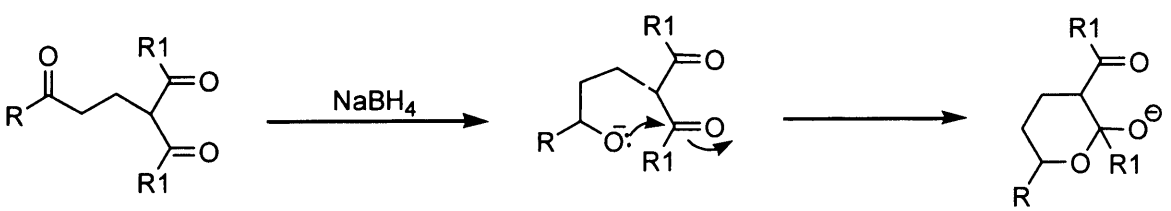
2.2.3 Hydride reductions of 1,3-dicarbonyl compounds

The reduction of alkylated 1,3-dicarbonyl compounds **79-80**, **82-83** and **86-90** was investigated, with the aim of synthesising the corresponding 1,3-diols. The synthesis of diols by reduction of 1,3-dicarbonyl compounds has previously been reported with both sodium borohydride and lithium aluminium hydride.[90-93]

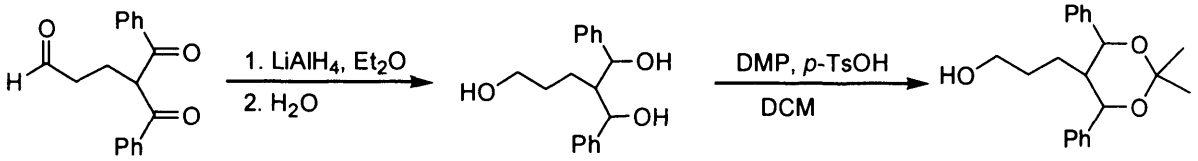
With $NaBH_4$-mediated reductions, the diol can be obtained in high yield from α-unsubstituted or α-monosubstituted 1,3-dicarbonyl compounds if the reaction is performed in neutral or mildly basic conditions, rather than the conventional strongly basic conditions, due to the acidity of the α-hydrogen atom(s).[90] This is to prevent formation of the enolate anion, which will not react with borohydride ions due to electrostatic repulsion.

High yields have also been reported in the lithium aluminium hydride reduction of various 1,3-diketones.[92,93] These reductions are problematic, however, for 1,3-diketones with a high enol concentration, due to formation of allylic and saturated alcohols as elimination products. For example, the major product in the reduction of pentane-2,4-dione with lithium aluminium hydride in ether is 3-penten-2-ol.[94] Clean reductions to the diol are generally less problematic for α-disubstituted 1,3-dicarbonyl compounds.[90]

The reductions of compounds **86-90** with an excess of sodium borohydride or lithium aluminium hydride were attempted with the aim of synthesising the corresponding triols. In all attempts, analysis of the crude reaction showed no evidence of unreacted carbonyl groups, but was shown to consist of a mixture of products, with unwanted side reactions apparently having occurred to a large extent, with compounds such as those arising from intramolecular cyclisation being detected (scheme 33).



Scheme 33

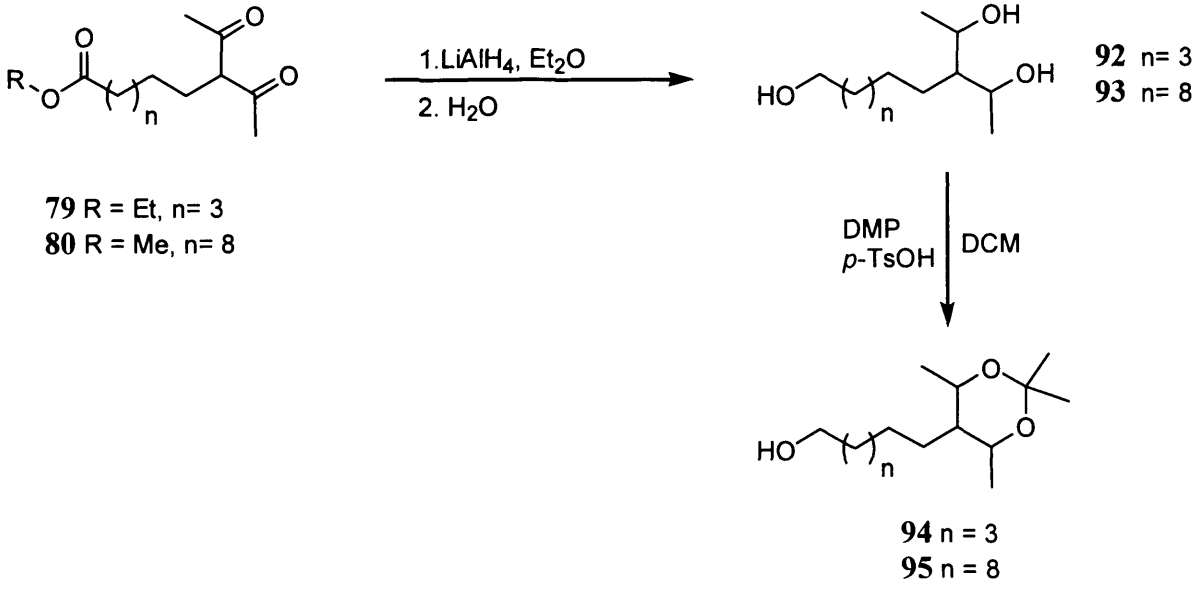


89 **91**

Scheme 34

It was found that a major problem with these reduction reactions was the purification of the crude reaction mixture, complicated by the presence of two or three hydroxyl groups in the products. Only in one instance was a desired product isolated as a pure compound. This was achieved by treatment of the crude mixture from the reaction of **89** with lithium aluminium hydride, with the conditions required for protection of the 1,3-diol as ketal **91**(scheme 34). After purification by column chromatography, ketal **91** was obtained pure in 10 % overall yield as a mixture of diastereoisomers. This approach of protecting any 1,3-diols in the crude reaction mixture as ketals, in order to facilitate purification by chromatography, failed to yield any desired product in the other reduction reactions investigated.

It was hoped that a cleaner reduction reaction would be observed for the longer-chain, ω-ester-functionalised 1,3-diketones **79** and **80**, due to the reduced likelihood of intramolecular cyclisation. Treatment of **79** and **80** with $LiAlH_4$ in ether in an attempt to form triols **92** and **93**, respectively, again led to a mixture of products being formed. The crude reaction mixtures were therefore treated directly, without purification, with acetone in anhydrous acid conditions in attempts to obtain ketals **94** and **95** (scheme 35). In each case, however, none of the desired ketals could be obtained. This was possibly due to high

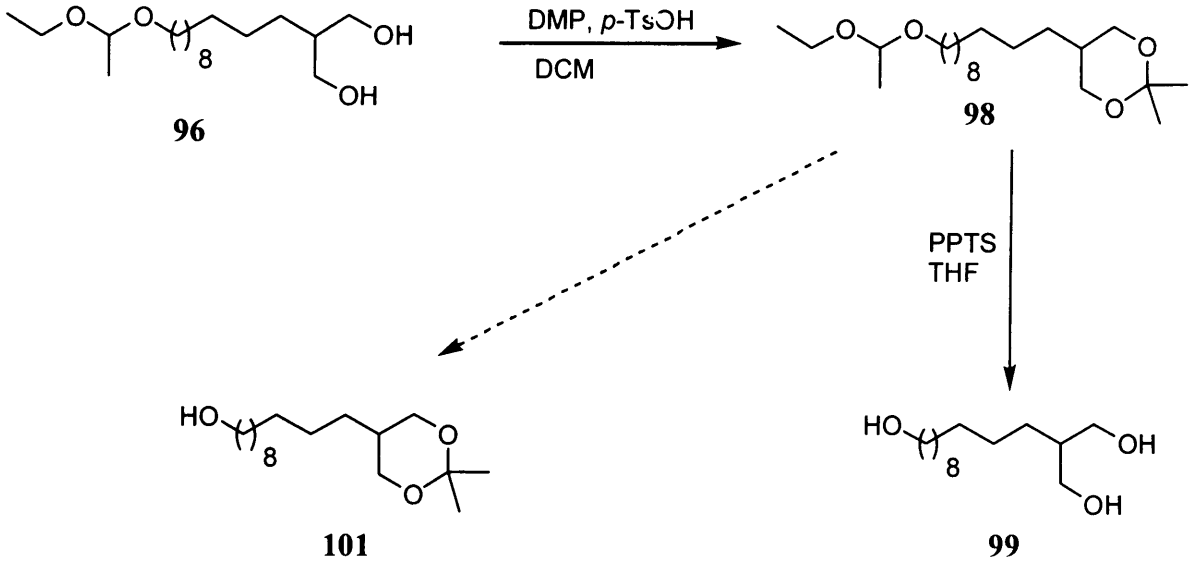


79 R = Et, n= 3
80 R = Me, n= 8

92 n= 3
93 n= 8

94 n = 3
95 n = 8

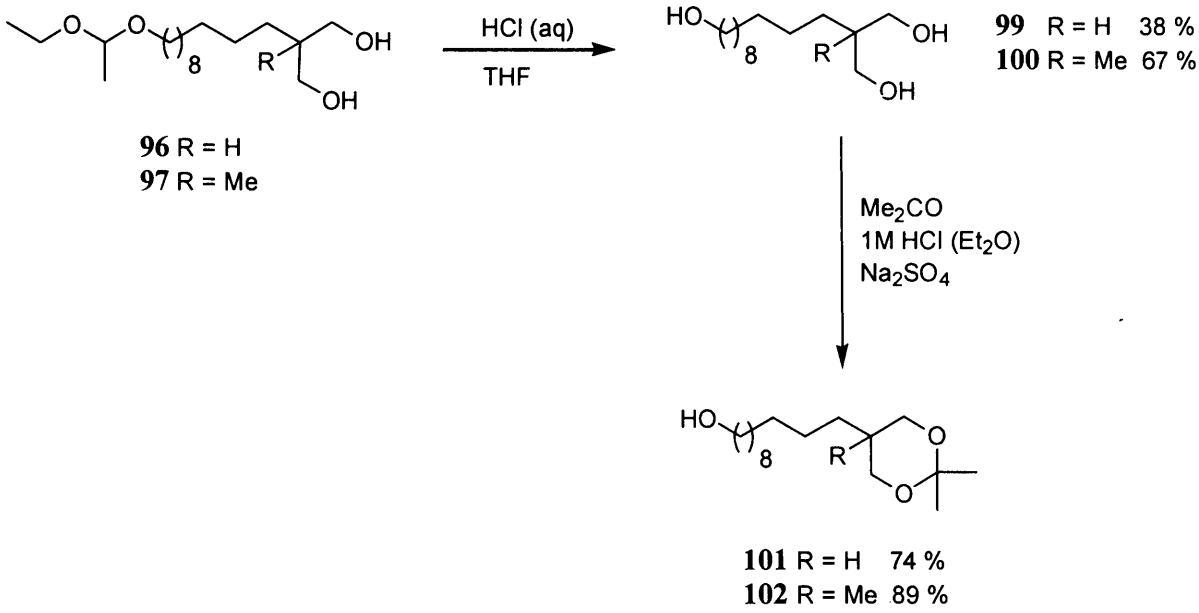
Scheme 35



Scheme 37

levels of impurity in the crude reaction mixtures resulting from the $LiAlH_4$ reduction, due to the occurrence of side reactions such as elimination.

Reduction of malonates **82** and **83** to 1,3-diols **96** and **97**, respectively, by treatment with $LiAlH_4$ in ether was achieved cleanly, in high yield. Following work-up, the ^{13}C and ^{1}H NMR spectra of the products showed complete reduction of the diester group had been achieved, with no signals attributable to a carbonyl species evident. Diol **96** was then protected as ketal **98**, with the aim of selectively cleaving the ethoxyethyl protecting group over the acetonide, to give ω-hydroxy ketal **101** (scheme 37). Selective cleavage of an ethoxyethyl group in the presence of an acetonide has previously been reported using pyridinium *p*-toluene sulfonate (PPTS), prepared from *p*-toluene sulfonate (PTS).[95] Thus, ketal **98** was treated with 5 mol % PPTS in THF at room temperature for 24 hours. No desired product was obtained as the conditions cleaved both protecting groups. Instead,



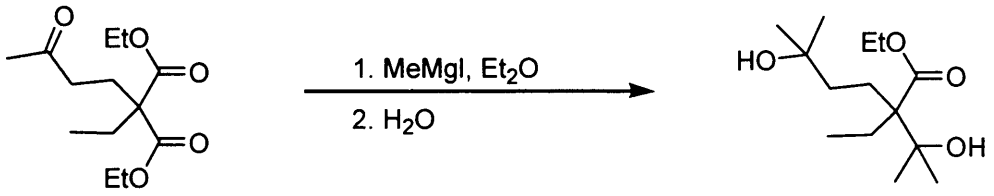
Scheme 38

triol **99** was obtained in moderate yield (41 %). Both ethoxyethyl and acetonide protecting groups are known to be cleaved by catalytic amounts of *p*-TsOH, so if the PPTS was slightly impure, and contained *p*-TsOH, then formation of triol **99** would be expected.

In an alternative approach, triols **99** and **100** were obtained directly by aqueous acid hydrolysis of the ethoxyethyl protecting group of the diols **96** and **97** (scheme 38). The reactions were attempted several times with a variety of acid concentrations, reaction times and temperatures, but yields obtained were moderate in all cases. Subsequently, triols **99** and **100** were converted to ketals **101** and **102** by treatment with anhydrous acid in acetone. The protection steps proceeded in near quantitative yields and the desired products obtained, pure, by column chromatography.

2.2.4 Organometallic additions to 1,3-dicarbonyl compounds

The reaction of tricarbonyl compounds **86-90** with Grignard reagents was also attempted in order to synthesise compounds with three tertiary alcohol groups. Triketone **87** was reacted with an excess of methyl magnesium iodide in ether, but resulted in a mixture of products being obtained. Due to the challenge presented by the separation of the products, no desired triol could be isolated. A quaternary signal at 99.9 ppm in the ^{13}C NMR spectrum of the crude product was evidence that an intramolecular cyclisation similar to that described in scheme 33 had occurred, at least partially.



88 **103**

Scheme 39

The reaction of α-disubstituted 1,3-diester **88** with methyl magnesium iodide was also attempted. It was thought that the increased steric bulk around the 1,3-dicarbonyl would hinder intramolecular cyclisation. After stirring at room temperature for 24 hours in the presence of twenty equivalents of methyl magnesium iodide, work up gave a crude product found to consist predominantly of 1,3-hydroxy ester **103** (scheme 39). Portions of the crude reaction mixture containing **103** were exposed to excess methyl magnesium

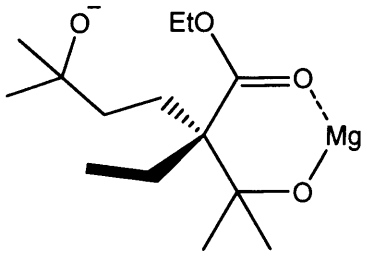
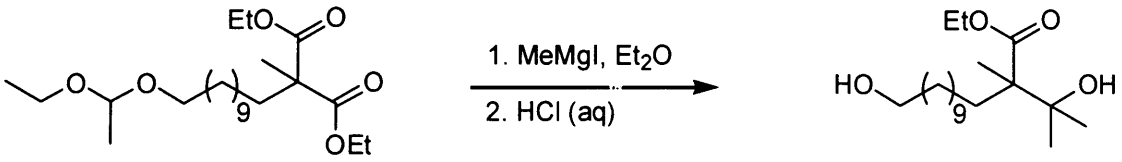


Fig. 18

iodide at elevated temperatures in a variety of solvents and also with other organometallic reagents (methyl lithium and trimethyl aluminium) in attempts to form the 1,3-dihydroxy compound, however in no case could the second carbonyl group be reduced. The lack of reactivity of this ester carbonyl bond towards nucleophiles could possibly be due to the formation of a six-membered chelate ring upon addition of the organometallic reagent (Fig. 18), with the steric bulk of the alkyl substituents α to the carbonyl blocking nucleophillic attack.



83 **104**

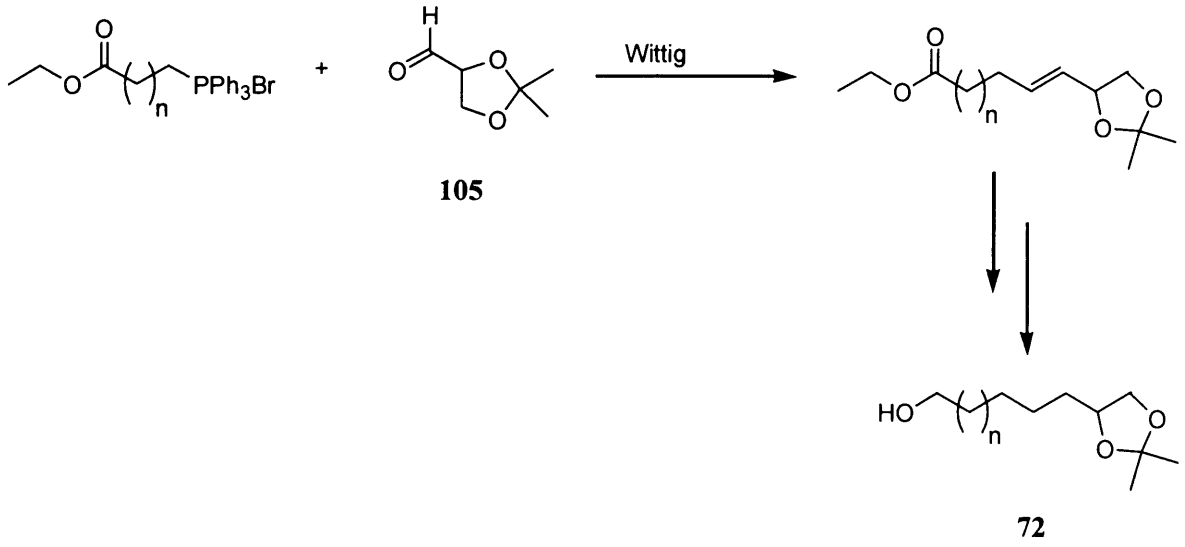
Scheme 40

The reaction of two other α-alkylated 1,3-diester compounds with methyl magnesium iodide was attempted. Treatment of the α-disubstituted 1,3-diester **83** with an excess of methyl magnesium iodide proceeded in a similar fashion to that of 1,3-diester **87**, described previously. It was hoped that being slightly less sterically hindered, with a methyl rather than an ethyl α-substituent, both carbonyl groups would be reactive and the 1,3-dihydroxy compound obtained. This was not the case, however, and 1,3-hydroxy ester **104** was obtained as the major product in good yield (78 %). The ethoxyethyl-ether protecting group was cleaved by the aqueous acid work-up conditions (Scheme 40).

The α-monosubstituted 1,3-diester **82** showed no reactivity toward methyl magnesium iodide. This lack of reactivity can be attributed to the acidic α-hydrogen atom. The Grignard reagent is a strong enough base to deprotonate the active hydrogen atom, leading to an enolate anion with a stable cyclic structure, with pseudo-aromatic character, which is hence inert towards nucleophilic attack. This explanation has previously been

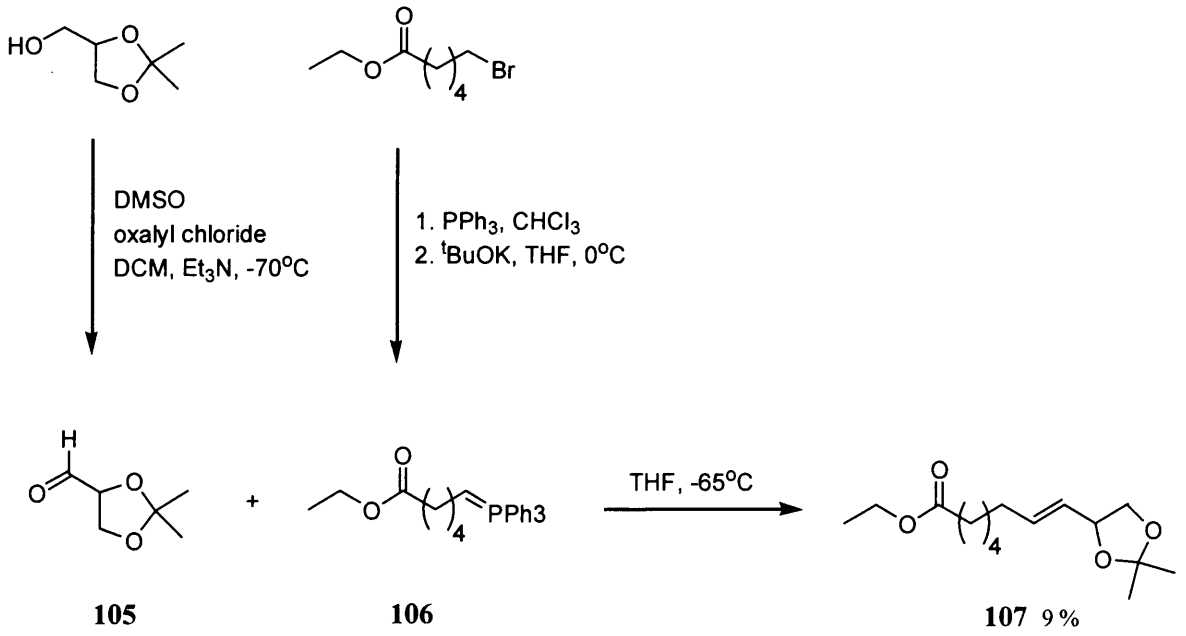
used to account for the unreactivity of the carbonyl groups of 1,3-diketones towards nucleophillic attack.[96]

2.3 Synthesis of γ-hydroxy-functionalised 1,2-diols



Scheme 41

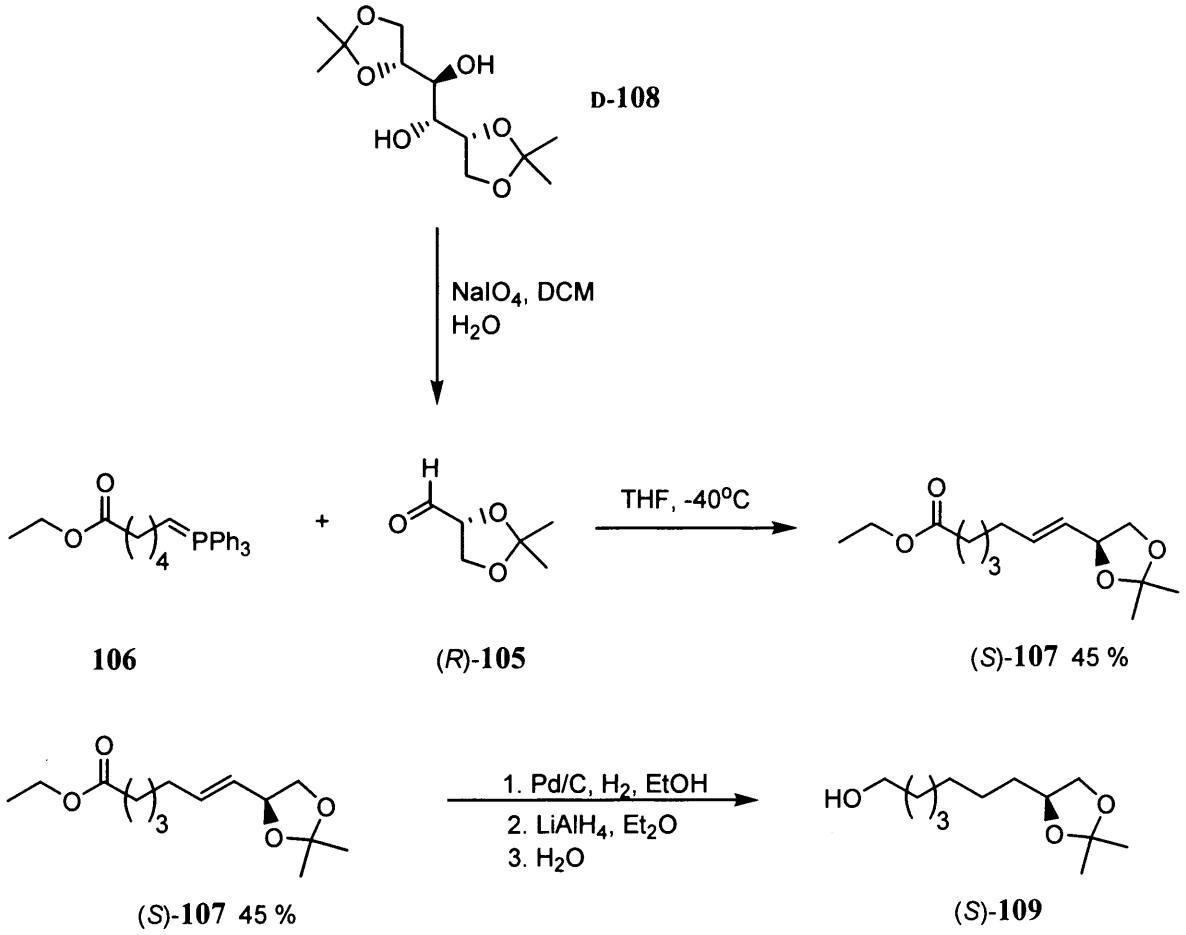
The synthesis of ketal-protected 1,2-diols with general structure **72** was desired for grafting onto polystyrene supports. A versatile route was proposed for the synthesis of these compounds that allows for the introduction of various alkyl chain lengths (Scheme 41). The strategy involved the Wittig reaction of 2,3-*O*-isopropylideneglyceral (**105**) with



Scheme 42

ylides prepared from α,ω-bromo esters. Hydrogenation of the resulting olefin, followed by reduction of the ester functionality would give the desired compounds.

The first Wittig reactions attempted involved synthesis of racemic 2,3-*O*-isopropylideneglyceral (**105**) *via* a Swern oxidation of solketal (scheme 42). Due to its unstable nature at room temperature, and tendency to polymerise, aldehyde **105** was synthesised *in situ*. Thus, solketal was treated with dimethyl sulfoxide-oxalyl chloride at -78°C and then added to a solution of ylide **106**. The ylide was prepared by heating ethyl bromohexanoate with triphenylphosphine in chloroform at reflux, followed by reaction with potassium *tert*-butoxide in THF at 0°C. Despite repeating the reaction several times the best yield of olefin **107** obtained by this method was just 9 %.



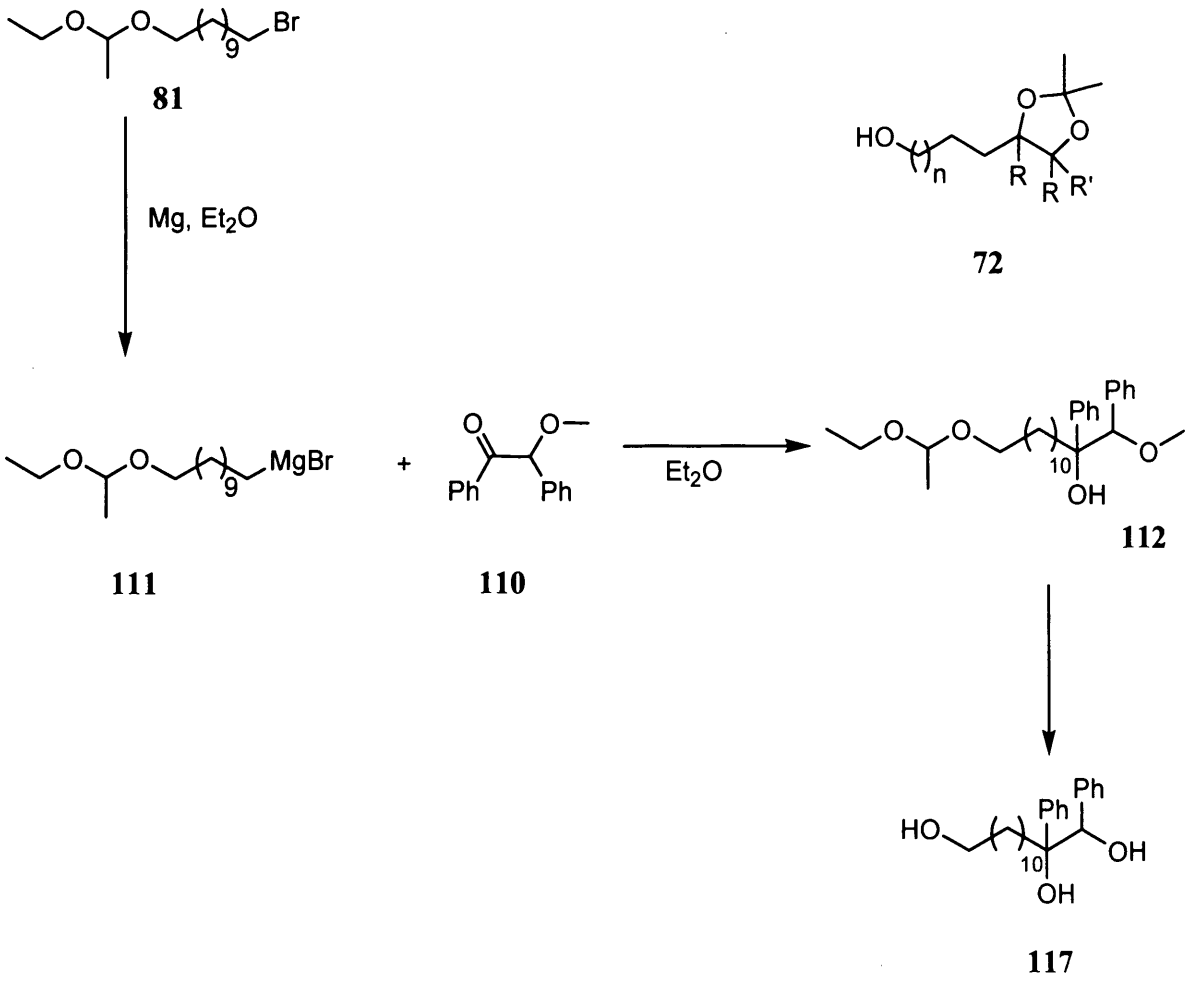
Scheme 43

In a second approach, a single enantiomer of the aldehyde was prepared by oxidative cleavage of cheap and readily available 1,2-5,6-di-*O*-isopropylidene-D-mannitol (**D-108**) (Scheme 43). Treatment of **D-108** with sodium metaperiodate and water in dichloromethane gave enantiopure (*R*)-2,3-*O*-isopropylideneglyceral {(*R*)-**105**} in near quantitative yield. Reaction of a solution of freshly prepared (*R*)-**105** with the ylide **106** at -40°C led to the synthesis of olefin (*S*)-**107** in 45 % yield, as a mixture of *cis*- and *trans*-

isomers. Hydrogenation of the double bond with palladium on carbon, followed by reduction of the ester with lithium aluminium hydride gave ketal-protected 1,2-diol (*S*)-**109**.

2.3.1 Synthesis of α-substituted γ-hydroxy-functionalised 1,2-diols

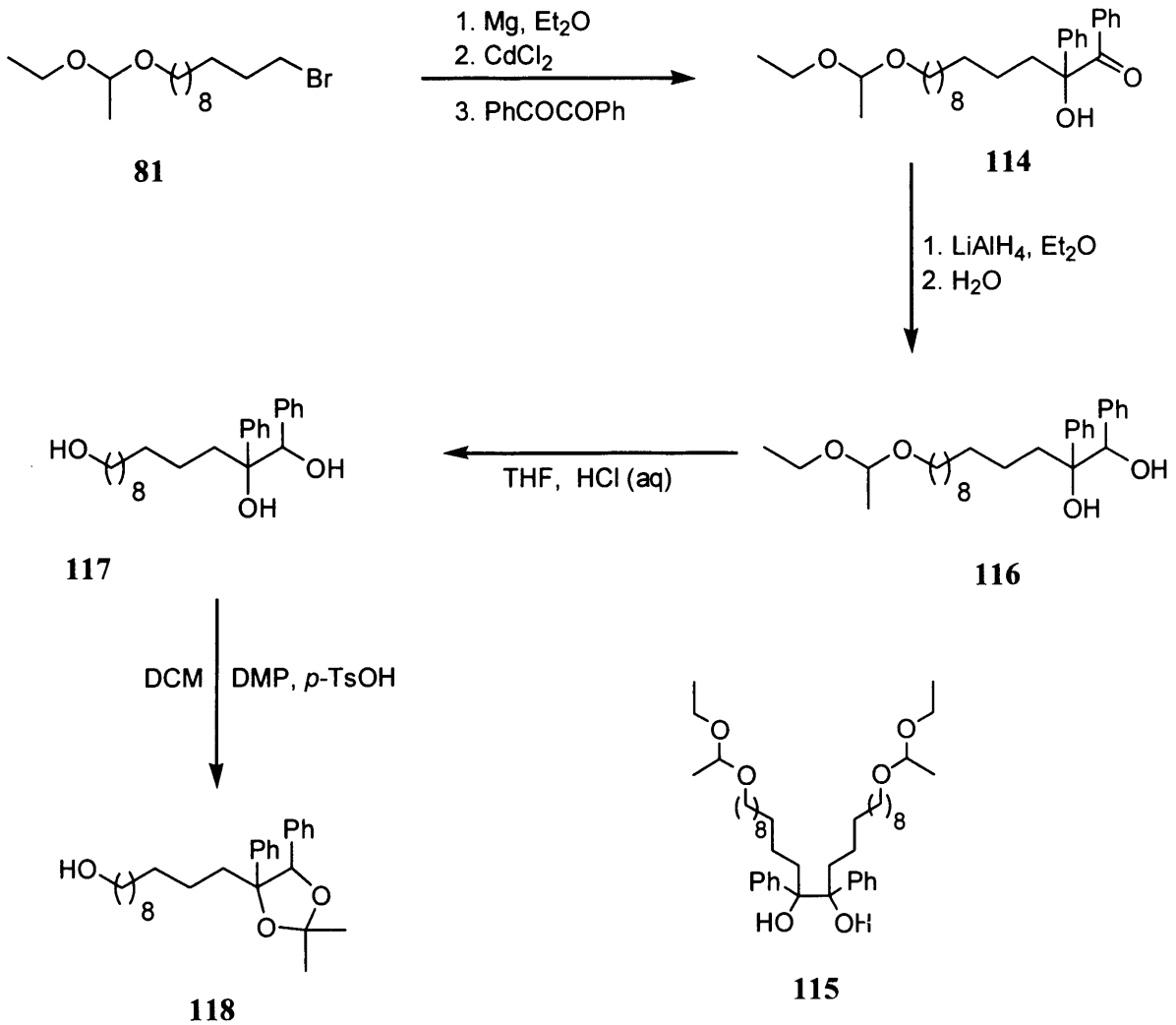
The synthesis of ketal-protected 1,2-diols of a general structure **72** (Scheme 44) with various substituents R, was desired for tethering to Merrifield resin. A route to these compounds that has been explored is shown in scheme 41. The hydroxy group of benzoin was protected as its methyl ether derivative **110** by reaction with methyl iodide in the presence of silver oxide in chloroform. Compound **110** was then reacted with the Grignard reagent **111**, prepared from ethoxyethyl-ether-protected bromoundecanol (**81**), to give **112** in 62 % yield. Cleavage of the methyl ether and ethoxyethyl-ether (EEO) protecting groups in one step was attempted with both aluminium trichloride/ethanethiol and trimethyl silyl iodide, however neither method afforded the desired product, namely triol **117**. Disappointingly, the mixture of products that resulted could not be separated.



Scheme 44

In a second route to compounds **72** that has been explored, an organocadmium reagent, CdR_2, was prepared by the reaction of two equivalents of the corresponding Grignard reagent, itself prepared from ethoxyethyl-ether-protected bromoundecanol (**81**), with anhydrous cadmium chloride (Scheme 45). This was reacted with benzil to afford α-hydroxyketone **114** in 80 % yield. The organocadmium reagent was used for this transformation as it has been shown previously to react with 1,2-diketones to give the α-hydroxyketone product, from addition of just one equivalent of the alkyl group to the twin carbonyl system, in good yield.[97] Organocadmium reagents are relatively unreactive towards isolated carbonyl groups, yet react readily with one of the activated carbonyl groups in 1,2-diketones. Were a more reactive organometallic reagent to be used, such as a Grignard, a higher yield of the unwanted pinacol (**115**), resulting from *bis*-addition might be observed.

The desired α-hydroxyketone **114** was reduced to 1,2-diol **116** with lithium aluminium hydride in ether. Cleavage of the ethoxyethyl-ether protecting group gave triol **117**. Subsequent protection of the 1,2-diol moiety as the isopropylidene ketal gave



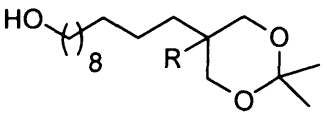
Scheme 45

compound **118** as a mixture of diastereoisomers, in 37 % overall yield based on **81**.

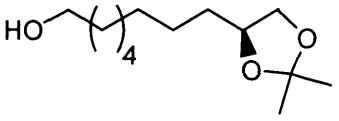
2.4 Grafting of ω-hydroxy ketal-protected diols to PS-DVB resins

2.4.1 Introduction and previous examples of solid phase etherification of chloromethylated PS-DVB Resins

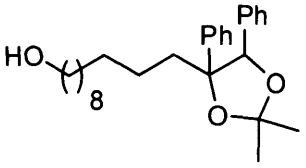
The synthetic schemes explored in sections **2.2-2.3** gave protected diols **101**, **102**, (*S*)-**109** and **118** (Fig. 19) suitable for grafting onto PS-DVB supports *via* reaction of the alcohol with pendant polymer-bound chloromethyl groups. Subsequent removal of the acetonide protecting group would give the desired diol-functionalised polymers.



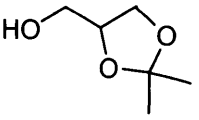
101 R = H
102 R = Me



(*S*)-**109**



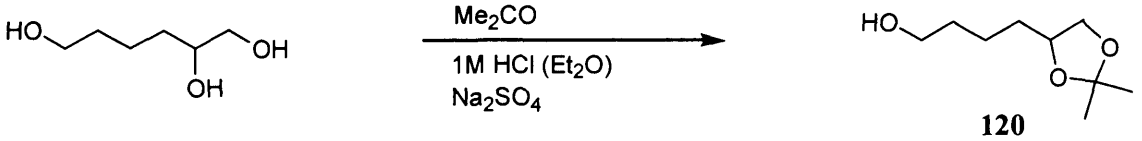
118



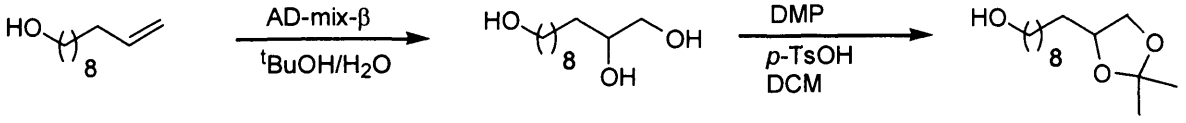
119

Fig. 19

A further range of ω-hydroxy ketals (**119-121**) appropriate for immobilisation, with alkyl chains of varying length, were either commercially available (solketal, **119,** Fig. 18) or easily obtained from commercially available precursors, expanding the range of



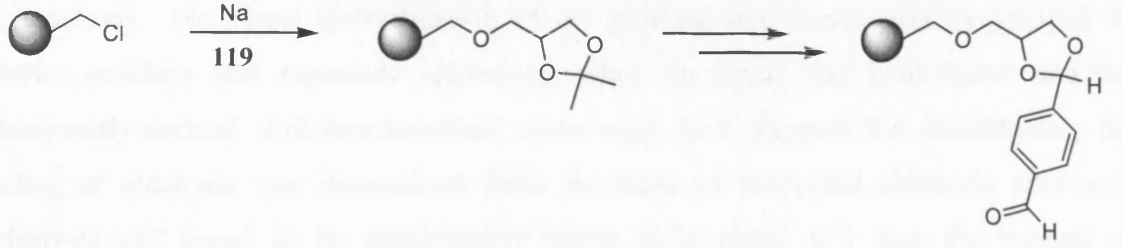
120



122 **121**

Scheme 46

diol-derivatised resins possible. Thus, **120** was obtained by protection of hexane-1,2,6-triol. Similarly, dihydroxylation of 11-undecen-1-ol followed by protection of the triol product (**122**) as the ketal gave **121** (scheme 46).

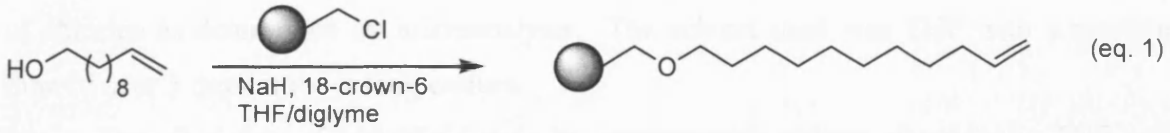


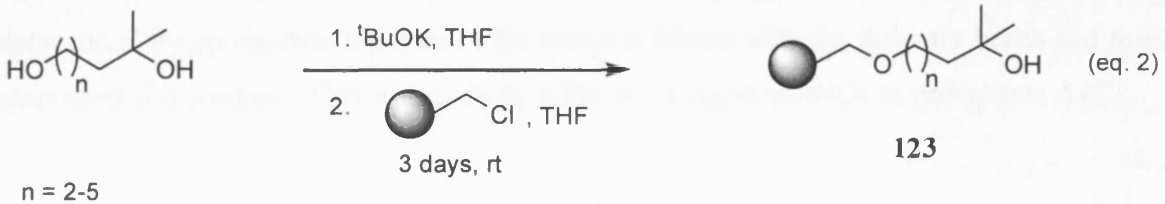
1.7 mmol g^{-1} Cl — 0.34 mmol g^{-1} aldehyde

Scheme 47

Several procedures have previously been reported for the attachment of alcohols to chloromethylated resins by formation of an ether linkage.[7] A variety of bases for alkoxide formation and reaction conditions have been used. However, the reaction has not been extensively investigated, due to it being a generally inconvenient method of immobilising substrates for SPOS, since the high stability of the ether bond would make recovery/removal of the bound substrate difficult. Chloromethyl-functionalised resins are more commonly used to immobilise carboxylic acids by ester formation, as in Merrifield's peptide synthesis (scheme 1), for example.

The immobilisation of solketal (**119**) on PS-DVB beads has been reported previously in the synthesis of a diol-functionalised resins for use as a support or "solid





123

n = 2-5

n = 0, 4,6,16

Scheme 48

phase" protecting group for aldehydes in SPOS (*e.g.* scheme 47).[98] In this case, grafting was achieved by reaction of Merrifield resin with the sodium salt of **119**, prepared by the addition of sodium to neat, excess solketal (acting as both the solvent and the substrate for the reaction). No direct quantification of the grafting step conversion by analysis of chlorine residues was reported. However, when the ketal was hydrolysed, and the subsequently-derived diol-functionalised resin used as a support for dialdehydes, the loading of aldehyde was determined from the mass of recovered aldehyde after acid hydrolysis and found to be considerably lower (0.34 mmol g^{-1}) than the loading of chloromethyl residues in the starting Merrifield resin (1.7 mmol g^{-1}). These results suggest a low incorporation of alcohol **119** in the initial grafting step.

During a study into the preparation of spacer-modified polymer-supported phase transfer catalysts, Tomoi conducted etherification of Merrifield resin with sodium 10-undecen-1-oate using sodium hydride in THF/diglyme (scheme 48, eq. 1).[99] Addition of 18-crown-6 was found to be necessary for optimal grafting of the alcohol. The reaction did not proceed when an alternative phase-transfer agent, namely the alkyl ammonium salt $(C_4H_9)_4NBr$, was employed. The success of the etherification step was not quantified, but was reported qualitatively as "in moderate yield," based on the results of further derivatisation.

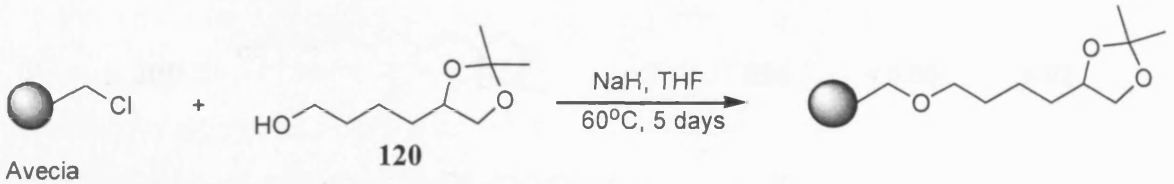
In another reported example, potassium *tert*-butoxide was used as the base in the selective etherification of a primary alcohol over a tertiary alcohol group of a range of aliphatic diols (scheme 48, eq. 2).[100] Resins **123** were prepared with near quantitative loss of chlorine as determined by microanalysis. The solvent used was THF with a reaction time of over 3 days at room temperature.

The alkylation of Merrifield resin by reaction with sodium alkoxides in THF was reported (scheme 48, eq. 3).[101] The alkoxides were generated by treating aliphatic alcohols with sodium. Here, the extent of substitution of the polymer chloromethyl groups was determined by gravimetric analysis of the reaction filtrate after the polymer beads had been recovered and washed. This was done by addition of $AgNO_3/HNO_3$ to precipitate AgCl.

2.4.2 Grafting of alcohols to (Avecia) Merrifield resin

The examples from the literature outlined in section **2.4.1** demonstrate how etherification of chloromethylated PS-DVB beads can be problematic, often resulting in incomplete substitution of chlorine. For many applications the presence of residual

chloromethyl groups is not a problem and does not interfere with subsequent applications. For our purposes, however, as the aim of the study is to investigate how variations in the structure of the tether affect the reactivity of a supported species, it is important that other factors related to the polymer structure remain constant. Thus, it is important that the loading of functional groups on the beads is always comparable. The obvious method of obtaining a consistent level of functionalisation following the reaction of alcohols with Merrifield resin is by quantitative incorporation of the alcohol. Hence, the reaction of **120** with Merrifield resin, obtained from Avecia, was attempted under a variety of conditions in order to optimise the resulting loadings. The use of potassium hydroxide base in methanol/1,4-dioxane gave no conversion, possibly due to poor swelling of the polymer beads in this solvent system.



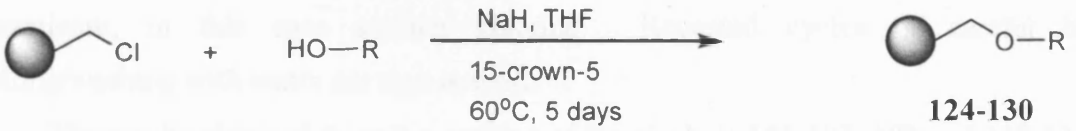
120

Avecia
Merrifield Resin

Entry	Catalyst	Cl content in product (%)	Conversion (%)
1	none	2.10	44
2	18-crown-6	0.61	82
3	15-crown-5	< 0.3	> 92

Scheme 49. Grafting of alcohol **120** to Avecia Merrifield resin.

When sodium hydride was used as the base, in THF at 60°C, conversion was *moderate* (44 %), but improved to *high* when the reaction was undertaken in the presence of a crown ether phase-transfer catalyst (scheme 49). The percentage conversion was determined from chlorine microanalysis results, with the new resins being characterised by gel-phase ^{13}C NMR spectroscopy. The use of 18-crown-6 led to an 82 % conversion, which was improved to being near-quantitative, within the limits of the analysis technique, when 15-crown-5 was used. The slightly better result observed with the use of the smaller 15-crown-5 is consistent with the greater ability of this crown ether to bind sodium cations compared with that of 18-crown-6. The method employed a large excess of both the alcohol (5 equivalents) and base (5 equivalents) to help drive the reaction to completion. In addition, the smallest volume of solvent as was practically possible, was used, in order to aid diffusion and concentration of reagents within the polymer beads.



124-130

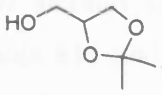
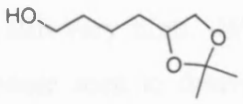
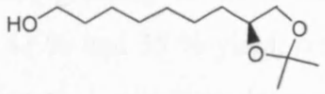
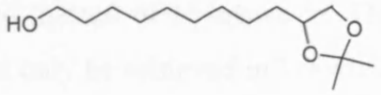
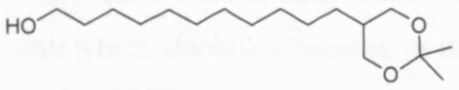
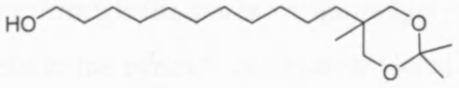
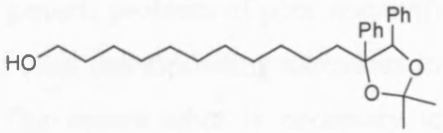
Entry	ROH	Structure	Product	Cl content of product (%)	Conversion (%)
1[a]	**119**		**124**	< 0.30	> 92
2[a]	**120**		**125**	< 0.30	> 92
3[a]	**109**		**126**	< 0.30	> 92
4[a]	**121**		**127**	0.44	89
5[a]	**101**		**128**	2.20	41
6[b]				2.84	24
7[a]	**102**		**129**	2.44	35
8[a]	**118**		**130**	3.06	18

Table 9. Grafting of alcohols to Merrifield resin; [a] In presence of 15-crown-5 (10 mol %); [b] in presence of 18-crown-6 (10 mol %).

Since all reactions (entries 1-8, Table 9) were undertaken under identical conditions, using exactly comparable work-up procedures, the fact that one reaction led to quantitative loss of chlorine is significant as it rules out the possibility that in other reactions, chlorine residues detected in the polymer product are due to precipitated sodium chloride trapped within the matrix, which had not been removed by the washing procedure. Removal of ionic by-products from such reactions involving gel-type PS-DVB resins can be difficult. This is due to the contradictory nature of solvents necessary to swell the beads

and, hence, to create access to the entire matrix, and those required to dissolve the contaminant, in this case sodium chloride. Repeated cycles of careful bead swelling/washing with water are thus needed.

The results obtained from the grafting of the alcohols **101-102**, **109** and **118-121** to Avecia Merrifield resin to give the ketal-functionalised resins (**124-130**) are displayed in Table 9. The same conditions were used as those that gave optimum conversion in the immobilisation of alcohol **120**. As was observed for the reaction involving **120**, the reaction of alcohols **119** and **109** proceeded smoothly with near quantitative conversion. For alcohol **121**, with a longer methylene carbon chain, the percentage conversion dropped slightly, but was still very high. With the longer chain and bulkier alcohols **101** and **102**, the conversions were seen to deteriorate with only one third of chloromethyl sites being substituted. Thus, grafting of both these alcohols with similar steric demands was achieved in only 41 % and 35 % yield, respectively. The results presented in table entry 6 (Table 9) demonstrate, again, how deterioration in the conversion was observed when 18-crown-6 was used instead of 15-crown-5. The grafting of the sterically more demanding alcohol **118** could only be achieved in low yield.

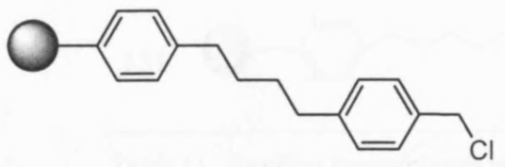
It is clear from these results that, under these conditions, there is a correlation between the ease with which alcohol substrates, as their alkoxides, can be grafted to lightly cross-linked gel-type PS-DVB beads and their steric bulk. This is presumably due to more hindered diffusion through the pores of the polymer matrix of the bulkier substrates, and thus reduced access to the pendant chloromethylated sites.

The fact that catalytic amounts of crown ethers are necessary for high conversion suggests that the general problem of poor reactivity of these alcohols is due, in part, to the poor solubility of their corresponding alkoxides in the reaction medium, which leads to a slow reaction. The crown ether is necessary to draw the alkoxide into solution and enhance its reactivity by promoting dissociation from the sodium cation. This problem is further compounded by the fact that there will be difficulties associated with the subsequent diffusion of the alkoxide into the polymer beads (a mass transport effect). Substrate diffusion may be unfavourable as a result of both steric interference from the insoluble polymer, and the slightly decreased polarity of the environment within the polymer beads, compared to the surrounding bulk solvent. Together, these problems mean that the reaction is generally slow and the size of the alcohol becomes a crucial factor in determining the extent of the reaction. It is not thought likely that the difference in reactivity of the substrates is due to differences in the solubility of the various alkoxides. Indeed, one may expect the alkoxides with longer methylene chains to be more soluble.

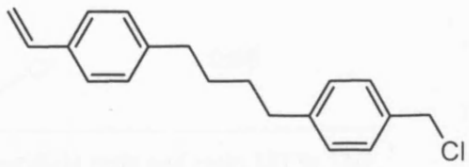
The method of synthesis of the polymer beads may also be a contributing factor. The beads used in this investigation were prepared by copolymerisation of styrene, DVB and *p*-vinyl benzyl chloride (designated in this report as Avecia Merrifield resin). This method leads to a relatively even incorporation of chloromethylated sites throughout the polymer matrix, compared to the method of introducing chloromethyl groups after polymerisation by modification of PS-DVB beads, where the more accessible aryl rings of the polymer are likely to be functionalised preferentially.[8] An even distribution of chloromethylated aryl rings throughout the polymer means some will be located in the regions of the matrix of higher cross-link density, the origins of which were explained in section **1.4.1**. These chloromethyl sites will be less accessible and, as the size of the alcohol substrate increases, a higher proportion of them will remain unsubstituted hence, the conversion will decrease.

2.4.3 Grafting of alcohols to (chloromethylphenylpentyl)-PS-DVB resin

A second strategy for the synthesis of spacer modified diol-functionalised PS-DVB beads is by grafting protected-diol compounds onto a functional polymer, previously modified with a spacer group (scheme 24, route a). A convenient route to the desired polymers using this strategy was made possible by the commercial availability of PS-DVB resin **131** that features a pendant chloromethylated alkyl linker (Fig. 20).



131 (chloromethylphenylpentyl)-polystyrene

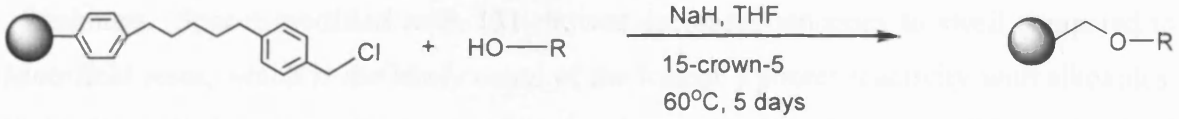


135

Fig. 20

The reactivity of ω-hydroxy-functionalised ketals with resin **131** was investigated, employing identical conditions to those applied previously in the grafting of alcohol **101-102**, **109** and **118-121** to Avecia Merrifield resin. The results obtained are summarised in Table 10. The aim was to synthesise a range of spacer-modified analogues of resins **124-130** for comparison as supports in catalysis. It was apparent, however, that resin **131** showed a decreased reactivity compared to that of the simple Avecia Merrifield resin used previously. Alcohols **119** and **120** were grafted in high, but not quantitative conversion to

give the functionalised polymer products **132** and **133**, respectively, but attempts to graft the larger alcohol **102** proceed with only very low conversion.



131 **132-134**

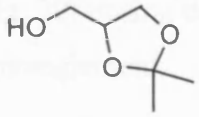
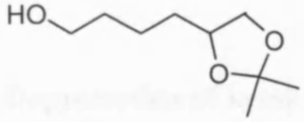
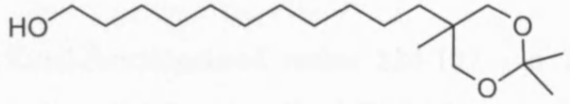
ROH	Structure	Product	Cl content of product (%)	Conversion (%)
119		**132**	0.70	81
120		**133**	0.38	90
102		**134**	3.7	1

Table 10. Grafting of alcohols to resin **131**.

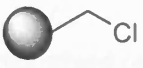
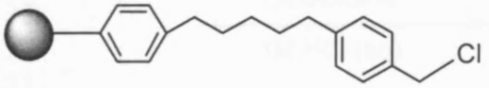
Resin	Swelling in THF (volume of 100mg of swollen beads, mL)
 (Avecia Merrifield resin)	0.85
131 	0.68

Table 11. Swelling measurements of Avecia Merrifield resin and resin **131** in THF.

It was hoped that the spacer-modified resin **131** would show improved reactivity due to the increased mobility and solution-like environment with the chloromethyl group distanced from the insoluble polymer backbone. The fact that poorer reactivity of **131**, compared to Avecia Merrifield resin, was observed has potentially been attributed to differences in morphology between the two polymers, which were obtained from separate sources and hence, not necessarily prepared in similar ways. Although the cross-linking ratio of the two resins was the same (2 % DVB in the comonomer mixture), the significant, relative differences in their swelling abilities (Table 11) are indicative of differing structures. The swelling measurements were taken by placing a known mass of dry,

unswollen beads in the barrel of a 1 mL syringe, which was plugged at one end, and recording the change in volume of the swollen beads on addition of THF after a period of 10 minutes. Spacer-modified resin **131** showed decreased tendency to swell compared to Merrifield resin, which is the likely cause of the former's poorer reactivity with alkoxides. If a resin swells less, then the pendant functional groups will be less accessible to dissolved substrates, compared to those of a resin that does swell. The reason for the inferior swelling of resin **131** is possibly due to the presence of the spacer-modified comonomer **135** (Fig. 20) during the copolymerisation process, which could lead to increased polymer chain entanglement.

2.4.3 Deprotection of ketal-functionalised resins

Ketal-functionalised resins **124-127** and **132-133** were deprotected to give the corresponding diol-functionalised PS-DVB beads **136-140** by heating to 70°C in a mixture of 1,4-dioxane and dilute hydrochloric acid (scheme 50). These conditions were employed

Ketal-functionalised resin

124
125
127
132
133

1,4-dioxane
1M HCl (aq)

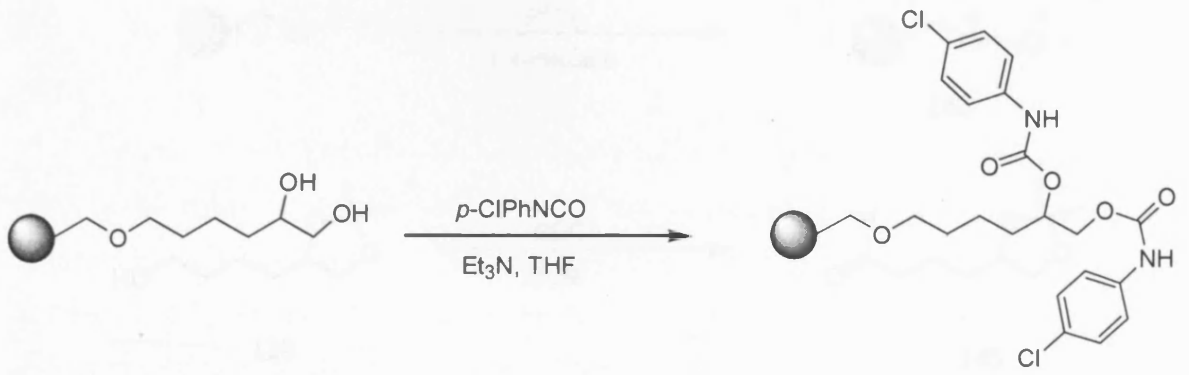
Diol-functionalised resin

136
137
138
139
140

Scheme 50

since it was found that the ketal group was not cleaved in a mixture THF and dilute hydrochloric acid at room temperature. Successful cleavage of the protecting group was confirmed by loss of methyl and quaternary carbon signals in the gel-phase ^{13}C NMR spectra of the various resins, with a simultaneous shift in the signals for the carbon atoms of the primary and secondary alcohol groups. The I.R. spectra for all the resins displayed a strong, broad absorption at ≈ 3400 cm^{-1} due to the resulting O–H functionalities.

In order to confirm the loading of the resulting diol residues on resin **125**, it was derivatised with *p*-chlorophenyl isocyanate in THF with triethylamine base to give urethane-functionalised resin **141**, suitable for chlorine and nitrogen elemental analysis



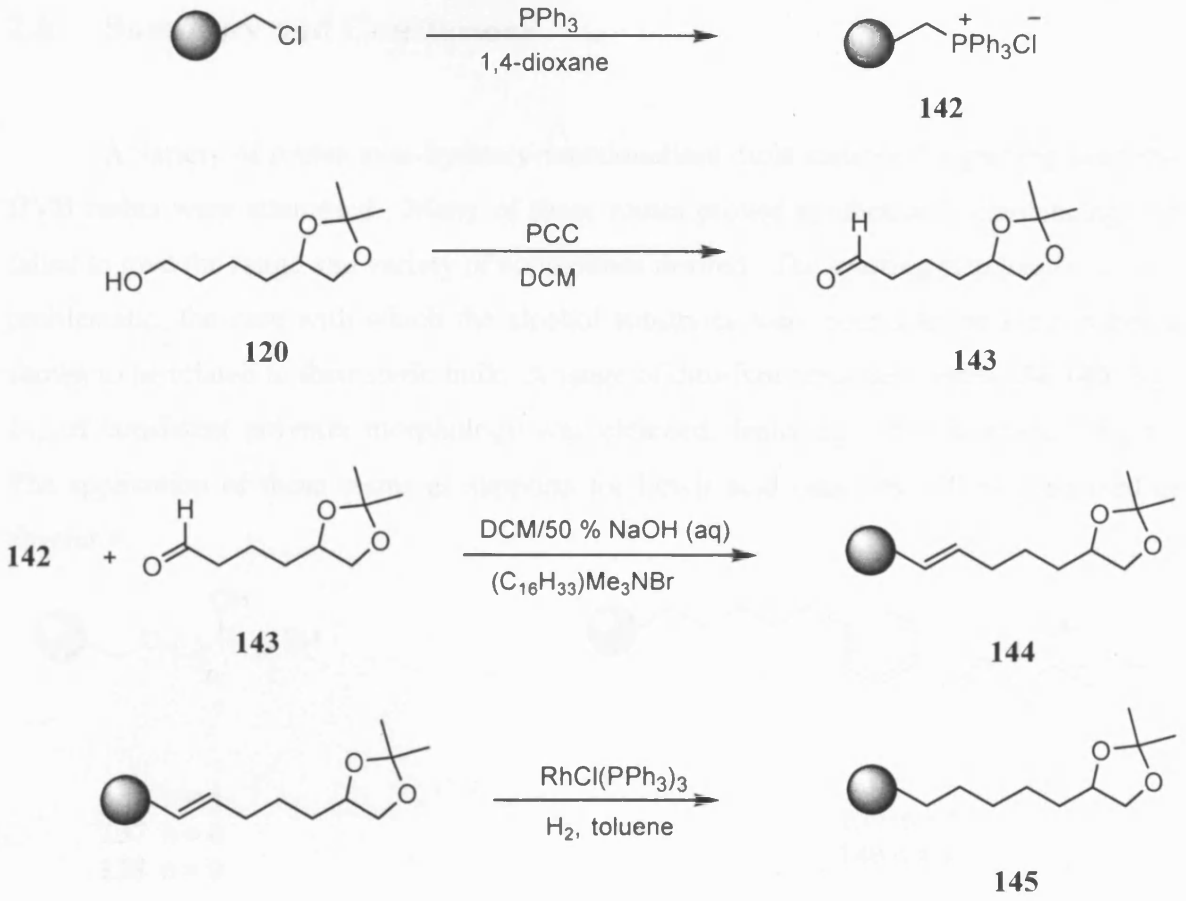
125 **141**

Scheme 51

(scheme 51). This method of derivatisation is usually successful for alcohol functionality analysis because of the clean, high yielding reaction between alcohols and isocynates to give urethanes. Elemental analysis of the resulting material, **141**, gave a chlorine content of 3.57 % and a nitrogen content of 1.35 %, which equates to an incorporation of 1.4 mmol g^{-1} of isocyanate. This corresponds to a diol loading of 0.7 mmol g^{-1} on resin **125**, or a conversion of 70 % from the starting chloromethylated resin. This technique was not used to analyse diol loadings of resins **124**, **126-130** or **132-133** due to the destructive nature of the technique and the significant uncertainty in the accuracy of values obtained, following a number of repetitions.

2.5 Attempted synthesis of a diol-functionalised resin with a carbon-carbon linker

An alternative route to an alkyl-linked diol-functionalised resin, utilizing a Wittig reaction followed by selective hydrogenation of the resulting olefin (scheme 52), has been investigated. Polymer-supported Wittig reagent **142** was prepared by reaction of chloromethylated polystyrene resin with triphenylphosphine in 1,4-dioxane. Such phosphonium salt-bearing resins have been applied previously in the tethering of aldehyde-functionalised substrates to polystyrene supports.[102-104] Conversion to the phosphonium salt **142** was quantitative as shown by phosphorous and chlorine elemental analyses, and gravimetric analysis. Phosphonium salt **142** was subsequently used in a Wittig reaction with aldehyde **143**, with conversion of **142** to its corresponding ylide achieved using a biphasic solvent system of dichloromethane/50 % aqueous sodium hydroxide, in the presence of a phase transfer catalyst (cetylammonium bromide). Analysis of the product,



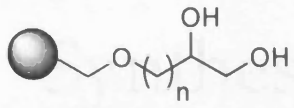
Scheme 52

olefin functionalised resin **144**, by phosphorous elemental analysis showed total removal of the Wittig reaction by-product, triphenylphosphine oxide, had been achieved upon washing of the beads. Aldehyde **143** was prepared from acetonide-protected alcohol **120** by oxidation with PCC in dichloromethane, in moderate (60 %) yield. A ketal protecting group was chosen for its high stability in the strongly basic conditions necessary for the Wittig reaction.

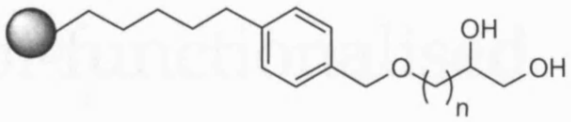
Hydrogenation of the double bond to form resin **145** was attempted using a modification of literature procedure for the homogenous hydrogenation of related olefins.[105] Thus, resin **144** was treated with Wilkinson's catalyst, $RhCl(PPh_3)_3$, in toluene under a slight pressure of H_2, at room temperature for one week. Although uptake of H_2 was observed, the polymer beads were, however, recovered as a dark brown solid, apparently contaminated with insoluble material resulting from decomposition of the metal catalyst, but still retaining the double bond (as observed by gel-phase ^{13}C NMR spectroscopy). The reaction was not repeated, however, and it may be the case that an increase in H_2 pressure or temperature is required to achieve successful hydrogenation. This alternative grafting procedure was not followed up.

2.6 Summary and Conclusions

A variety of routes to ω-hydroxy-functionalised diols suitable for grafting onto PS-DVB resins were attempted. Many of these routes proved synthetically challenging and failed to give the range and variety of compounds desired. The grafting step itself was also problematic, the ease with which the alcohol substrates were bound to the support being shown to be related to their steric bulk. A range of diol-functionalised resins **136-140** (Fig. 21) of consistent polymer morphology was obtained, featuring different spacer lengths. The application of these resins as supports for Lewis acid catalysts will be discussed in chapter 4.



136 n = 1
137 n = 4
138 n = 9



139 n = 1
140 n = 4

Fig. 21

Chapter 3

Synthesis of diol-functionalised PS-DVB resins *via* asymmetric dihydroxylation

3.1 Introduction

As was discussed in chapter 1, chiral diols have found use as ligands for catalysts that have been used in both asymmetric Diels-Alder reactions and additions of dialkylzinc reagents to aldehydes. In these processes, chiral diols were chosen for their ability to form rigid, cyclic dialkoxide complexes with Lewis acids, leading to rigid conformations in transition states and often good enantioselectivities. Additionally, the increased Lewis acidity, resulting from the presence of the strongly electron-withdrawing alkoxide ligands, enhances selectivity.

The development of polymer-supported variants of these types of oxygen-based ligands has focused, to some considerable extent, on the preparation of immobilised 1,4-diol-functionalised TADDOLs (see section **1.8.2**). This is due, in part, to the availability and ease of further functionalisation of enantiopure tartrate esters from which TADDOL ligands are derived.

In contrast, examples of chiral 1,2-diols bound to polymer supports (*e.g.* Fig. 22) are comparatively rare. In this chapter the synthesis of some novel PS-DVB resins functionalised by this type of moiety will be discussed. In the strategies examined, use is made of the well-established asymmetric dihydroxylation (AD) process to introduce the chiral diol.

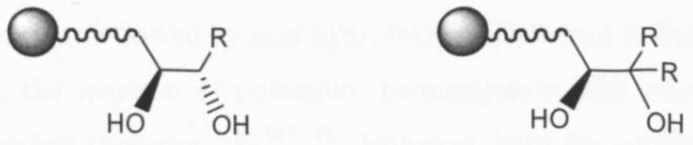
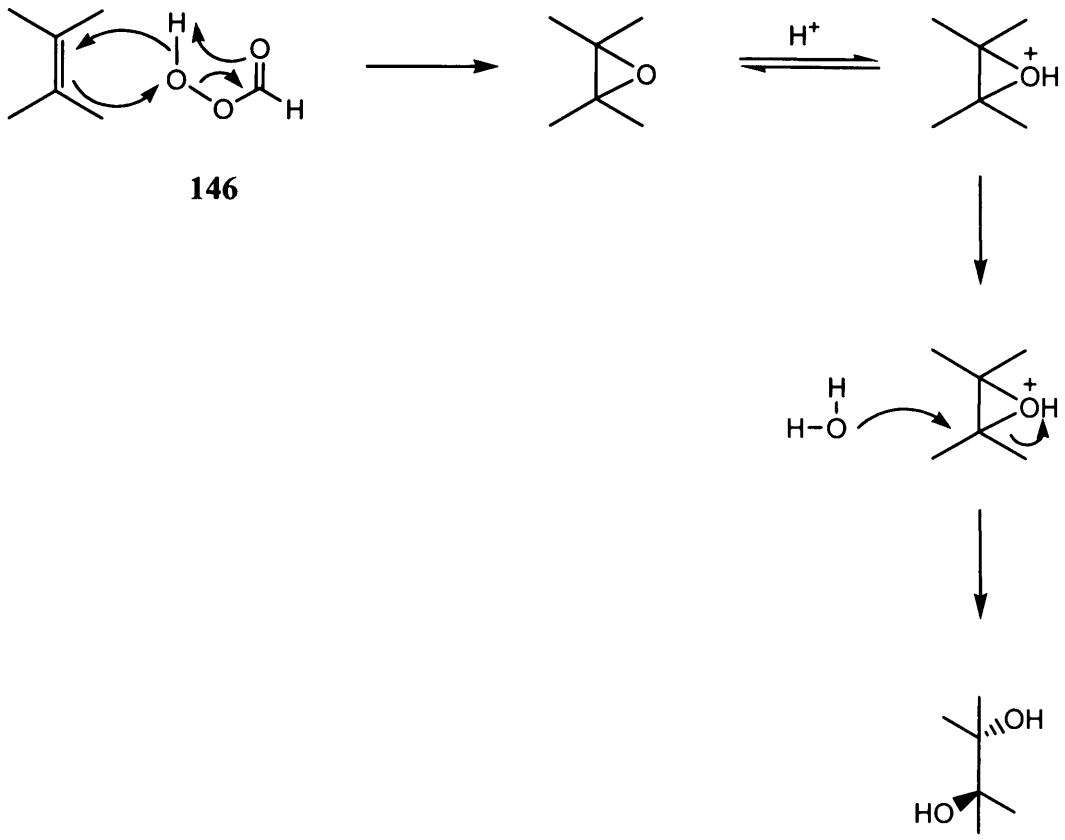


Fig. 22

3.2 Dihydroxylation of alkenes

The dihydroxylation of alkenes, where two hydroxyl groups are added to the double bond to form a 1,2-diol (scheme 53), can be carried out using a variety of oxidizing agents. Two of the more common oxidizing agents used to perform this transformation are peroxy acids (*e.g.* peroxyformic acid **146**) and cold, alkaline potassium permanganate ($KMnO_4$).[106]

Scheme 53

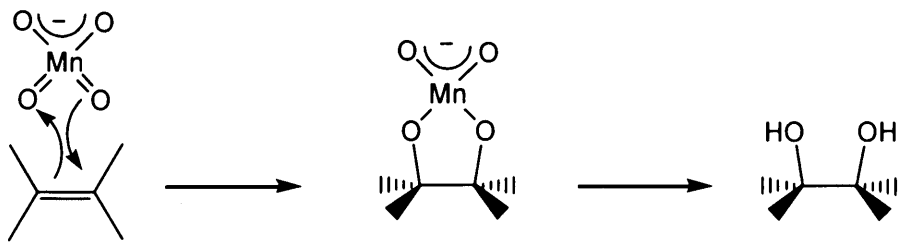


146

Scheme 54

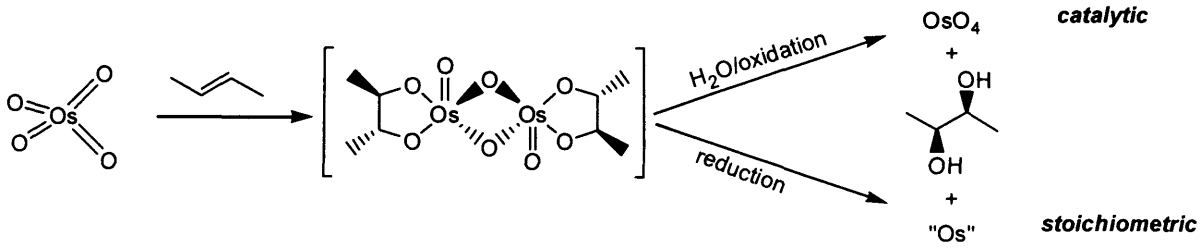
The dihydroxylation of alkenes by peroxy acids gives 1,2-diol products with *anti* configuration relative to the carbon-carbon double bond. The reaction proceeds *via* formation of an epoxide, followed by acid hydrolysis as illustrated in Scheme 54.

In contrast, the reaction of potassium permanganate with alkenes gives the *syn* dihydroxylation product (Scheme 55).[107-110] However, here the conditions must be mild and carefully controlled to prevent this powerful oxidizing agent from over-oxidizing the substrate. The application of heat or use of acidic conditions can cause further oxidation of the diol and cleavage of the carbon-carbon bond. Yields of the desired diol are rarely over 50 %, though they can be improved in biphasic systems employing phase-transfer catalysts such as crown ethers or alkyl ammonium salts.[111-112] The reaction proceeds through the formation of a cyclic manganese (V) intermediate **147**, which is unstable and rapidly



147

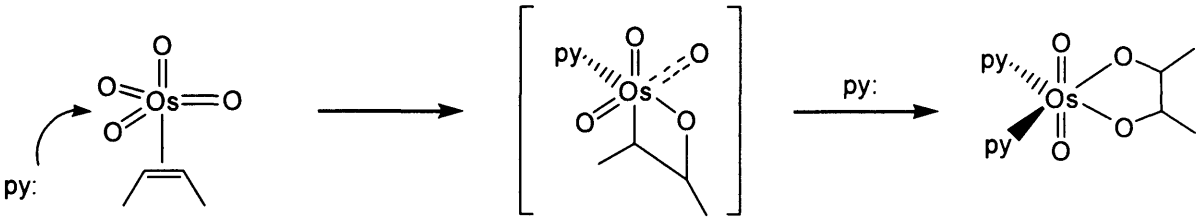
Scheme 55



Scheme 56

hydrolyses at both C—O—Mn bonds to give the desired hydroxylation product.

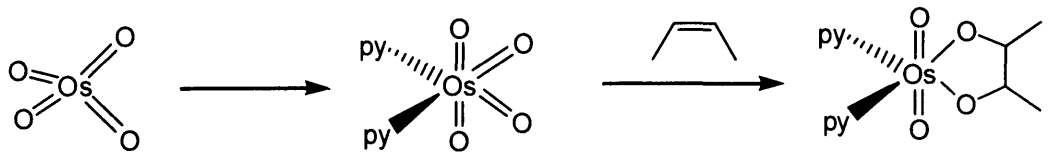
A more widely used method of dihydroxylation of alkenes that gives the diol product with *syn* stereochemistry, employs osmium tetroxide (OsO_4) (osmylation, scheme 56).[112] Osmium tetroxide reacts with olefins to initially give dimeric osmium (VI) glycolates (an oxo-bridged dimer), which can subsequently react further to give the diol product. The stoichiometric process shown in scheme 56 is not ideal, due to the high toxicity and cost of osmium. With this in mind, methods were developed that are catalytic with respect to osmium, by adding a stoichiometric amount of an inexpensive secondary oxidant to reoxidise the osmium. Reoxidants, which have been successfully used, include *tert*-butyl hydroperoxide in the presence of Et_4NOH,[114] *N*-methylmorpholine *N*-oxide (NMO, The Upjohn process),[115-116] potassium hexacyanoferrate (III)[117-118] and oxygen.[119]



148

Scheme 57

Osmate esters isolated from the reaction of an alkene with OsO_4 in the presence of pyridine (py) often have two molecules of py bound to the metal centre (scheme 57).[120-121] This has been explained by Sharpless who proposed that coordination of one pyridine to an



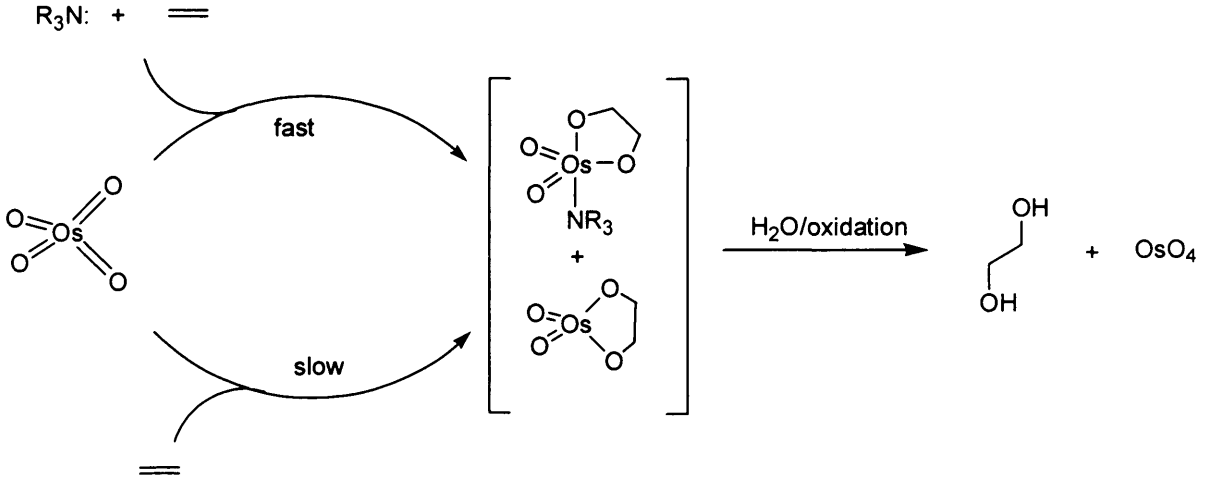
149

Scheme 58

osmium-olefin complex induces the formation of an oxa-metallacycle (**148**) intermediate. This idea has been supported by a frontier orbital study on the reaction of olefins with OsO_4.[122] It revealed that direct reaction of an olefin with OsO_4 would result in a highly disfavoured d^2 tetrahedral complex. Thus, the role of the amine is to generate an octahedral complex (scheme 58, **149**) in which the equatorial O-atoms are physically closer together and hence electronically activated. Both the HOMO and LUMO of the adduct have the correct symmetry to interact with the π and π^* orbitals of the olefin; thus the reaction can be viewed as a concerted [3+2] cycloaddition.

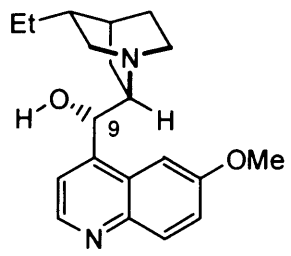
3.3 Catalytic asymmetric dihydroxylation (AD)[123-124]

The development of the asymmetric dihydroxylation (AD) reaction arose directly from the discovery that the stoichiometric reaction of OsO_4 with olefins was considerably accelerated by the addition of pyridine (as illustrated above). Following the achievement of catalytic dihydroxylation, it was thought that this ligand acceleration effect[125] could be combined with a chiral influence, namely using a chiral base, to promote the reaction through a pathway involving a chiral catalyst (scheme 59). It was hoped that this could influence the favoured sense of approach of the olefin to the osmium species, by differentiating between its two prochiral faces and hence, lead to the preferential formation of one enantiomer of the chiral diol product.

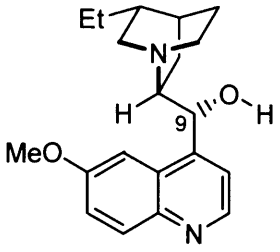


Scheme 59

Attempts to use chiral pyridine-based ligands failed because of weak binding of these ligands to osmium tetroxide, as a result of steric hindrance close to the reacting centre.[121] On the other hand, the use of more strongly-binding chiral bidentate diamine



150 dihydroquinidine (DHQD)

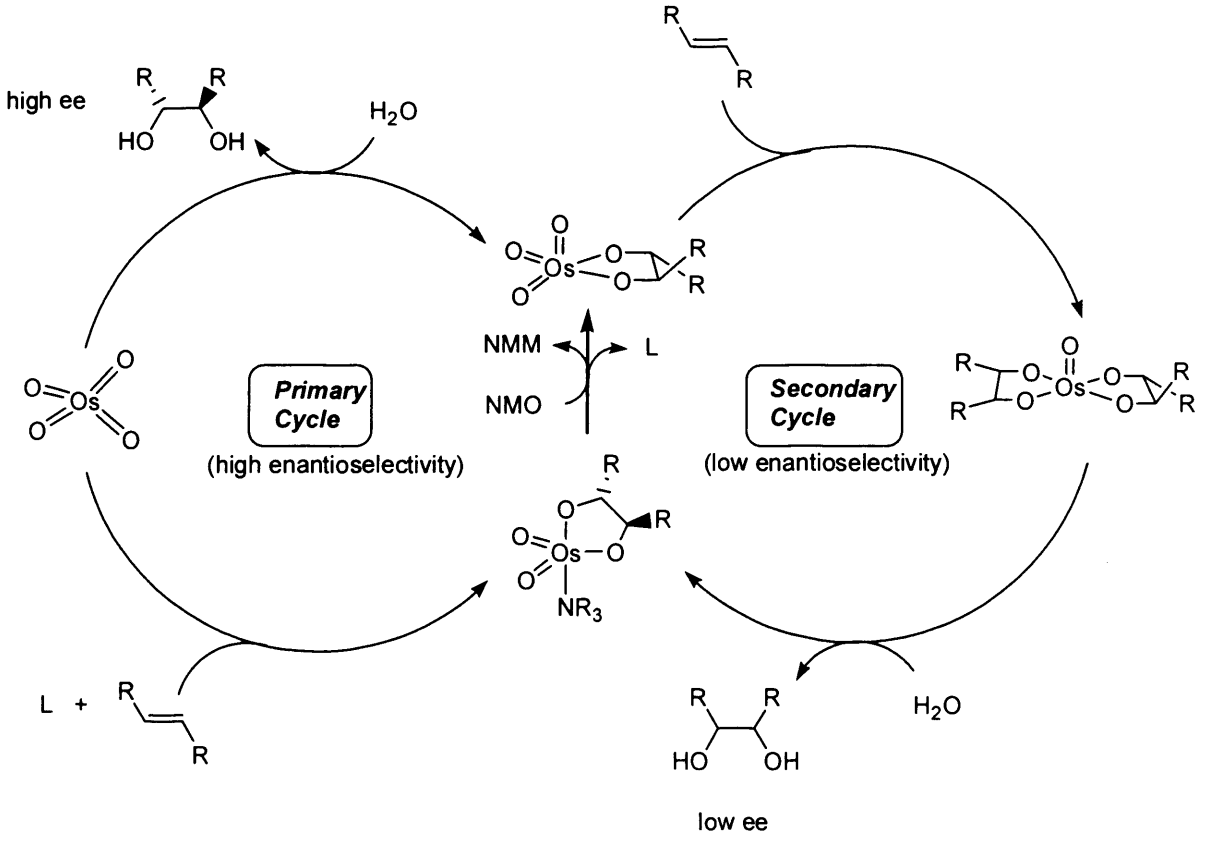


151 dihydroquinine (DHQ)

Fig. 23

ligands has only been successful in stoichiometric asymmetric reactions due to the formation of very stable chelate complexes with the osmium (VI) glycolate intermediates. This inhibited hydrolysis of these intermediates preventing *in situ* regeneration of the osmium.[126-127]

The first breakthroughs in obtaining optically active diols in a catalytic AD reaction were reported when quinuclidine derivatives, such as cinchona alkaloids **150** and **151** (Fig. 23), were used. The most successful ligands for AD that have been developed since then are derived from these diastereomeric cinchona alkaloids, dihydroquinidine (DHQD, **150**)

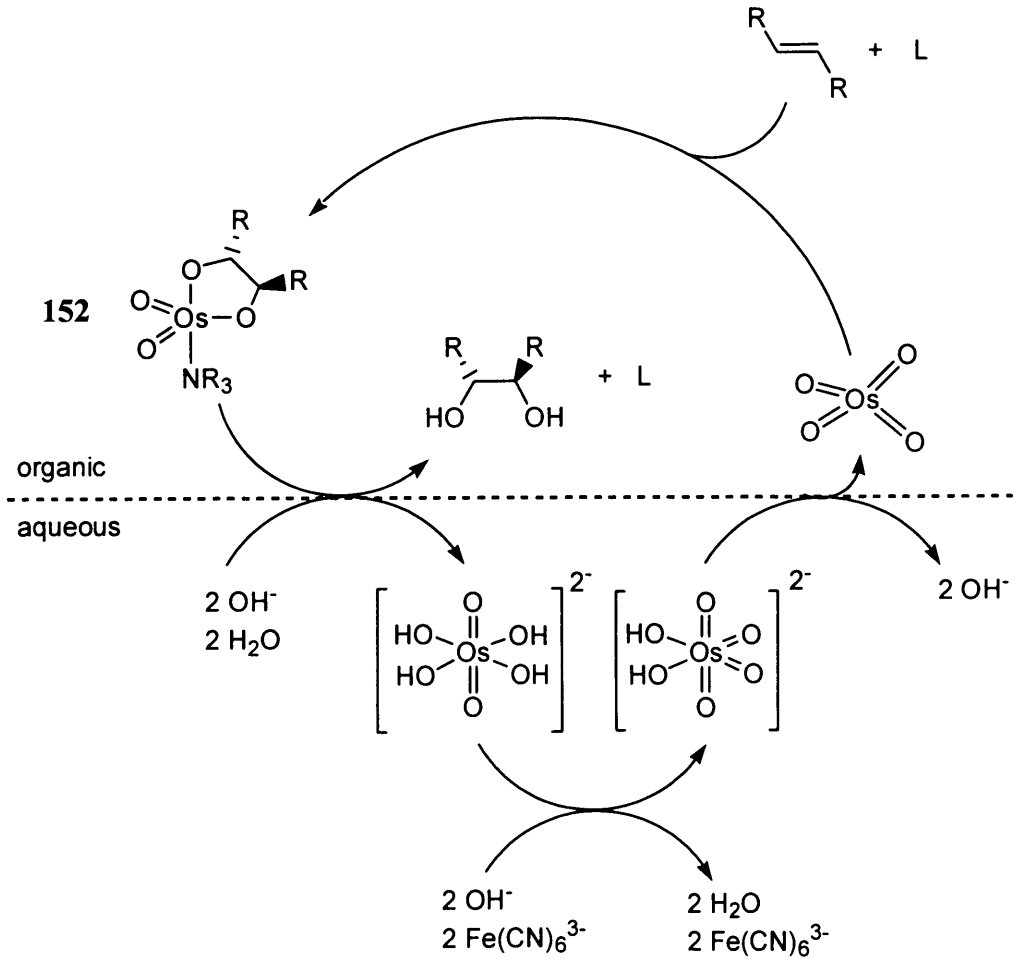


Scheme 60

and dihydroquinine (DHQ, **151**).[123] These "pseudoenantiomeric" ligands lead to diols of opposite absolute configuration in AD reactions. Several hundred derivatives of these two ligands have been screened, differing primarily in the nature of the O9 substituent of the backbone. Changing the functional group at this particular position was found to induce the most significant effects upon the enantioselectivity in subsequent AD reactions.

Initially, derivatives of cinchona alkaloids **150** and **151** were used in stoichiometric AD reactions, affording diols with high ee's. The process was made catalytic by the addition of NMO as a secondary oxidant,[128] but this led to a slight decrease in the observed ee's, compared to the stoichiometric reaction. This was attributed to a competing non-selective catalytic cycle (scheme 60).[129]

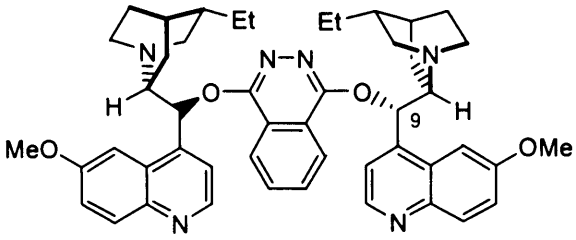
Three key discoveries led to the development of the AD reaction as a useful tool for converting almost any olefin into a chiral diol in high ee. The first was the use of $K_3Fe(CN)_6$ as the stoichiometric reoxidant in biphasic reactions.[130] This ensures that OsO_4 is the sole oxidant in the organic phase, eliminating the possibility of entering the second catalytic cycle, something that occurs with the homogenous reaction involving NMO (scheme 60). Osmylation takes place in the organic layer forming the osmium (VI) monoglycolate ester **152** (scheme 61). Hydrolysis of **152** leaves the diol product and



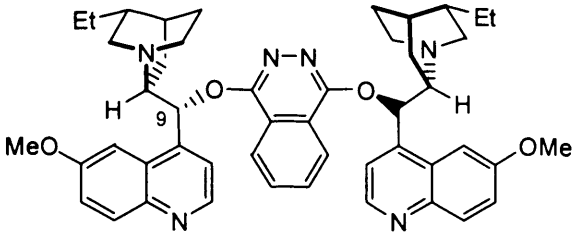
Scheme 61

alkaloid ligand in the organic phase with the osmium (VI) species transferred to the aqueous phase before reoxidation can occur. The osmium glycolate is therefore prevented from entering the detrimental second catalytic cycle.

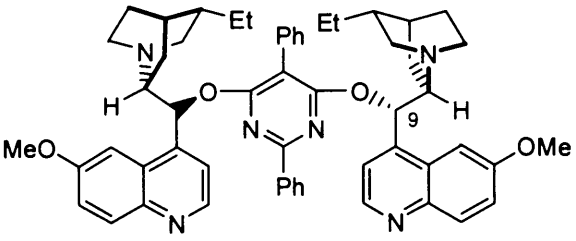
The second discovery was that methane sulfonamide ($MeSO_2NH_2$) greatly increases the rate of hydrolysis of the osmium (VI) glycolate intermediate.[131] For non-terminal olefins, and especially tri- and tetra-substituted olefins, the hydrolysis step is catalyst turnover-limiting. In these cases, addition of $MeSO_2NH_2$ led to far shorter reaction times and enabled reactions to be conducted at 0°C, lower temperatures generally being beneficial for enhanced selectivity.[132]



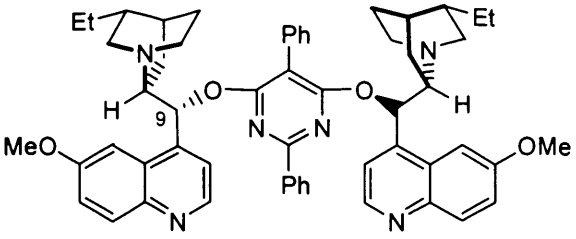
153 $(DHQD)_2$-PHAL



154 $(DHD)_2$-PHAL



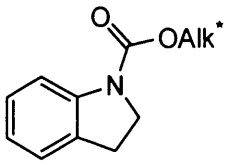
155 $(DHQD)_2$-PYR



156 $(DHD)_2$-PYR

Fig. 24

The third advancement was in the use of ligands containing two cinchona alkaloid units linked together at the O9 position by heterocyclic spacer units.[123] The most notable example of these types of ligand are $(DHQD)_2PHAL$ (**153**)[131] and $(DHQ)_2PHAL$ (**154**),[133] where the alkaloids are linked by a phthalazine, and the $(DHQD)_2PYR$ (**155**) and



157 IND-class
(Alk^* = DHQD, DHQ)

Fig. 25

$(DHQ)_2PYR$ (**156**) class of ligand, featuring a pyrimidine-based linker (Fig. 24). The use of these dimeric ligands **153-156** generally gave better selectivity and were found to be useful for a wider range of olefin substrates. They were shown to be the ligands of choice in the AD reactions of five of the six classes of olefins (table 12).[123] For only one class, namely *cis*-olefins, is a different ligand (non-dimeric indoline-based {IND}ligands **157**, Fig 25) required to achieve optimal enantioselectivity.[133]

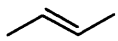
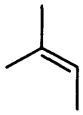
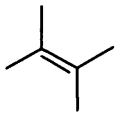
Olefin class	Preferred ligand class	ee range (%)
	PHAL PYR	30-97
	PHAL	70-97
	IND	20-80
	PHAL	90-99.8
	PHAL	90-99
	PHAL PYR	20-97

Table 12

The PHAL class of ligands (**153** and **154**) are preferred in AD reactions of 1,1- and 1,2-*trans*- di- and also tri-substituted olefins. It is this class of ligand that is found in the commercially available 'AD-mixes' – a convenient source of AD reagents ready-mixed in the correct proportions. 'AD-mix-α' contains $(DHQ)_2$-PHAL, while 'AD-mix-β' contains $(DHQD)_2$-PHAL, both in addition to K_2CO_3, $K_3Fe(CN)_6$ and $K_2OsO_4.2H_2O$, a non-volatile source of OsO_4.

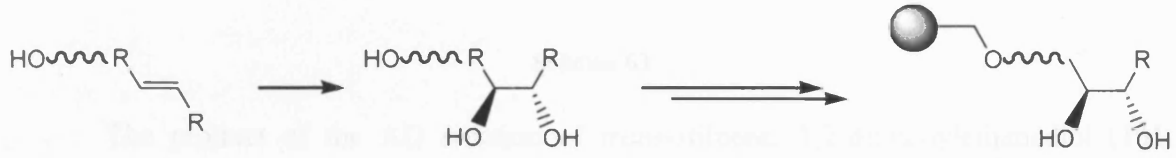
The source of the enantioselectivity that is achieved in the AD reactions with these dimeric ligands has been shown to be due to a binding site in their structure which hosts the olefin substrate.[123] A recent study has shown that the two alkaloid units of the PHAL- and PYR-type ligands do not operate in concert, but have differing functions.[135] One alkaloid is directly involved in the reaction with OsO_4 and the olefin, while the second, in combination with the heterocyclic spacer, provides a chiral binding pocket for the olefin. The orientation of the olefin within the binding pocket is well controlled, particularly for

olefins with an aryl substituent, due to favourable parallel π-stacking interactions that occur with the phthalazine or pyrimidine rings.[123]

3.4 Synthesis of diol-functionalised resins by AD / grafting routes

3.4.1 Synthetic strategy

A possible strategy for the synthesis of diol-functionalised PS-DVB resins of general structure **160,** featuring pendant chiral 1,2-diol groups, which exploits the high



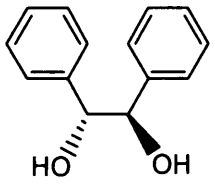
158 **159** **160**

Scheme 62

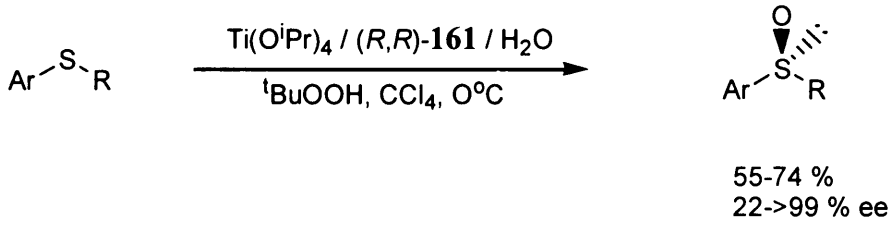
stereoselectivity of the AD reaction described in section **3.3**, is outlined in scheme 62. The strategy is to use the conventional solution phase AD reaction to synthesise compounds **159** suitable for subsequent grafting onto chloromethylated PS-DVB beads. As in chapter 2, grafting of alcohols was desired in order to form an ether linker to the support, as these were deemed to be relatively unreactive, and robust, in comparison with other tethering methods.

3.4.2 Synthesis of diol-functionalised resins *via* solution-phase AD of *trans*-stilbenes

Initially, routes that proceeded *via* AD of a *trans*-stilbene-based substrate to form chiral 1,2-diarylethanediols were investigated. *trans*-Stilbenes are known to be excellent substrates for the AD reaction, providing almost a perfect match with the ideal requirements of the PHAL and PYR ligands for the binding of olefins in the catalytic site.[123] The AD of *trans*-stilbene performs the best of any substrate known, with transformation to the diol occurring in 99 % yield and 99.8 % ee using $(DHQD)_2$-PHAL ligand (**153**) under standard AD conditions.[131]



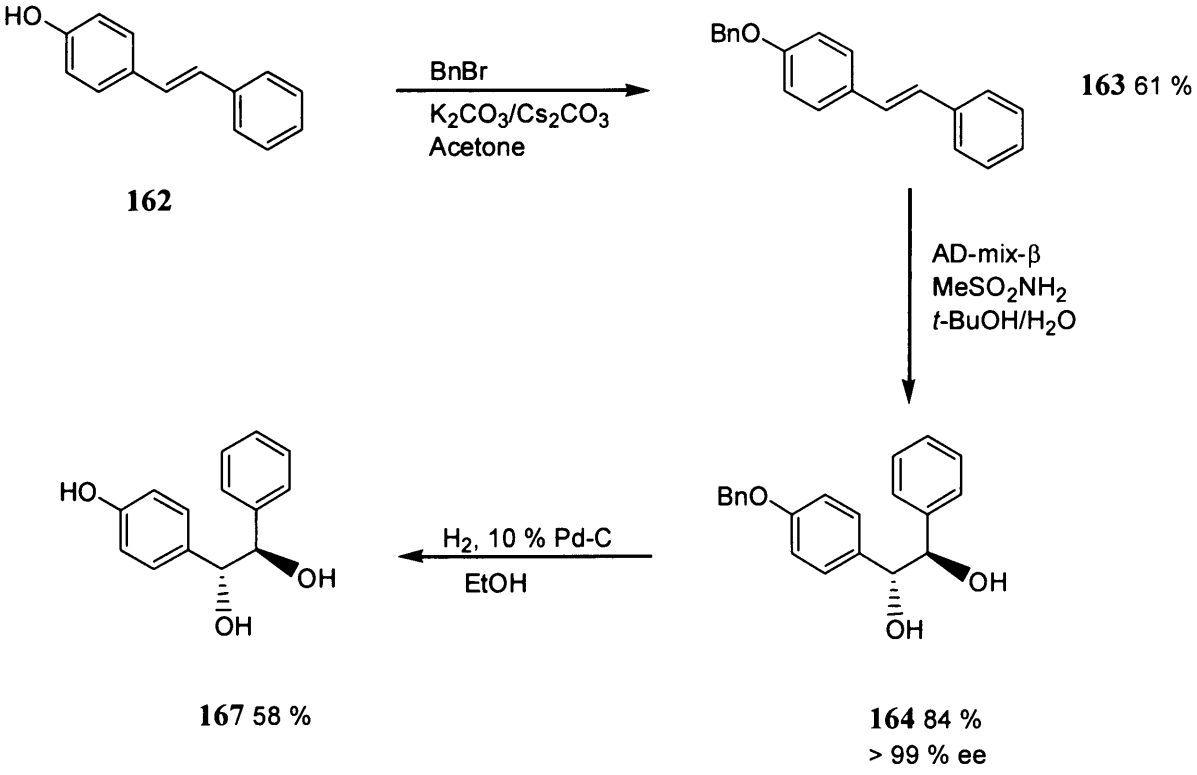
(*R*,*R*)-**161**



Scheme 63

The product of the AD reaction of *trans*-stilbene, 1,2-diphenylethanediol (**161,** scheme 63), has been applied as a chiral ligand for catalysts and auxiliaries in the asymmetric Diels-Alder reaction[48] and diethylzinc addition to aldehydes.[65] It has also been shown to be an effective ligand in the catalytic asymmetric oxidation of aryl sulfides (scheme 63).[136] Here diol (*R*),(*R*)-**161** was heated with Ti(O^{i}Pr)$_4$ and H_2O to give a chiral titanium complex that catalysed the synthesis of optically active sulfoxides by asymmetric oxidation of prochiral sulfides with ee's up to 99 %.

A convenient precursor to 1,2-diarylethanediols suitable for grafting to PS-DVB



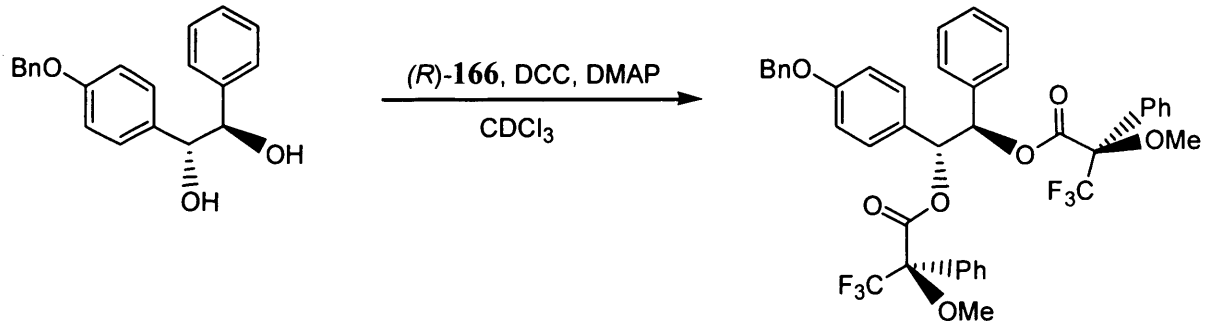
Scheme 64

beads was commercially available *p*-hydroxystilbene **162** (scheme 64). A 1,2-diol derived from this *trans*-stilbene could either be grafted directly onto chloromethylated polystyrene by etherification of the phenol, or *via* an incorporated ω-hydroxy-functionalised spacer group.

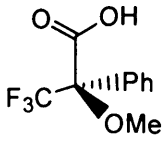
For the first of these options, namely direct grafting by reaction of the phenol hydroxy group with the resin, it was necessary to protect the acidic phenol with a base-stable protecting group due to the basic conditions necessary for the later AD reaction. Therefore, *p*-hydroxystilbene (**162**) was converted to benzyl aryl ether **163** by reaction with benzyl bromide in acetone using a mixture of K_2CO_3, and a catalytic amount of Cs_2CO_3, as the base (scheme 64). Ether **163** was obtained in moderate (61 %) yield, the remainder being unreacted phenol.

Dihydroxylation of **163** was conducted under standard AD conditions[130] using AD-mix-β, containing the $(DHQD)_2$-PHAL ligand (**153**). One equivalent of methane sulfonamide was added to accelerate the rate of osmate (VI) ester hydrolysis, as is routine in the AD of non-terminal olefins.[132] The reaction was carried out in a 1:1 mixture of *tert*-butanol/H_2O at 0°C for 24 hrs and gave the diol product **164** in 84 % yield. The ^1H NMR spectrum of **164** exhibited an AB coupling system for the two doublets of the methine protons of the diol, with the signal appearing as a pseudo-quartet at 4.75 ppm ($^3J_{HH}$ = 7.4).

The enantiomeric excess of product **164** was determined by ^1H and ^{19}F NMR analysis of its bis(Mosher's ester) **165**.[137] This was prepared by treating **164** with (*R*)-(+)-α-methoxy-α-(trifluoromethyl) phenyl acetic acid **166** in the presence of DCC and a catalytic quantity of DMAP (scheme 65). By both ^{19}F and ^1H NMR spectroscopy, only one diastereomer was detected. Thus, it is reasonable to suggest that, as expected for a



164 **165**



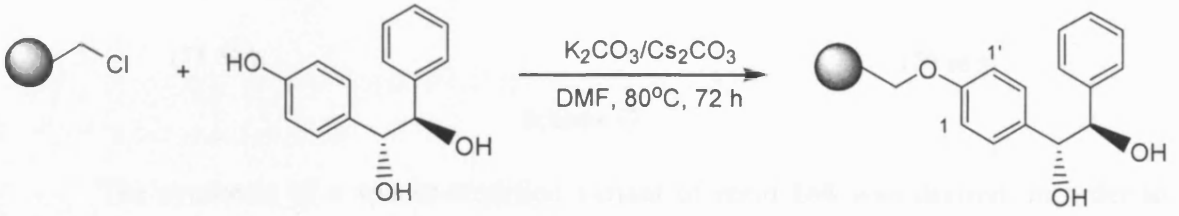
(*R*)-(+)-α-methoxy-α-(trifluoromethyl) phenyl acetic acid

(*R*)-**166**

Scheme 65

stilbene, the product **164** was obtained in high ee. The absolute configuration of the diol was not determined, however it was predicted to be the (*R*),(*R*)-diol using Sharpless' mnemonic predicting device.[123]

Removal of the benzyl protecting group to regenerate the phenol (**167**) was achieved by hydrogenation in absolute ethanol, using 10 % palladium on charcoal as the catalyst (scheme 64). The isolated yield of **167** from **164** was moderate (58 %). Grafting of **167** to chloromethylated PS-DVB beads *via* deprotonation of the phenol hydroxyl group selectively over the aliphatic hydroxyl groups was attempted in a reaction employing one equivalent of sodium hydride, in THF in the presence of 15-crown-5. However no etherification of the support was observed.

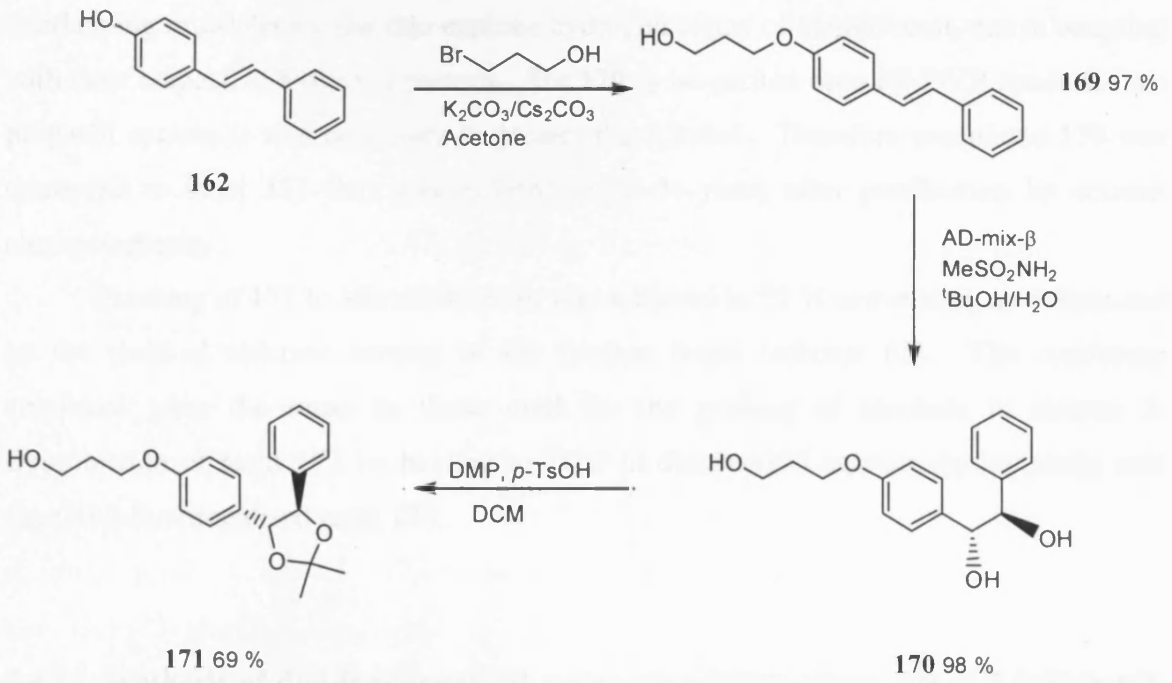


167 **168**

Scheme 66

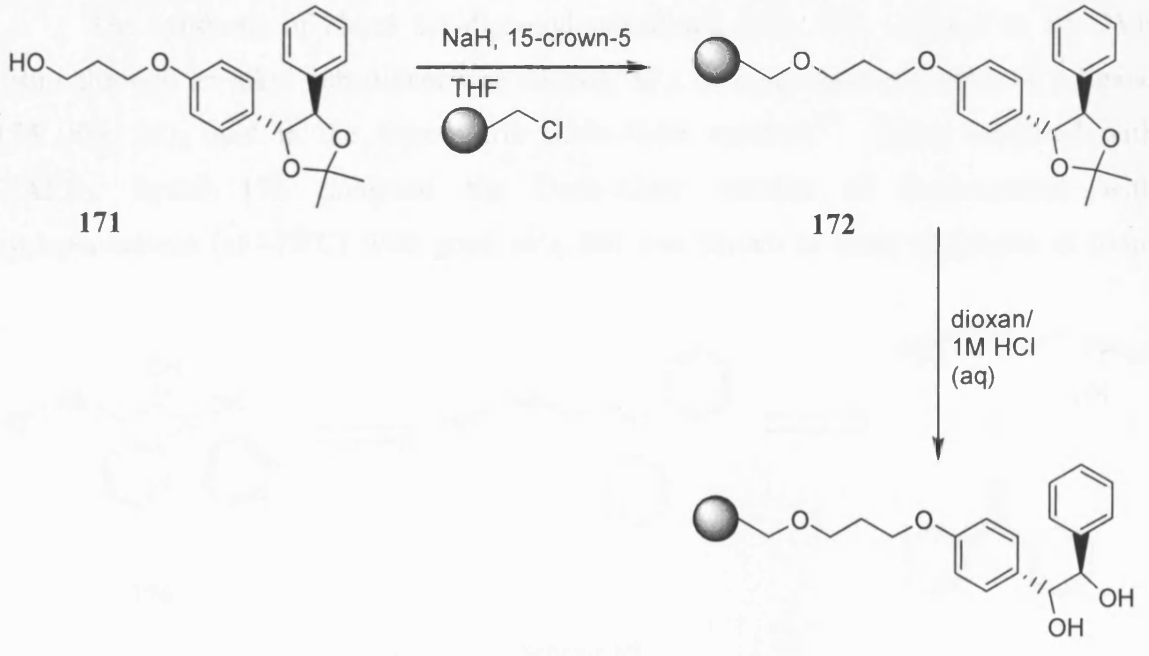
In a second attempt to bring about the formation of the desired ether, phenol **167** was reacted with chloromethylated polystyrene in the presence of excess K_2CO_3 base and a catalytic quantity of Cs_2CO_3 (scheme 66). The reaction was performed in DMF at 80°C for 3 days and resulted in a polymer product that was shown by elemental analysis to have a chlorine content of 0.59 %. This equates to an 85 % yield in the etherification of chloromethyl groups to give resin **168**. Gel-phase ^{13}C NMR spectroscopy confirmed the presence of an aryl benzyl ether bound to the resin, exhibiting a signal at 115.1 ppm for the *ortho*-carbon atoms C1 and C1' of the benzyloxy-substituted aryl group. In addition, a broad peak was observed at 78.8 ppm that was attributed to unresolved signals from the two alcohol-bearing carbon atoms.

The grafting success that resulted from using K_2CO_3/Cs_2CO_3 as the base in contrast to NaH/15-crown-5, is most likely to be due to being able to employ an excess of base, since milder K_2CO_3 will not deprotonate the hydroxyl groups of the diol, and cause unwanted competing side reactions. The change of solvent from THF to DMF may also have been beneficial, by increasing the amount of the sparingly soluble phenol that was in solution and allowing a higher temperature to be used.



Scheme 67

The synthesis of a spacer-modified variant of resin **168** was desired, in order to distance the diol from the insoluble polymer matrix. The synthetic route by which this was achieved is shown in scheme 67. *p*-Hydroxystilbene (**162**) was alkylated by reaction with 3-bromopropan-1-ol in acetone, again with K_2CO_3/Cs_2CO_3 used as the base. This enabled the introduction of an ω-hydroxy-functionalised tether in the *para* position of the *trans*-stilbene. The yield of **169** obtained was high (97 %). The AD reaction of **169** proceeded in near quantitative yield to give 1,2-diol **170**. The product **170** was found to be only sparingly soluble in chloroform. The ^1H NMR spectrum in dry DMSO showed an

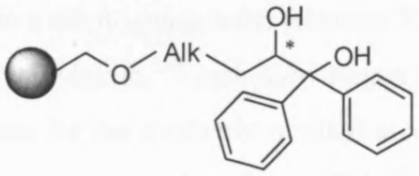


Scheme 68

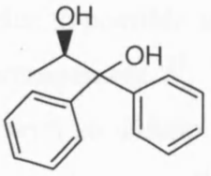
overlapping multiplet for the two methine hydrogen atoms of the diol unit, due to coupling with their respective hydroxyl protons. For **170** to be grafted onto PS-DVB beads *via* the propanol spacer, it was necessary to protect the 1,2-diol. Therefore compound **170** was converted to ketal **171** that was isolated in 69 % yield, after purification by column chromatography.

Grafting of **171** to Merrifield resin was achieved in 93 % conversion, as determined by the residual chlorine content of the product beads (scheme 68). The conditions employed were the same as those used for the grafting of alcohols in chapter 2. Deprotection of resin **172** by heating to 70°C in dioxane/1M aqueous hydrochloric acid gave diol-functionalised resin **173**.

3.4.3 Synthesis of diol-functionalised resins *via* solution-phase AD of 1,1-diphenyl-substituted olefins



174

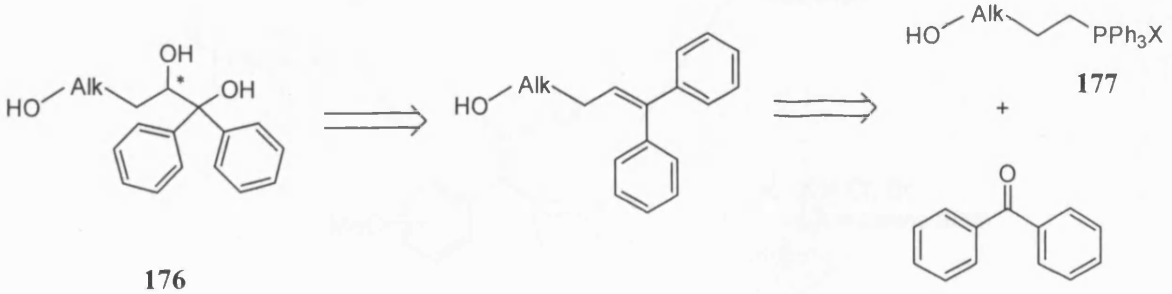


175

Alk = alkyl or alkyl/aryl spacer

Fig. 26

The synthesis of chiral 1,1-diphenyl-substituted diols **174**, tethered to PS-DVB resins through an alkyl substituent was desired, as a heterogenised analogue of a ligand **175** (Fig. 26), used in the asymmetric Diels-Alder reaction.[47] When modified with $EtAlCl_2$, ligand **175** catalysed the Diels-Alder reaction of methacrolein with cyclopentadiene (at –78°C) with good ee's, but was shown to form oligomers at room



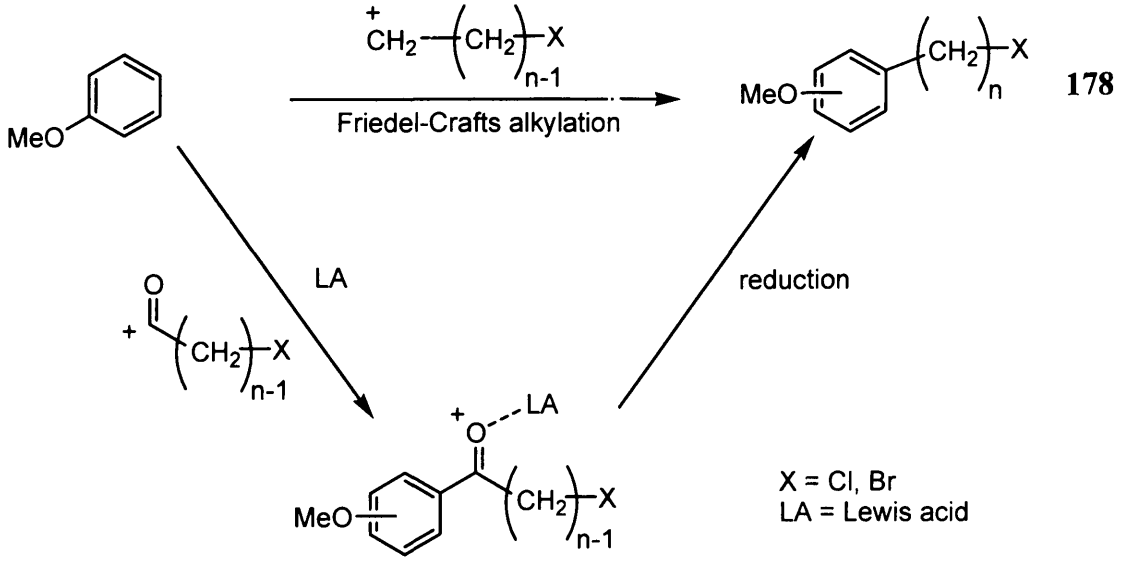
176

Scheme 69

temperature or with extended periods of time, resulting in a catalyst of that gave decreased enantioselectivity. It was hoped that by immobilisation of ligands of type **175** on a polymer support, their utility as ligands for catalysis might be enhanced, since oligomerisation of the corresponding metal complexes should be inhibited.

Retrosynthetic analysis of diol **176** gave a route for its preparation, proceeding *via* a combination of a Wittig reaction and an asymmetric dihydroxylation (scheme 69). The phosphonium salt substrate **177** was required to have a remote hydroxyl functionality, suitable for etherification by reaction with chloromethylated polystyrene. Due to the lack of commercially available α,ω-haloalcohols, a route was proposed employing a Friedel-Crafts alkylation reaction to give a *para*-substituted anisole (**178**, scheme 70), from which a phenol could be derived. The polymer-grafting of compounds containing both phenol and aliphatic alcohol functionalities selectively, by using a mild base (K_2CO_3), was described in section **3.4.2**. This strategy avoids steps necessary to protect/deprotect the diol.

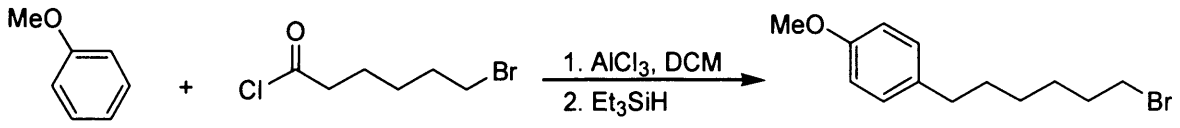
Synthesis of compounds **178** by means of a conventional Friedel-Crafts alkylation starting from a dihalogenoalkane (scheme 70), is problematic due to possible side-reactions such as polyalkylation,[138] carbon/hydrogen migration and rearrangement.[139] However, an efficient route for the synthesis of alkyl aromatic compounds with an ω-halo functionality (**178**), has been reported (scheme 70).[140] The method proceeds *via* a Friedel-Crafts acylation, which is more chemoselective than the corresponding type of alkylation due to formation of the product Lewis acid-base adducts **179**. These are less reactive than either the starting aromatic compound or the acylium ion, formed from the acyl halide and Lewis acid. Intermediate **179**, which is therefore deactivated towards further acylation, can be



179

Scheme 70

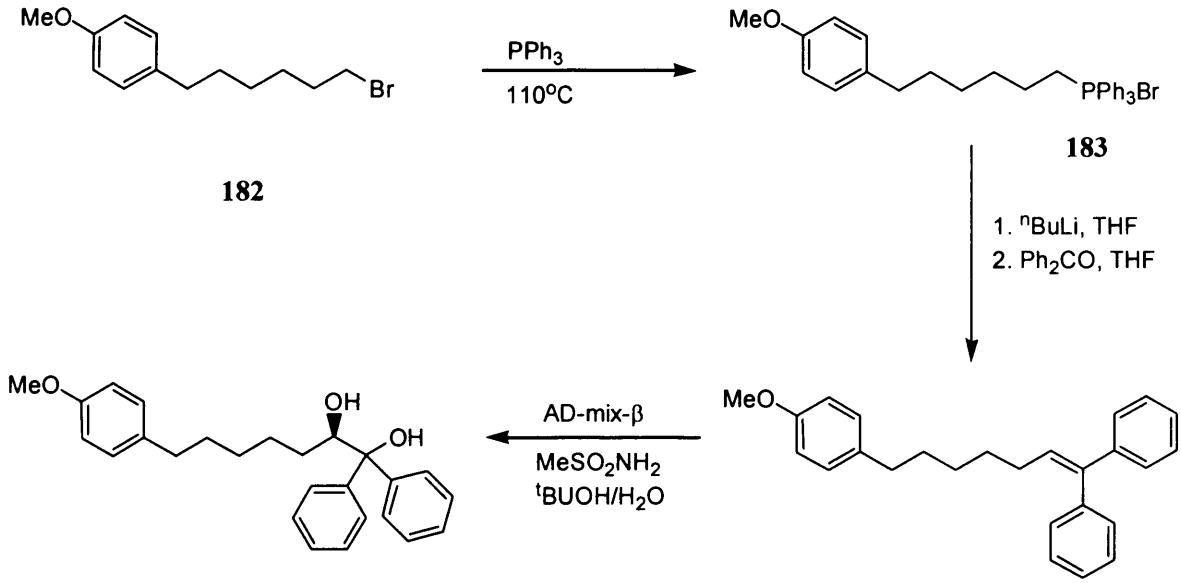
reduced *in situ* by a source of hydride to give the desired alkylated product.



180 **181** **182** 82 %

Scheme 71

Anisole (**180**), which possesses an *ortho*- and *para*-directing methoxy group, was acylated with 6-bromohexanoyl chloride (**181**) in the presence of aluminium chloride (scheme 71). The reaction mixture was subsequently treated *in situ* with triethylsilane, to give the alkylated product **182** in 82 % yield. Analysis by ^1H NMR spectroscopy confirmed the formation of only the *para*-substituted aryl product, a clearly-resolved AA'XX' system being observed in the aromatic region. No *ortho*-substituted product was observed.

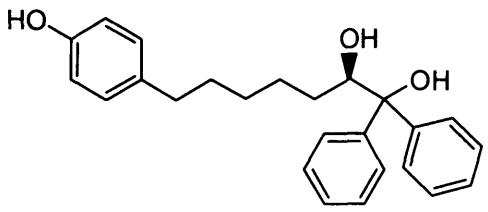


182 **183**

185 95 % **184** 20 %

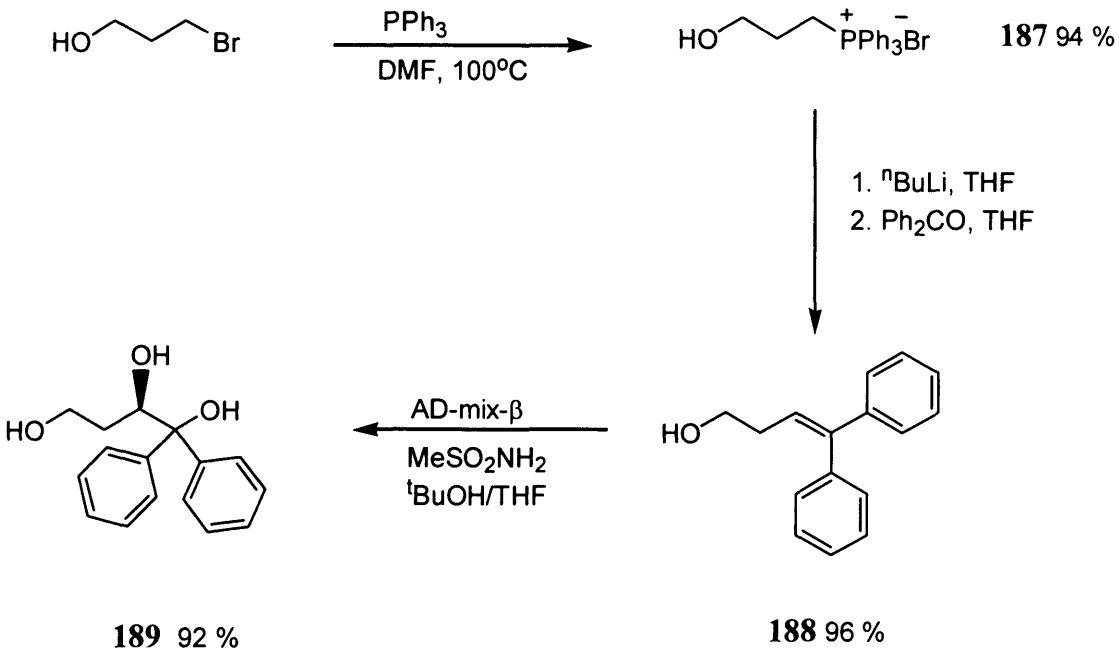
Scheme 72

Alkyl bromide **182** was converted to phosphonium salt **183** and used directly in a Wittig reaction with benzophenone, using *n*-butyl lithium to form the ylide. The 1,1-diphenyl-substituted olefin **184** was obtained in low overall yield (20 %, based on **181**), after purification by column chromatography. Olefin **184** was dihydroxylated using standard AD conditions, to give the chiral diol **185** in 95 % yield. However, attempts to form its corresponding phenol **186** (Fig. 27) by removal of the methoxy protecting group, using BBr_3, failed to give any of the desired product.



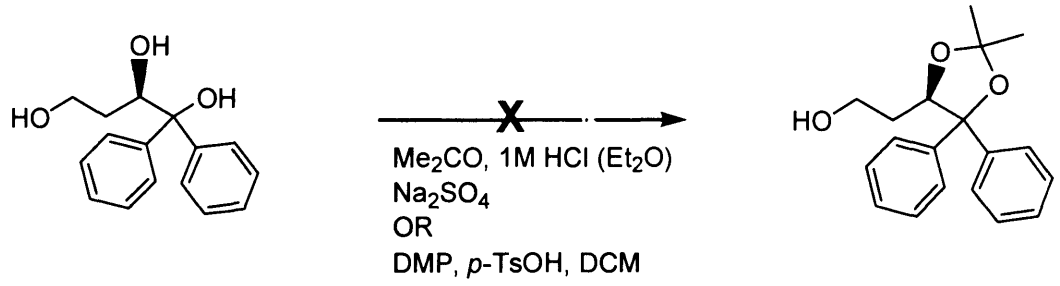
186

Fig. 17



Scheme 73

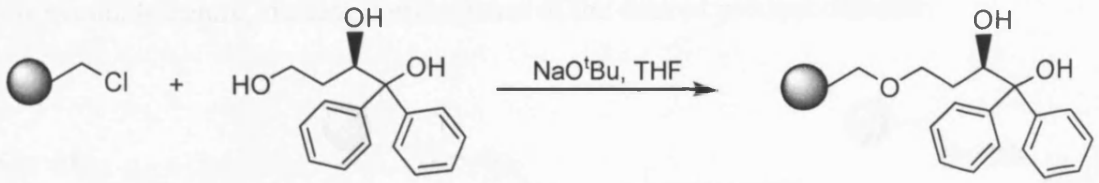
In order to circumvent this problem, a second route to a 1,1-diphenyl-substituted chiral diol was investigated (scheme 73). 3-Bromopropan-1-ol was converted to phosphonium salt **187**, and then treated with two equivalents of n-BuLi to form the ylide. This was reacted with benzophenone to give 1,1-diphenyl-substituted olefin **188** in high yield. Subsequent dihydroxylation with AD-mix-β gave the chiral diol product **189** in 92 % yield. Various attempts to protect the 1,2-diol **189** as its isopropylidene acetonide **190** failed, presumably due to the presence of the sterically demanding tertiary alcohol group



189 **190**

Scheme 74

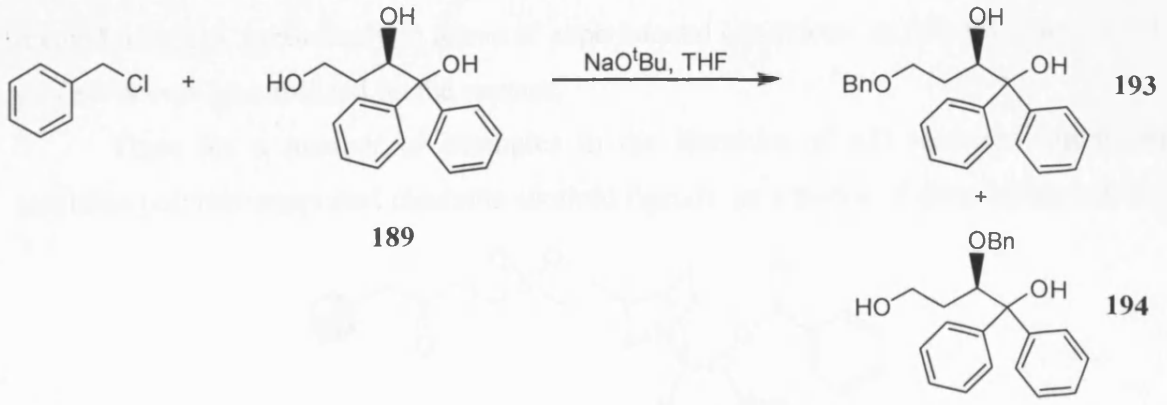
(scheme 74). Instead, grafting of triol **189** directly onto chloromethylated beads by selective etherification of the primary alcohol was attempted. Treatment of a cold (0°C) THF solution of **189** with a hindered base, sodium *tert*-butoxide, in order to selectively form the primary alkoxide, was followed by addition of chloromethylated PS beads (scheme 75). After stirring at 60°C for 72 hours, the product polymer **191** was found by elemental analysis, to have a chlorine content of 2.95 %, indicating just 21 % of chloromethyl groups had undergone substitution. The low reactivity observed is most likely to be due to low solubility of the triol **190** and its alkoxide in THF.



189 **191**

Scheme 75

The characterisation of resin **191** was problematic due to the low loading of the functionality on the beads. This prevented the use of ^{13}C NMR spectroscopy for the determination of the selectivity of etherification of the primary alcohol over the secondary and tertiary alcohols. In order to probe the effectiveness of the polymer grafting reaction, treatment of **189** with the homogenous analogue of chloromethyl PS-DVB, namely benzyl chloride, was attempted under the same conditions (scheme 76). The crude product from this reaction was analysed by GC-MS and ^1H NMR spectroscopy and was shown to contain 90 % of the desired primary benzylated product **193**, with the remainder being the benzyl ether of the secondary alcohol (**194**).



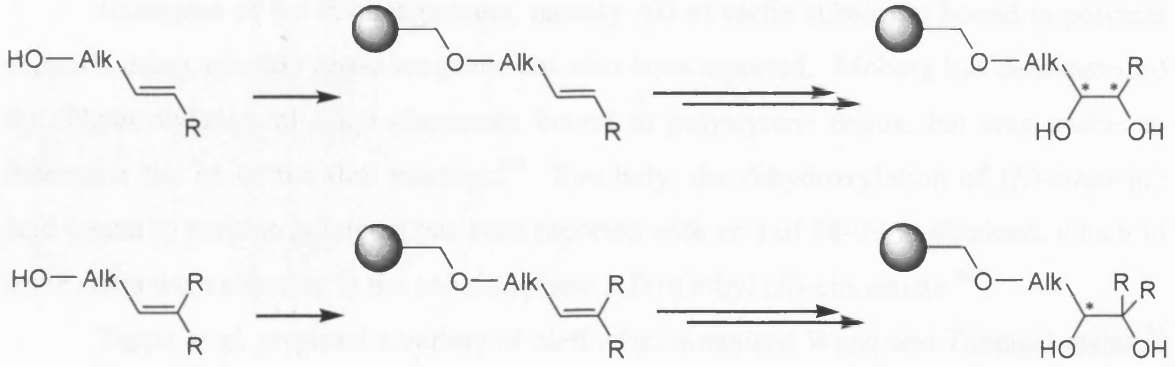
189 **193** **194**

Scheme 76

3.5 Synthesis of diol-functionalised resins *via* solid-phase AD

3.5.1 Synthetic strategy and previous examples of solid-phase AD

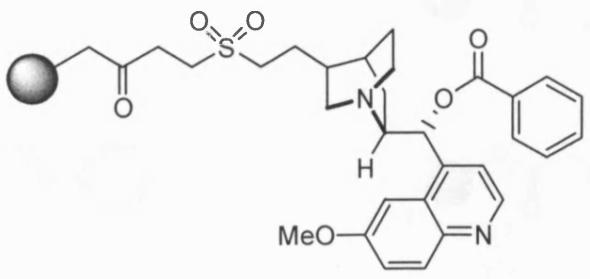
An alternative route to chiral 1,2-diol-functionalised polymers, in potentially fewer steps, is to proceed by asymmetric dihydroxylation of olefin substrates already bound to the support (scheme 77). It should be noted however, that a limitation of this approach is that the final analysis of the products is made considerably more difficult, as a result of their insoluble nature, making confirmation of the desired product difficult.



Scheme 77

Previous solid-phase AD reactions can be divided into two categories: (a) those that use polymer-supported reagents for AD of solution-phase olefin substrates and (b) those where the AD of polymer-bound olefins is performed in an SPOS manner (as in scheme 77). Previous examples of both can be considered in order to gain an insight into methodology (b), particularly in terms of experimental conditions, as in both cases the AD process occurs immobilized on the support.

There are a number of examples in the literature of AD reactions employing insoluble polymer-supported cinchona alkaloid ligands, as a means of simplifying reaction



195

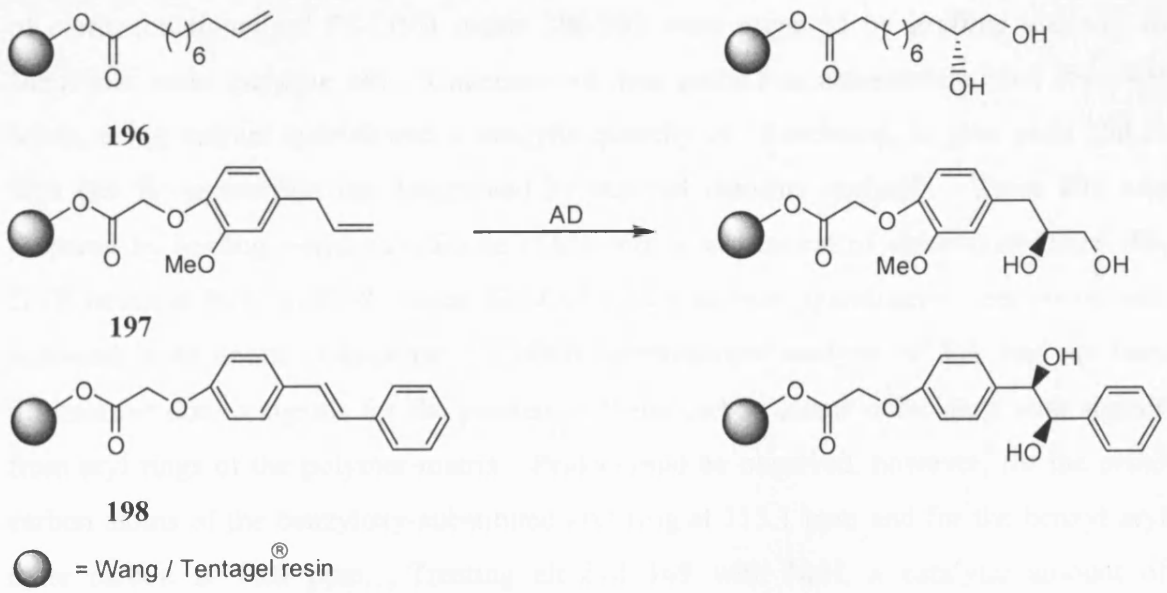
Fig. 28

purification and recovering the expensive ligand and osmium catalyst after use.[141] Success has been reported in the immobilisation of cinchona alkaloids on soluble, uncross-linked polystyrene[142] and insoluble polyacylonitriles.[143-144] Of greater relevance to this work is the application of ligands supported on PS-DVB supports in AD reactions.

PS-DVB-functionalised cinchona alkaloid **195** (Fig. 28), with a spacer group between the quinine derivative and polymer backbone, was used in OsO_4-catalysed AD of *trans*-stilbene.[145] Using NMO as the secondary oxidant, in a solvent mixture of acetone/H_2O (10:1), good stereoselectivity was observed (87 % ee). In contrast, no reaction occurred using $K_3Fe(CN)_6$ as the stoichiometric reoxidant, in *tert*-butanol/H_2O (1:1), presumably as a result of poor swelling of the polymer in this solvent mixture.

Examples of the inverse process, namely AD of olefin substrates bound to polymer supports using solution phase reagents, has also been reported. Moberg has demonstrated the dihydroxylation of ethyl cinnamate bound to polystyrene resins, but was unable to determine the ee of the diol product.[146] Similarly, the dihydroxylation of (*E*)-cinnamic acid bound to various polymers has been reported with ee's of 88-99 % obtained, which in some cases were superior to the solution phase AD of ethyl (*E*)-cinnamate.[147]

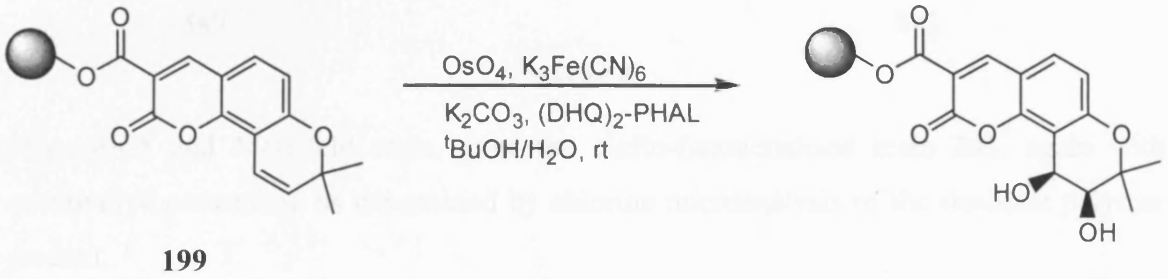
Tappe *et al.* prepared a variety of olefin-functionalised Wang and Tentagel resins.[31] Here ester linkages were used to tether 10-undecenoic acid (**196**), 2-methoxy-4-(2-propenyl)phenol (**197**), and *p*-hydroxystilbene (**198**) to a resin (scheme 78). The alkene moieties were subsequently dihydroxylated using a variety of cinchona alkaloid ligands, in yields ranging from moderate to high. Enantiomeric excesses were found to be low for terminal olefins **196** (20-45 %), but much higher (97 %) for the *trans*-stilbene substrates **198**. Virtually no stereoselectivity was observed for olefin substrates **197**, the homogenous



Scheme 78

analogue of which is known to be a troublesome substrate for AD reactions (*c.f.* 32 % ee in solution). The reactions were conducted in a mixture of THF/H_2O (1:1) using $K_3Fe(CN)_6$ as the secondary oxidant. Yields and ee's were determined by cleavage of the substrate from the support by hydrolyis of the ester linkage. The ee in the dihydroxylation product of terminal olefin **196** was also determined by ^{13}C HR MAS NMR analysis of it's bis(Mosher's ester), and the value obtained was found to be consistent with that determined following its cleavage of the diol from the support.

A final example of AD of a polymer-bound olefin was reported in the synthesis 3'*R*,4'*R*-di-O-cis-acyl-3-carboxyl khellactones.[148] Intermediate **199**, with a tethered styrene-like olefin contained in a six-membered ring fused with benzene, was dihydroxylated in 91 % ee using the $(DHQ)_2$-PHAL ligand and OsO_4. The reaction proceeded in high yield in a mixture of *tert*-butanol/H_2O (scheme 79).

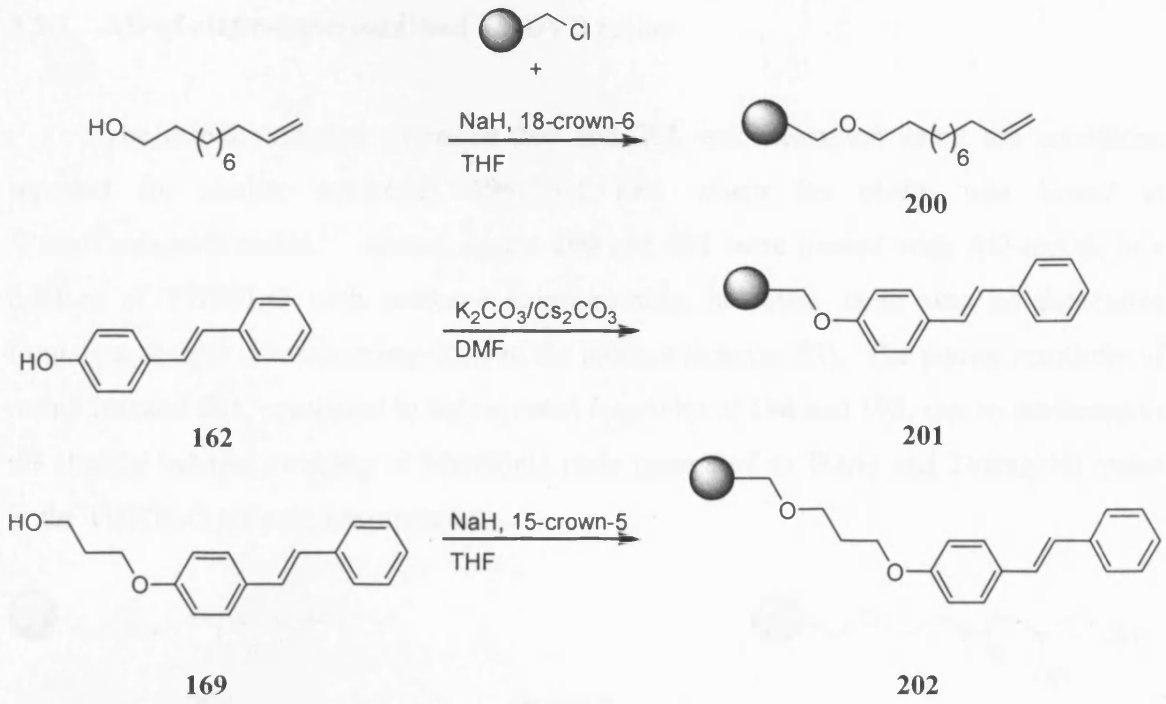


199

Scheme 79

3.5.2 Synthesis of olefin-functionalised PS-DVB resins

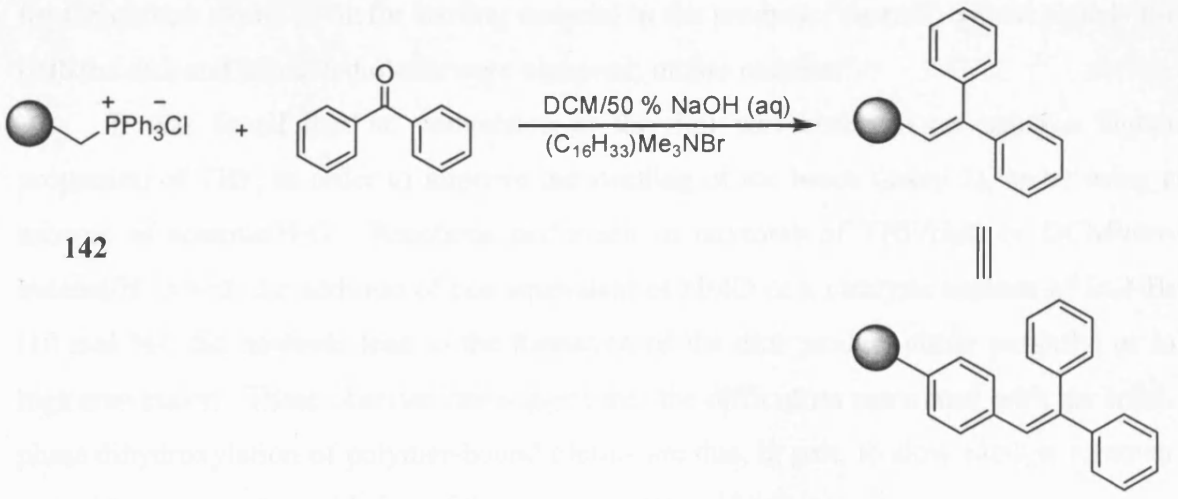
In order to synthesise polymer-supported chiral 1,2-diol ligands for use as supports for Lewis acids in asymmetric synthesis using this solid-phase AD methodology, a variety of olefin-functionalised PS-DVB resins **200-202** were prepared by grafting alcohols to Merrifield resin (scheme 80). Undecen-1-ol was grafted to chloromethylated PS-DVB beads, using sodium hydride and a catalytic quantity of 18-crown-6, to give resin **200** in high (88 %) conversion (as determined by residual chlorine analysis). Resin **201** was prepared by heating *p*-hydroxystilbene (**162**) with a suspension of chloromethylated PS-DVB beads at 80°C in DMF, using K_2CO_3/Cs_2CO_3 as base; quantitative conversion was achieved in 48 hours. Gel-phase ^{13}C NMR spectroscopic analysis of **201** was not very informative due to signals for the pendant stilbene carbon atoms coinciding with signals from aryl rings of the polymer-matrix. Peaks could be observed, however, for the *ortho* carbon atoms of the benzyloxy-substituted aryl ring at 115.1 ppm and for the benzyl aryl ether carbon at 70.0 ppm. Treating alcohol **169** with NaH, a catalytic amount of



Scheme 80

15-crown-5 and Merrifeld resin, gave the olefin-functionalised resin **202**, again with quantitative conversion as determined by chlorine microanalysis of the resultant polymer product.

Triaryl-substituted olefin **203**, with the pendant aryl ring of the polystyrene backbone as one of the substituents, was prepared by a Wittig reaction between the phosphorous ylide prepared from phosphonium chloride-functionalised resin **142** and benzophenone (scheme 81), using the same phase-transfer-catalysed reaction as described in section **2.4**. The polymer product **203** obtained was found by microanalysis to have lost almost all chlorine and phosphorous content (0.09 % and 0.18 %, respectively), consistent with clean reactions occurring at each stage of the synthesis.



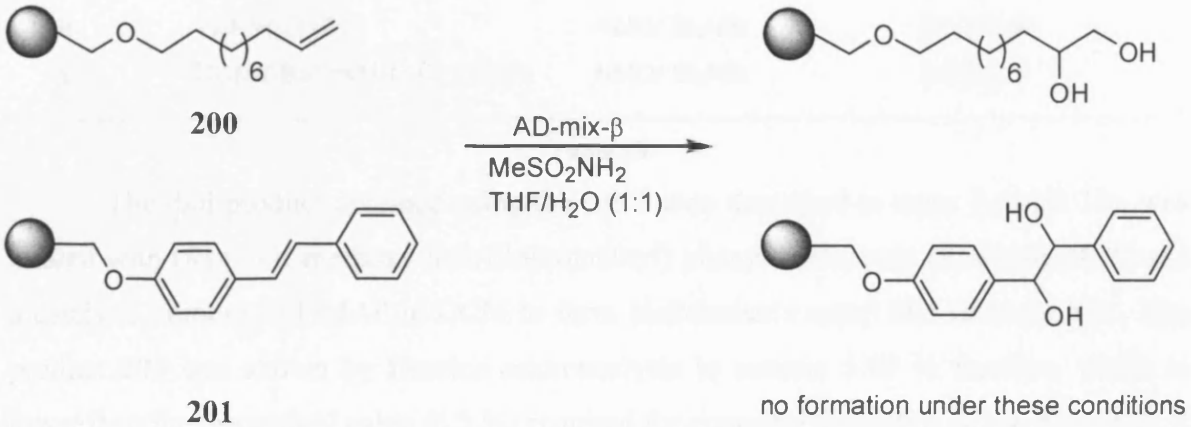
142

203

Scheme 81

3.5.3 AD of olefin-functionalised PS-DVB resins

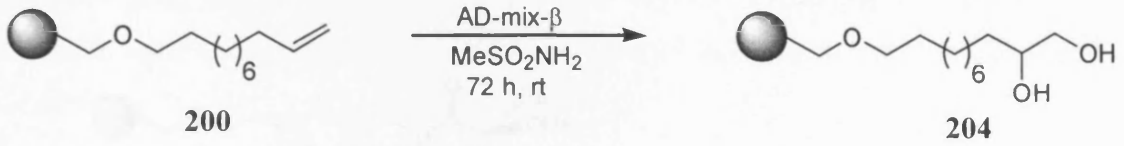
The dihydroxylation of resins **200** and **201** was attempted using the conditions reported for similar substrates **196** and **198**, where the olefin was bound to Wang/Tentagel® resins.[31] Hence, resins **200** and **201** were treated with AD-mix-β, in a mixture of THF/H_2O with methane sulphonamide, however, there was no detectable formation of their corresponding diols in the product (scheme 82). The poorer reactivity of resins **200** and **201**, compared to the reported reactivity of **196** and **198**, can be attributed to the slightly inferior swelling of Merrifield resin compared to Wang and Tentagel® resins in the THF/H_2O solvent mixture used.



Scheme 82

To try and get around this problem, the reaction of polymer **200** with AD-mix-β was then attempted under a variety of conditions (table 13), with qualitative determination of the extent of formation of the diol product **204** assessed by ^{13}C NMR spectroscopy, as shown. Thus, reactions have been classified as "complete", where no signal was detected for the carbon atoms of olefin starting material in the product; "partial", where signals for both the diol and unreacted olefin were observed; or "no reaction".

It was found that no conversion to the diol was observed on using a higher proportion of THF, in order to improve the swelling of the beads (entry 2), or by using a mixture of acetone/H_2O. Reactions performed in mixtures of THF/H_2O or DCM/*tert*-butanol/H_2O with the addition of one equivalent of NMO or a catalytic amount of Et_4NBr (10 mol %), did however lead to the formation of the diol product either partially, or in high conversion. These observations suggest that the difficulties associated with the solid-phase dihydroxylation of polymer-bound olefins are due, in part, to slow catalyst turnover caused by restricted reoxidation of the osmium (VI) products.

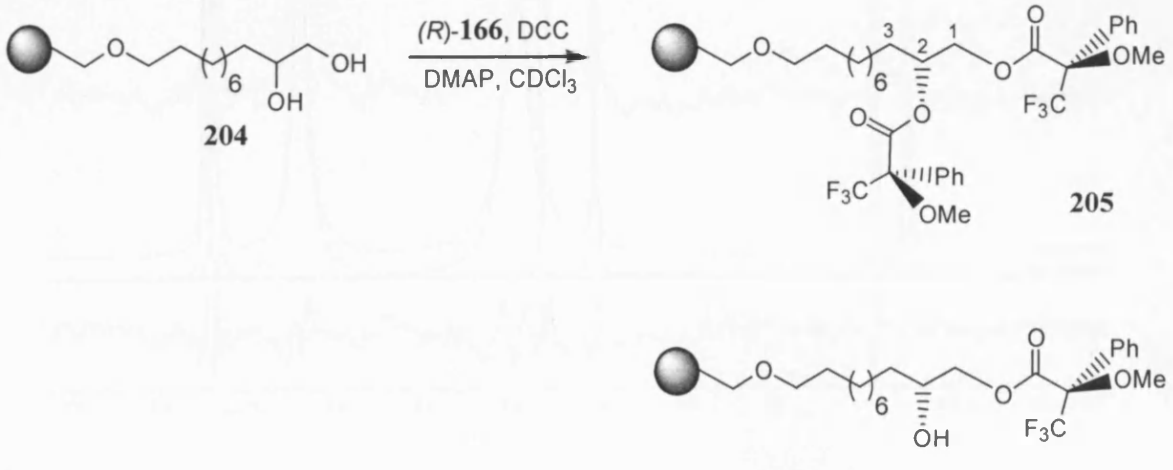


200 **204**

Entry	Solvent	Additive	Formation of **204**
1	THF/H_2O (1:1)	none	No reaction
2	THF/H_2O (4:1)	none	No reaction
3	Acetone/H_2O (5:1)	none	No reaction
4	THF/H_2O (2:1)	NMO	complete
5	THF/H_2O (2:1)	Et_4NBr	complete
6	DCM/*t*-BuOH/H_2O (2:1:0.05)	NMO	partial
7	DCM/*t*-BuOH/H_2O (2:1:0.05)	Et_4NBr	complete
8	THF/H_2O (2:1)	NMO/ Et_4NBr	complete
9	DCM/*t*-BuOH/H_2O (2:1:0.05)	NMO/ Et_4NBr	complete

Table 13

The diol product obtained using the conditions described in entry 7 (table 13), was treated with (*R*)-(+)-α-methoxy-α-(trifluoromethyl) phenyl acetic acid (*R*)-(**166**), DCC and a catalytic amount of DMAP in DCM to form bis(Mosher's ester) **205** (scheme 83). The product **205** was shown by fluorine microanalysis to contain 5.39 % fluorine, which is lower than the theoretical value (6.3 %) required for complete formation of the bis(ester), if the dihydroxylation step gave the diol in quantitative yield. This discrepancy was found to be, at least partly, due to incomplete formation of bis(ester) **205**, some of the mono-ester **206** was observed in the gel-phase MAS ^{13}C NMR spectrum (Fig. 29). The ee of the transformation was determined by deconvolution of the pairs of signals from the diastereotopic terminal and internal α-carbon atoms (C1 and C2, respectively, see Fig. 30) of the bis(ester), and methylene carbon atom C3 (not shown). The relative intensities of



204 **205**

206

Scheme 83

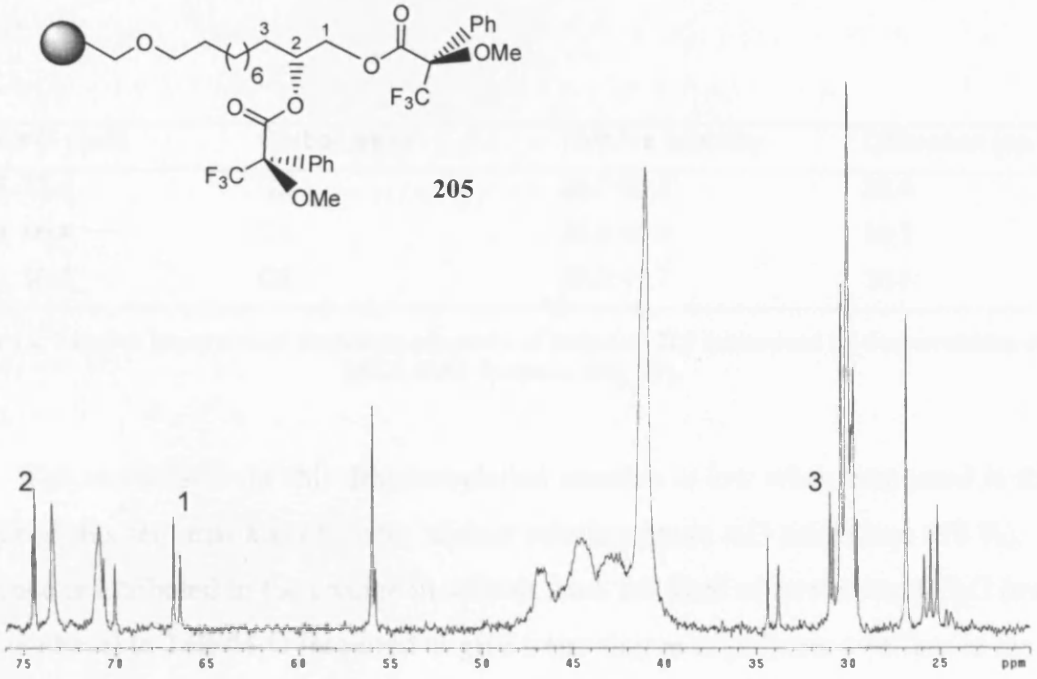


Fig. 29. ^{13}C MAS NMR spectrum of **205**, contaminated with mono-ester **206**.

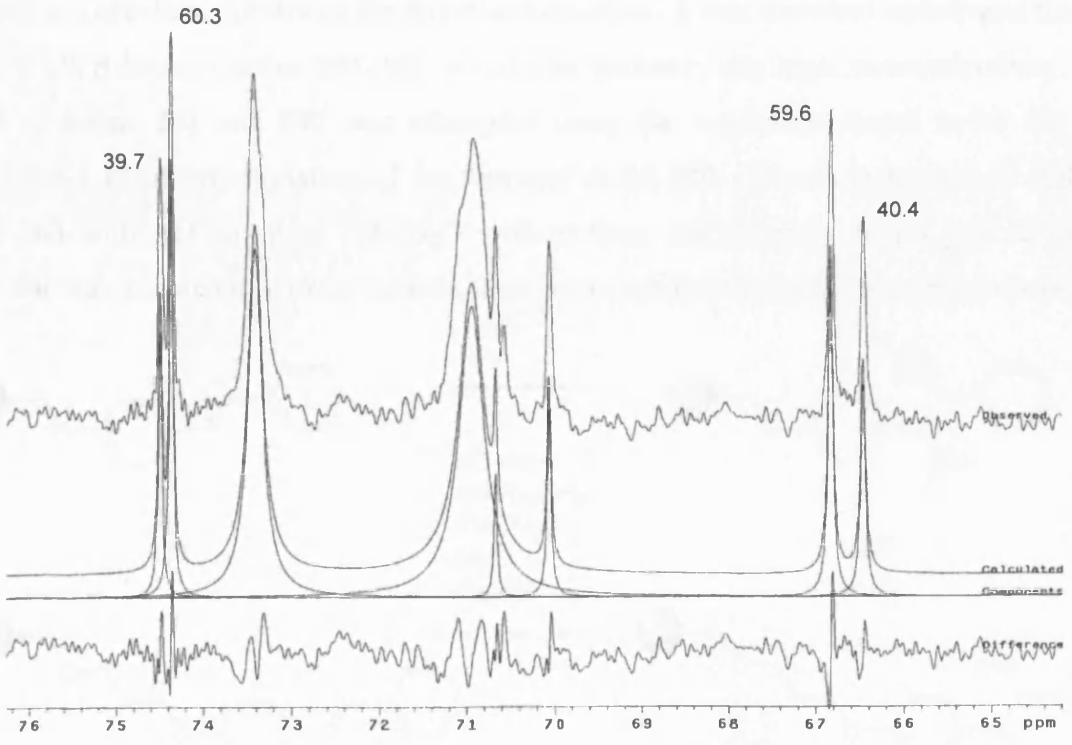


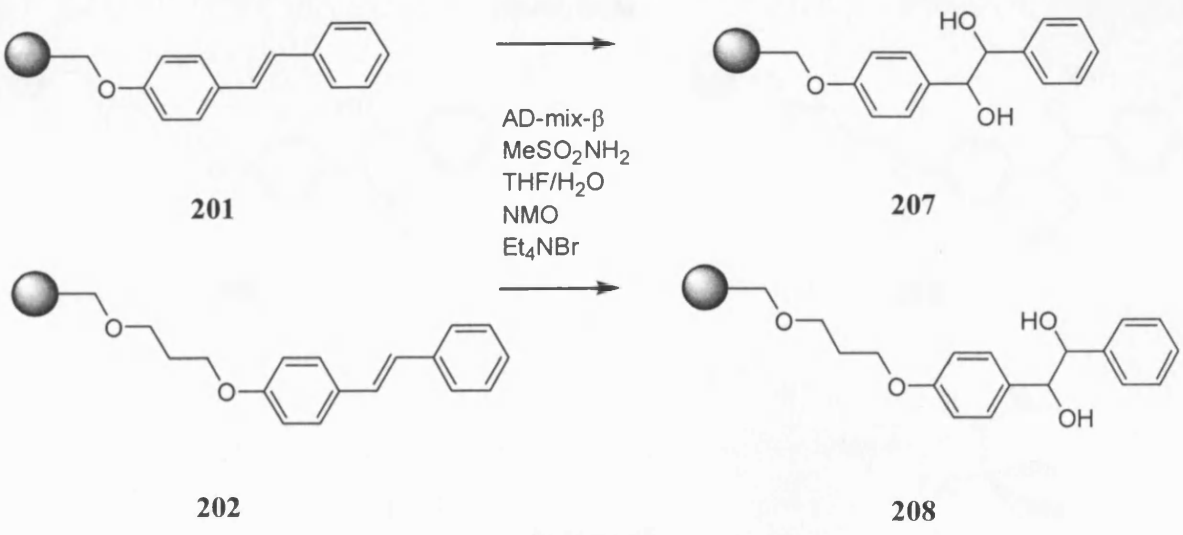
Fig. 30. Deconvolution of diastereotopic peaks from the spectrum shown in Fig. 28.

these pairs of signals all indicated an ee of 19-20 % (table 14), with the consistent ratio of the values determined for each pair of peaks suggesting accuracy in the deconvolution method.

Peaks (δ ppm)	Carbon atom	Relative Intensity	Difference (ee %)
73.5, 73.4	C2	39.7:60.3	20.6
66.8, 66.4	C1	59.6:40.4	19.2
31.0, 30.8	C3	58.3:41.7	16.6

Table 14. Relative intensities of diastereotopic peaks of bis(ester) **205** determined by deconvolution of ^{13}C MAS NMR spectrum (Fig. 29).

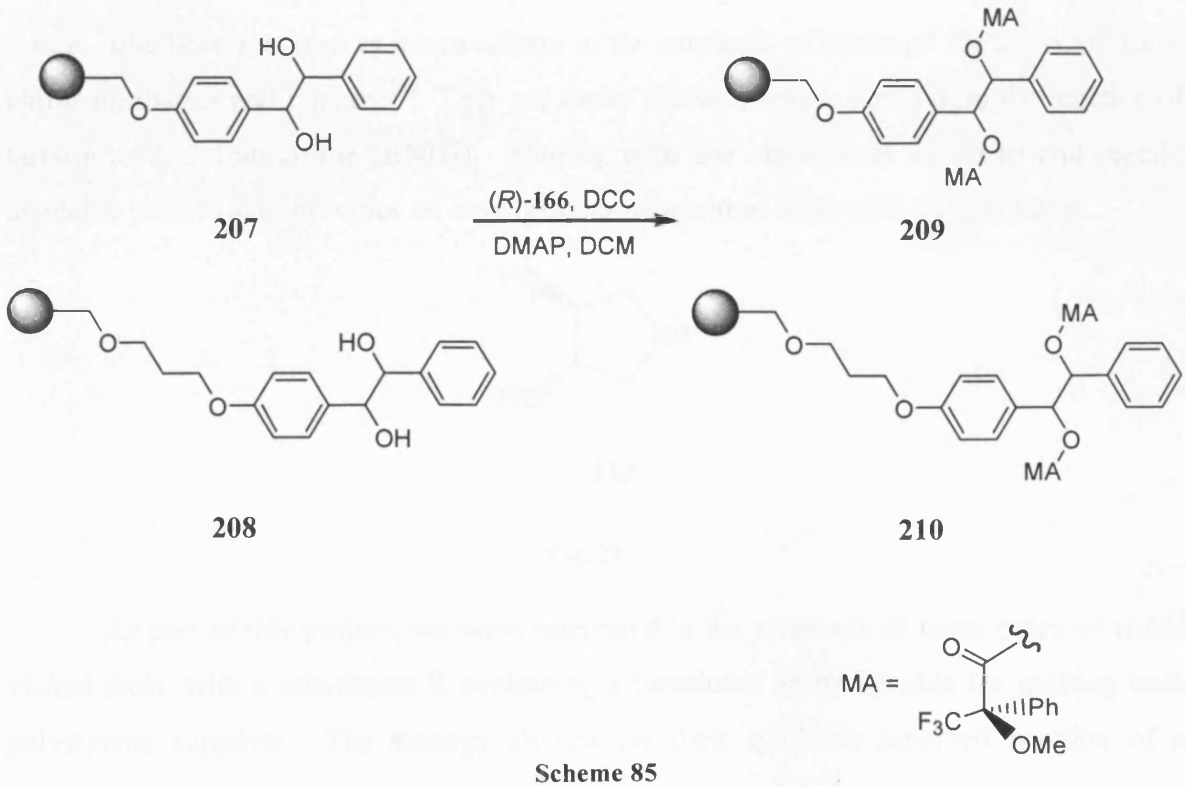
The ee of 20 % for this dihydroxylation reaction is low when compared to that of the AD of this terminal alkene under normal solution phase AD conditions (78 %). This difference is attributed to the change in solvent from the ideal of *tert*-butanol/H_2O (used in solution phase) to THF/H_2O (required to give some degree of polymer swelling in the solid pahse). The use of solvents that are less polar than *tert*-butanol has previously been shown to cause a drop in enantioselectivity.[123] The ee, however, is consistent with the value reported for the dihydroxylation of terminal olefin **196**, bound to the Wang resin and dihydroxylated in THF/H_2O using $K_3Fe(CN)_6$ as the secondary oxidant. As was discussed previously, these conditions still lead to high ee's in the AD reactions of *trans*-stilbenes, which are excellent substrates for this transformation. It was therefore anticipated that AD of PS-DVB-bound olefins **201-203** would also proceed with high stereoselectivity. The AD of resins **201** and **202** was attempted using the conditions found to be the most successful for dihydroxylation of the terminal olefin **200**. Hence, treatment of stilbenes **201-203** with AD-mix-β in THF/H_2O with methane sulfonamide, NMO and 10 mol % Et_4NBr was attempted in order to form their corresponding diols **207** and **208** (scheme 84).



Scheme 84

Diol-functionalised resins **207** and **208** were both formed to some extent, as shown by gel-phase ^{13}C NMR spectroscopy. Determination of the extent of the reaction was problematic, due to being unable to observe loss of signals from the double bond carbon atoms in the spectrum, because of interference from the polymer backbone.

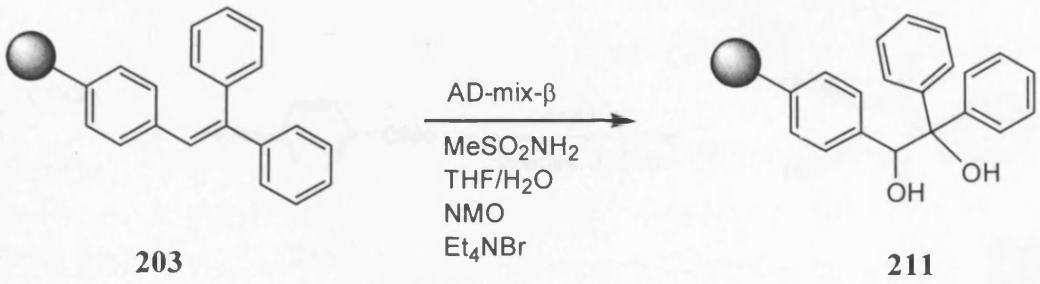
An indication of the loading of the diol in resins **207** and **208** was obtained by derivatisation as their bis(Mosher's esters) **209** and **210** (scheme 85). This method is not accurate however, due to uncertainty in the extent of formation of the bis(ester). The reaction of terminal diol-functionalised resin **204** with Mosher's acid was shown to be incomplete with a mixture of the mono- and bis-(ester) being formed. Indeed, it is not unreasonable to suppose that formation of **209** and **210** would be harder due to increased steric hindrance of the secondary alcohols. Microanalyses of the products **200** and **210** gave fluorine contents of 1.30 % and 4.57 %, respectively, suggesting conversion to the diol was higher for **210** than for **209**. These results suggest a dihydroxylation yield for product **207** of between 28 %, based on formation of only the mono(ester), down to 14 % based on the clean formation of the bis(ester) **204**. For resin **202** the results show complete formation of at least the monoester and suggest a 54 % yield of dihydroxylated product **208**, based on complete formation of the bis(ester) **210**. It was not possible to determine accurately the ratio of mono- to bis-(ester) formed by ^{13}C NMR spectroscopy, and hence the yield of diol, due to excessive line broadening and overlap of the signals for the C—O carbon atoms. For the same reason, the ee of the AD step in forming resins **207** and **208** could not be determined.



207 **209**

208 **210**

Scheme 85



203 **211**

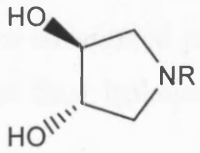
Scheme 86

The apparently inferior reactivity of resin **201** compared to **202** in the AD reaction could be attributed to lack of a spacer group, which can improve the reactivity of polymer-bound functional groups. Unfortunately, the same explanation could be used to suggest that a less efficient reaction with Mosher's acid, to form the fluorinated derivative, is occurring for diol **201** compared to diol **202**.

Attempts to dihydroxylate resin **203** were unsuccessful, none of the diol **211** could be detected by gel-phase ^{13}C NMR spectroscopy (scheme 86), presumably due to a combination of increased steric hindrance of a trisubstituted olefin, and decreased reactivity of the tethered olefin caused by its direct attachment to the polystyrene chain.

3.6 Synthesis of a 3,4-Dihydroxypyrrolidine-functionalised PS-DVB resin

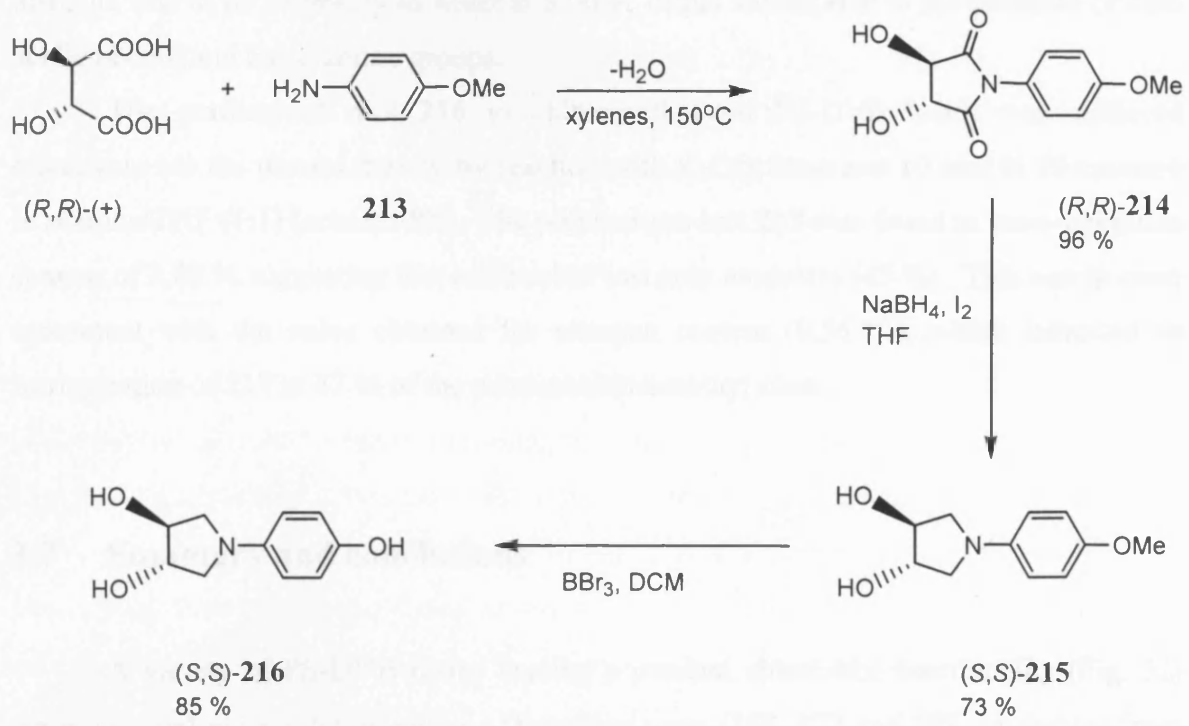
3,4-Dihydroxypyrrolidine compounds **212** (Fig. 31), where R is a simple alkyl group, have been reported as intermediates in the synthesis of diamines for applications as chiral auxiliaries and ligands.[149] They are easily derived, in two steps, from the reaction of tartaric acid and an amine (RNH_2). Starting with one enantiomer of cheap and readily available tartaric acid provides an easy route to homochiral diols with C_2 symmetry.



212

Fig. 21

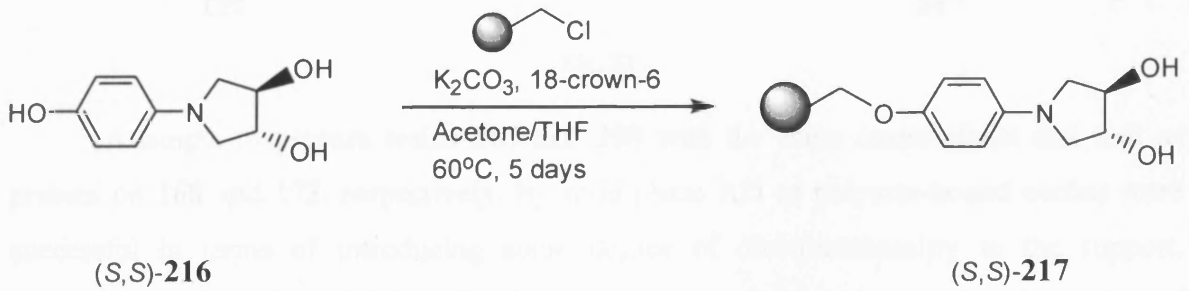
As part of this project, we were interested in the synthesis of these types of chiral vicinal diols, with a substituent R containing a functional group suitable for grafting onto polystyrene supports. The strategy chosen for their synthesis involved reaction of a



Scheme 87

hydroxyl-protected *para*-aminophenol-derived compound, with tartaric acid. Following conversion to the 3,4-dihydroxypyrrolidine, the phenol could then be deprotected and grafted onto Merrifield resin by selective coupling of the phenol hydroxyl with polymer-bound chloromethyl groups.

Thus, *p*-anisidine **213** was reacted with one equivalent of (+)-tartaric acid by azeotropic dehydration with boiling xylenes in a Dean-Stark apparatus (Scheme 87). 3,4-Dihydroxypyrrolidinedione (*R*,*R*)-**214** was obtained in 95 % yield. This was reduced to enantiopure 3,4-dihydroxypyrrolidine (*S*,*S*)-**215** by reaction with diborane, generated *in situ* from sodium borohydride and iodine, in 71 % isolated yield. Cleavage of the methyl aryl ether protecting group was attempted with aluminium trichloride and pyridinium hydrochloride with little success. The use of boron tribromide in dichloromethane at 0°C proved successful, however, and *para*-substituted phenol (*S*,*S*)-**216** was obtained in near quantitative yield. Unfortunately, the final isolation of the dihydroxy / phenol **216** was



(*S*,*S*)-**216** (*S*,*S*)-**217**

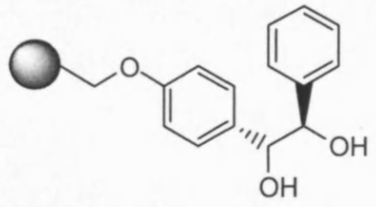
Scheme 88

difficult, due to its solubility in water at a range of pH values, due to the presence of both acidic phenol and basic amine groups.

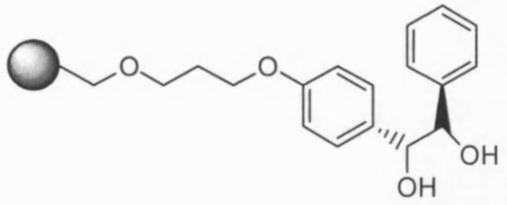
The grafting of diol **216** to chloromethylated PS-DVB beads was achieved selectively *via* the phenol moiety by reaction with K_2CO_3 base and 10 mol % 18-crown-6 in acetone/THF (1:1) (scheme 88). The polymer product **217** was found to have a chlorine content of 2.08 % suggesting that conversion was only moderate (45 %). This was in close agreement with the value obtained for nitrogen content (0.56 %), which indicated an incorporation of **217** at 47 % of the pendant chloromethyl sites.

3.7 Summary and conclusions

A variety of PS-DVB resins bearing a pendant chiral diol functionality (Fig. 32) were prepared *via* a solution-phase AD/grafting route (**168**, **173** and **191**) or derived from tartaric acid (**217**). The conversions obtained in the grafting step were nearly quantitative in the syntheses of resins **168** and **173**, but only moderate in the preparation of resins **191** and **217**.



168



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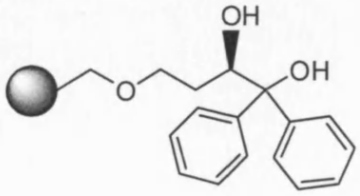
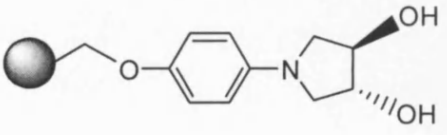


191



217

Fig. 32

Attempts to prepare resins **207** and **208** with the same immobilised diol unit as present on **168** and **173**, respectively, by solid-phase AD of polymer-bound olefins were successful in terms of introducing some degree of diol-functionality to the support. However, the benefits of this solid-phase AD approach, namely a reduced number of

synthetic steps, and ease of product purification, were outweighed by major disadvantages associated with this strategy, problems commonly observed in solid-phase synthesis. Firstly, there was the difficulty of determining the extent of reaction (and hence an accurate value for the loading of diol on the support), something that was suggested to be incomplete (in this case) from analysis of the material following attempts to prepare the corresponding Mosher's ester. Secondly, the nature of the resin meant that in order to swell the polymer beads (something desirable in terms of ensuring good reactivity), a change in the solvent system was dictated away from the ideal used to achieve highly enantioselective solution phase AD reactions; hence a loss of enantioselectivity is possible. The final disadvantage is being unable to quantify any changes in selectivity resulting from heterogenisation of the reaction, due to being unable to determine the ee on the resin. Because of these problems, it can be concluded that a strategy utilising a solution-phase AD to form the chiral diol, followed by grafting to the support, is preferable in the synthesis of functionalised PS-DVB resins using this type of synthetic strategy.

Chapter 4

Catalysis

4.1 Lewis acid catalysis

The use of Lewis acid catalysts in organic synthesis, particularly for carbon-carbon bond forming reactions such as the Diels-Alder reaction[42] and dialkylzinc additions to aldehydes,[58,59] has been well researched. In such processes, the catalysts often function through coordination of a substrate's carbonyl oxygen atom, for example, leading to activation of the carbon-oxygen double bond (Fig. 33). These transformations are catalysed by a range of Lewis acids including B(III), Al(III) or Ti(IV), *etc.*; and the topics have been well reviewed.[43, 150-153]

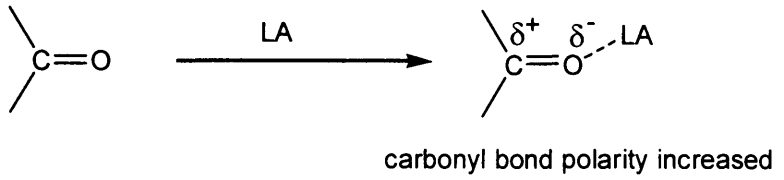


Fig. 33

Asymmetric variants of these types of catalyst are often prepared from halide, alkyl or alkoxy derivatives of the central Lewis acidic component modified with a chiral chelating ligand. These chelating ligands generally have "hard" donor atoms such as N or O, the electron-withdrawing power of which enhances the overall Lewis acidity of the ensemble. Examples of chiral chelating ligands that have been shown to give good stereo- and enantio-selectivity in Lewis acid-catalysed reactions include amino alcohols,[154] binaphthol-based ligands,[59,155] diamines and diols.[48] Strong Lewis acidity is desired as this property is generally proportional to the rate of acceleration of the reaction in question, giving faster reaction rates and/or promoting a selective asymmetric catalysed route relative to any competing non-selective routes. It is important to note, however, that complexes should not be so Lewis acidic that reactants are decomposed or polymerised.

Lewis acids based on B(III), Al(III) or Ti(IV) are highly oxophilic, so both the reactants and products often bind very strongly to the metal centre something that can result in reaction inhibition by the product, leading to slow catalyst turnover. In addition, these reagents are also water/moisture sensitive. This combination of unfavourable factors means the Lewis acid complexes are frequently employed at relatively high loadings (up to 20 mol %). This requirement means that for enantioselective reactions, the high cost of the chiral ligands (more so than the relatively inexpensive metals) makes heterogenisation of such systems desirable as a means of catalyst and ligand recovery. One method for achieving this is by immobilisation of the Lewis acid/ligand combination on an insoluble polymer-support.

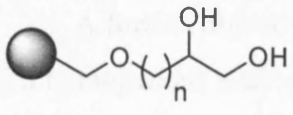
The preceding two chapters have described the synthesis of a variety of diol-functionalised PS-DVB resins. In this chapter, the use of these resins as supports for heterogenised Lewis acid catalysts in organic transformations will be explored. The work's objective was to probe the influence of incorporation of polymer-catalyst spacer modifications on reactivity. Comparisons will be made with 'model' homogeneous systems in order to assess the impact of the polymeric matrix and the polymer-catalyst spacer upon catalysis. In order to do this, well-established, reliable reactions were chosen for the investigation, namely the Diels-Alder reaction and diethylzinc addition to benzaldehyde.

The first part of this chapter explores the reactivity of simple spacer-modified diols as supports for titanium Lewis acids in the Diels-Alder reaction of methyl acrylate and cyclopentadiene. In the second part of this chapter, the results of some exploratory reactions of novel chiral diol-functionalsied resins as ligands for Lewis acid catalysts in both the asymmetric Diels-Alder reaction of methacrolein and cyclopentadiene, and the addition of diethylzinc to benzaldehyde, will be discussed.

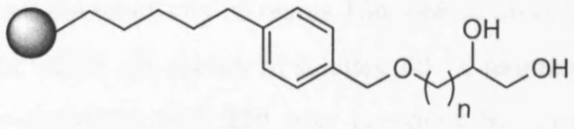
4.2 Effect of alkyl spacer-groups on the reactivity of supported Lewis acid catalysts in the Diels-Alder reaction of methyl acrylate and cyclopentadiene

4.2.1 Introduction and synthesis of homogenous analogues

In chapter 2, the grafting of alcohols to gel-type chloromethylated PS-DVB beads en route to the synthesis of diol-functionalised polymers **136-140** (Fig. 34) was reported. The strategy used in preparing these resins was chosen so as to minimise possible variations in the morphology and properties of the polystyrene support. In order to draw



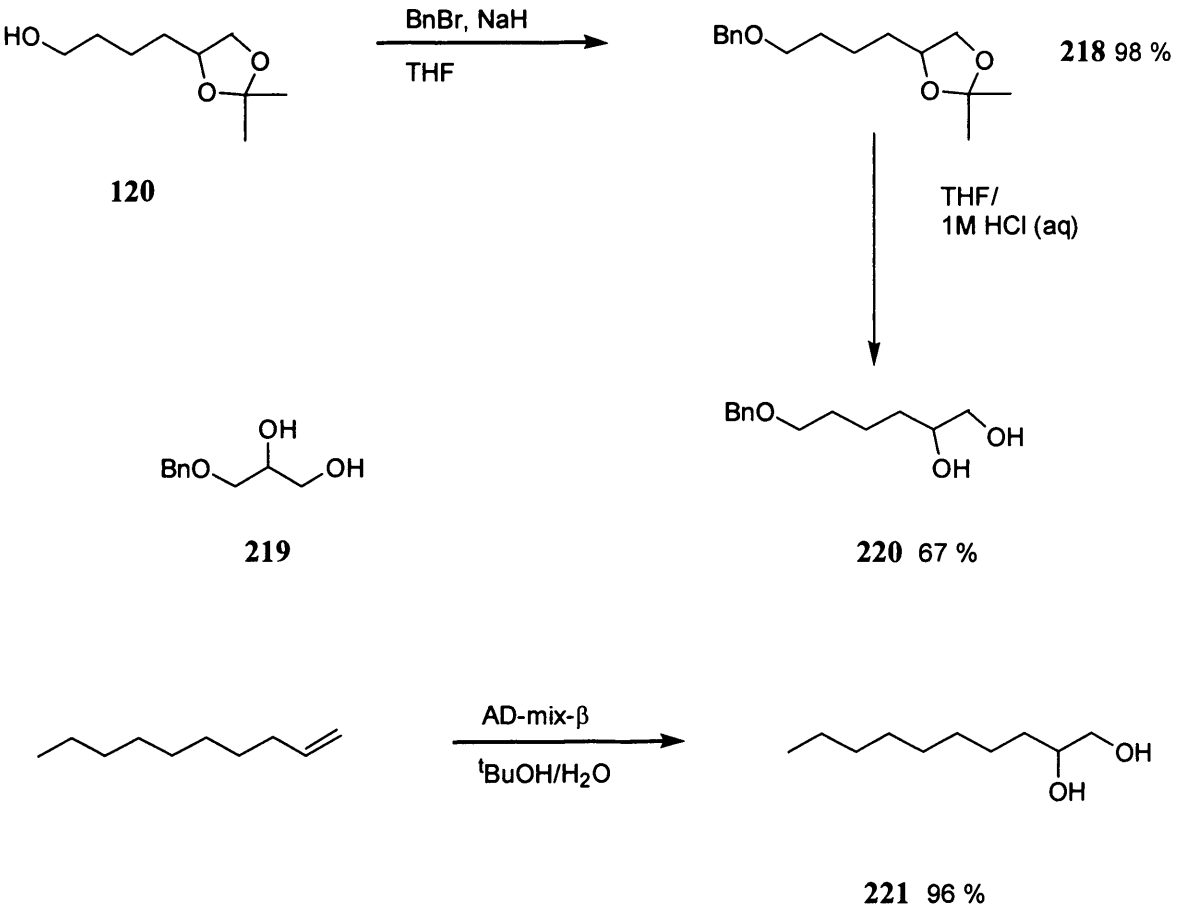
136 n = 1
137 n = 4
138 n = 9



139 n = 1
140 n = 4

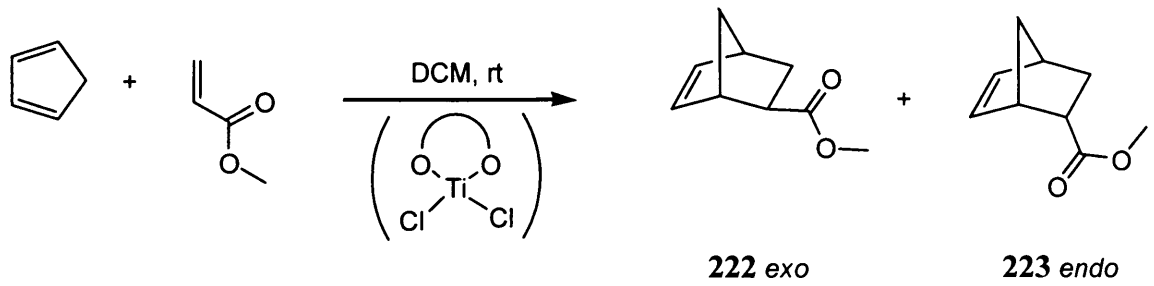
Fig. 34

legitimate conclusions about the effect of varying tether length in resins **136-140** on the reactivity of supported species, it is important that other factors that may influence their behaviour remain constant. These factors include the swelling ability of the resin, the loading of functionality on the support and the presence of other functional groups resulting from unwanted side-reactions or incomplete reactions during functionalised resin synthesis. Consequently, a route involving minimal modification steps of the polymer during the synthesis of resins **136-140** was used, with reactions utilised that were high yielding and consistent for the synthesis of each resin (*i.e.* the synthesis of each resin was achieved using the same reaction conditions, the sole difference being the structure of the grafted alcohol). Thus only resins **136-140** from the syntheses described in chapter 2, where grafting of an alcohol was quantitative, were used in the investigation.



Scheme 89

A further objective was also to compare the reactivity of resins **136-140** in catalysis with homogenous analogues, the syntheses of which are shown in scheme 89. Compound **219** is commercially available. Benzyloxy-protected diol **220** was prepared by initial protection of **120** as its benzyl ether **218**, followed by selective deprotection of the 1,2-diol (66 % overall yield). Diol **221** was prepared by dihydroxylation of dec-1-ene with AD-mix-β, in 96 % yield.



222 *exo* **223** *endo*

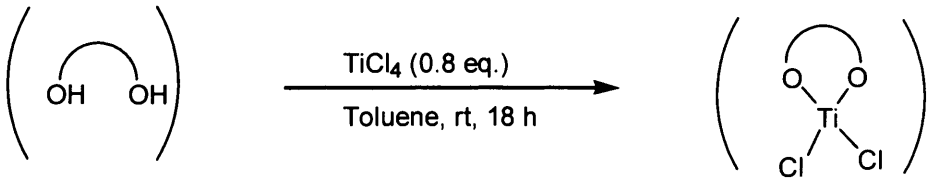
Scheme 90

It was anticipated that reaction rates would be increased with spacer-modified resins compared to those achieved using their non-spacer-modified resin equivalents and that the performance of the former would be closer to that of the corresponding solution phase species. The expected increase in activity that should be observed can be attributed to a decrease in steric interference from the polymer-backbone and increased mobility of a species that is separated from the polymer matrix by an alkyl spacer. The resulting more solution-like environment that results is expected to lead to increased interactions with reactants diffusing through the polymer pores. Hence, an important objective of the work was to try and probe whether such changes in behaviour were indeed observed, initially by studying a judiciously chosen test reaction.

For convenience, the well-established titanium-catalysed Diels-Alder reaction between cyclopentadiene and methyl acrylate (scheme 90) was chosen. The Lewis acid-catalysed cycloaddition of this poorly reactive ester dienophile with cyclopentadiene is known to generally proceed slowly (over minutes/hours) at room temperature.[48] For our purposes, this facilitated the determination of the quantity of the *exo* and *endo* products, **222** and **223**, formed as a function of time, achieved by withdrawing and quenching aliquots of a known volume of the reaction mixture by micro-syringe, prior to GC-MS analysis. Attempts to follow the Diels-Alder reaction of methacrolein and cyclopentadiene (at -78°C, in order to slow the reaction to a timescale which could be monitored) in the same way, failed since during removal of aliquots, the rate of reaction between substrates in a non-catalysed process was accelerated due to warming, before the mixture could be fully quenched.

4.2.2 Preparation of polymer-supported catalysts

In all cases, the Ti(IV) dialkoxide catalyst was formed by addition of 0.8 equivalents of titanium tetrachloride to the diol, this stoichiometry being used in order to



219-221
136-140

Scheme 91

favour formation of the chelate. It was necessary to filter and wash the titanium-functionalised-beads prior to use so as to ensure catalysis was truly being conducted by supported species rather than traces of titanium species in solution. Resins **136-140** were shaken with $TiCl_4$ in toluene, before being filtered and washed with further portions of toluene (scheme 91). Reactions were agitated by shaking rather than conventional stirring with a magnetic bead so as to prevent damage to the fragile polymer beads caused by mechanical degradation between the stirrer bead and reaction vessel. The uptake of titanium by the resin was ascertained, indirectly, by ICP-AE analysis of the titanium content in the combined polymer washings (table 15). Attempts to analyse the titanium content on the resin in a direct manner was problematic and impractical due to having no access to laser ablation ICP-MS. Attempts to cleave off the titanium using acid digestion (aqua regia) gave results that were extremely variable due to the low reactivity of the resin with the acid (even following attempts to facilitate digestion by microwave heating). Similar problems of incomplete digestion were previously reported in an effort to analyse molybdenum loadings on a PS-DVB support in this way.[156]

In order to at least partially verify the validity of this approach to analysis, a sample of "blank", unfunctionalised chloromethylated PS-DVB beads was treated with titanium tetrachloride in toluene for 18 hours. Subsequent analysis of the polymer washings, obtained following filtration, revealed a near-quantitative recovery of titanium (entry 6). The level of titanium found in the washings of resins **136-140** that were used subsequently in the Diels-Alder reactions, was found to be virtually zero, confirming all titanium used was bound to the polymer. It should be noted that trace levels of titanium were present in the reagent solutions (nitric acid and deionised water) used to prepare the samples for ICP-AE analysis. Since this " background" value (approximately 2 ppm, equivalent to 0.05 mg) was determined by analysis of a sample exposed to no possible sources of titanium, this discrepancy can, in part, explain slight deviations from the zero values expected for total heterogenisation of titanium. The experimental error in the ICP-AE values reported is +/- 5 %.

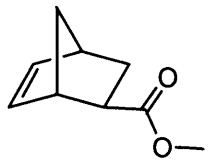
Entry	Resin	Ti added (mg)	Ti recovered (mg)
1	**136**	7.66	0.09
2	**137**	7.66	0.04
3	**138**	7.66	0.09
4	**139**	7.66	0.15
5	**140**	7.66	0.17
6	Merrifield resin	7.66	7.63

Table 15: Results of Ti ICP-AE analysis of resin washings after treatment with $TiCl_4$.

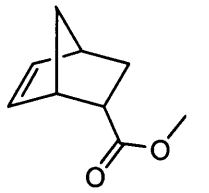
4.2.3 Catalysis results – an overview and validation of "heterogenisation"

The results obtained from the cycloaddition reactions between methyl acrylate and cyclopentadiene that employed 2 mol % of titanium catalyst modified by diols **219-221** and **136-140** are shown in table 16. Reactions were conducted in DCM by shaking at room temperature. The yield displayed is the combined yield of *exo* and *endo* products obtained.

Entry	Diol	Yield **222** + **223** (%)
1	**219**	60
2	**220**	90
3	**221**	94
4	**136**	61
5	**137**	61
6	**138**	73
7	**139**	51
8	**140**	53



222 *exo*



223 *endo*

Table 16. Diels-Alder reaction of cyclopentadiene and methyl acrylate catalysed by 2 mol % Ti.

It is important to note the extent of reaction in the absence of an added catalyst. With no Lewis acid present, the cycloadducts do form, albeit slowly, with a 20 % combined yield of **222** and **223** obtained after 8 hours at room temperature.

In any type of application in which a heterogeneous or immobilised catalyst system is employed, it is essential to verify that the actual catalysis is occurring at a support-bound

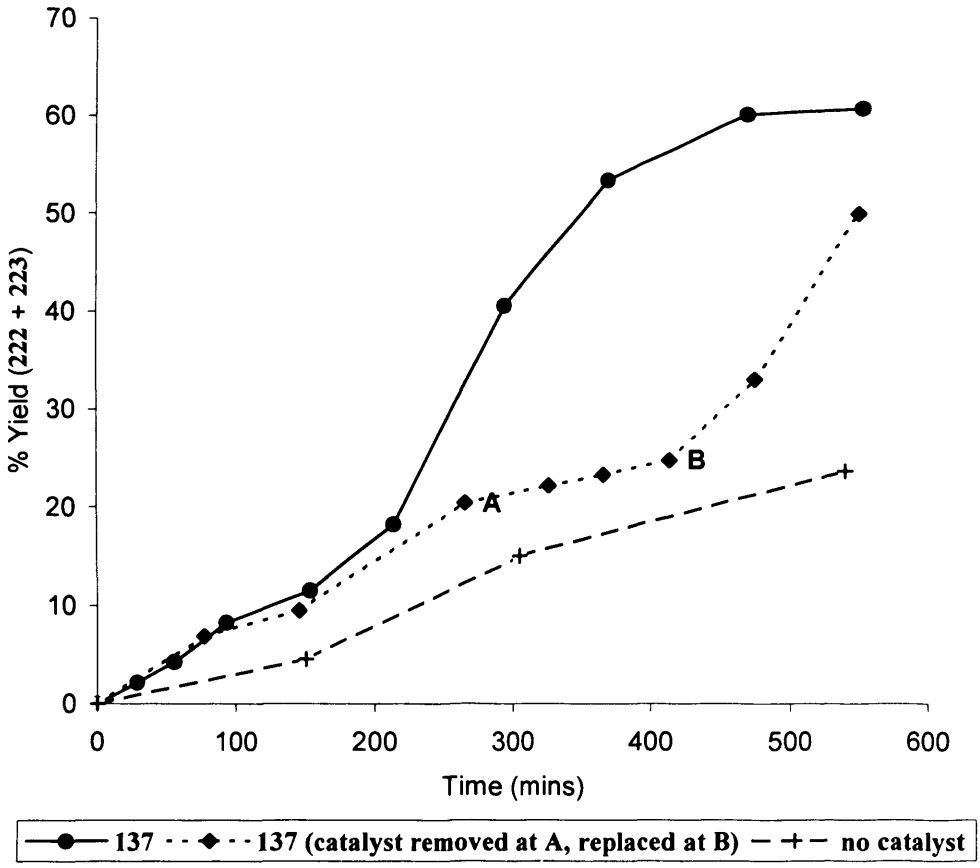


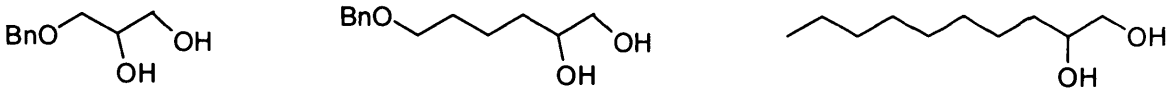
Fig. 35. Reaction profile for the reaction of cyclopentadiene and methyl acrylate using Ti catalyst derived from **137**, or in the absence of an added catalyst.

reagent rather than *via* any residual species that may not have been bound to the support during synthesis, or which may have leached from the support during reaction. Thus, it was deemed necessary to show that catalytic activity was solely due to titanium moieties bound to the support and not from any in the solution phase, after leaching from the polymer. To this end, the catalyst derived from diol **137** was employed in the reaction between methyl acrylate and cyclopentadiene. The reaction profile shown in figure 35, shows the progress of product formation (combined **222** and **223**) in comparison with a reaction where the polymer beads were removed midway through the reaction. After a reaction time of 250 minutes, the polymer beads were separated from the reaction mixture by filtration under an inert atmosphere (Fig. 35, point A). Monitoring of the formation of products **222** and **223** by GC-MS continued, before the solution was remixed with the polymer-bound catalyst (Fig. 35, point B). Removal of the beads was shown to revert the reaction progress to the slow rate of cycloaddition that occurs in an uncatalysed reaction at room temperature (Fig. 35, hashed line). This demonstrates that in this case, there were no appreciable amounts of catalytically active species in solution. Further confirmation that catalysis was indeed being induced by the insoluble initiator system, can be inferred from the observation that

upon returning the reaction mixture to the polymer beads (Fig. 35, point B) the reaction restarted. The fact that the final yield was tending towards being approximately the same when the catalyst was removed as when the reaction progress was not halted, suggests there was little deterioration of the catalyst in the separation/reuse process.

4.2.4 Reactivity of homogenous analogues

The reaction profiles of the cycloaddition of methyl acrylate and cyclopentadiene catalysed by titanium initiators derived from the soluble diols **219-221** (Fig. 36) are show in figure 37. This set of ligands was chosen to act as homogenous analogues of the polymer-bound



219 **220** **221**

Fig. 36

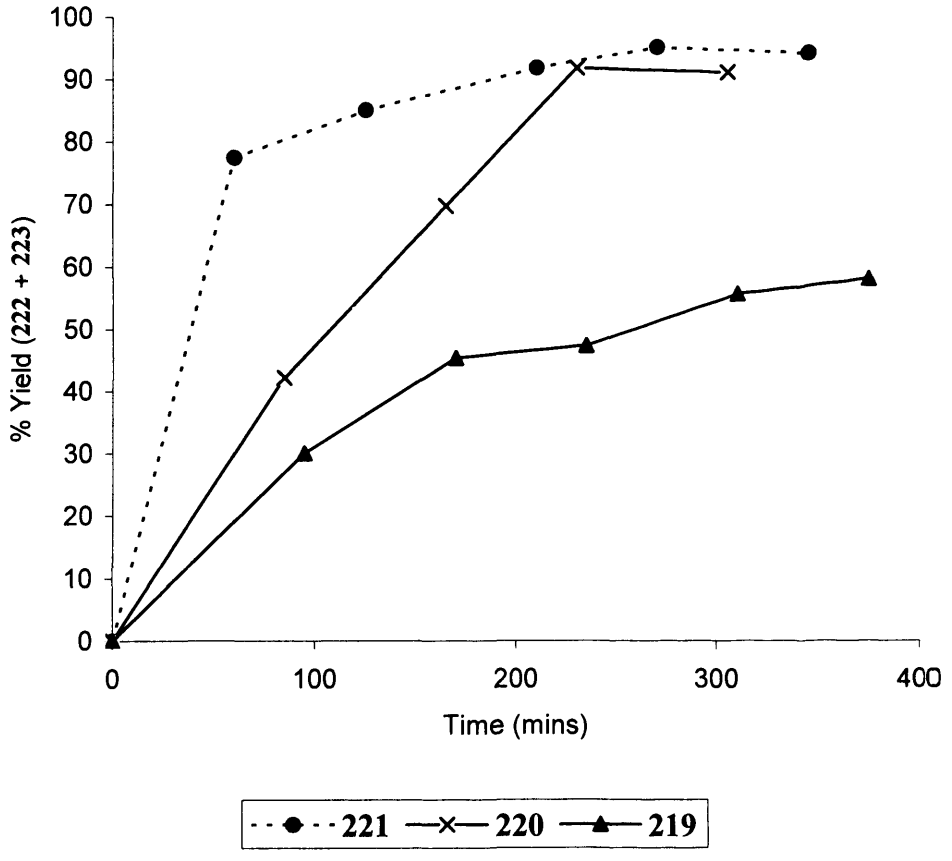


Fig. 37. Reaction of cyclopentadiene and methyl acrylate using 2 mol % Ti catalysts derived from diols **219-221**.

species discussed above. The reaction employing 2 mol % of titanium modified with diol **221** was shown to proceed in high (90 %) yield within 100 minutes, which is in contrast to the results for the benzyloxy-protected-analogues **219** and **220** where reaction was slower and poorer yields were obtained. It is presumed from these results that the presence of the benzyloxy group has a detrimental effect on the activity of the catalyst. This is possibly due to coordination of the oxygen atom in the tether to the metal centre, which competes with coordination of the methyl acrylate dienophile. It could be envisaged that binding of the ether oxygen atom could occur either in an inter- or intra-molecular fashion (see Fig. 38). For the dialkoxide obtained from diol **219**, the intramolecular mode is unlikely, and this is a possible explanation for the improved activity achieved with this particular system compared to its spacer-modified equivalent derived from diol **220**. In contrast, intramolecular interaction of the benzyl oxygen atom with the titanium centre in the complex obtained from diol **220** is quite possible, *via* formation of an eight-membered cyclic structure (Fig. 38, b). A similar effect arising from the negative influence of a remote donor atom in the structure of a catalyst was previously reported in the use of TADDOL-type ligands.[54]

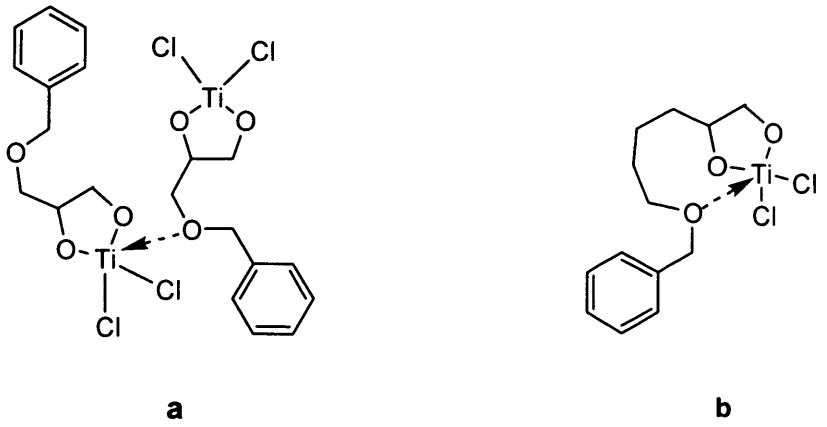


Fig. 38. a) Example of intermolecular coordination of oxygen tether atom to titanium; b) Intramolecular coordination in catalyst derived from **220**.

The results obtained in reactions using the homogenous ligands **219-221** demonstrate that care is needed in deciding which of these constitutes the most appropriate homogenous analogue for comparison with the reaction of PS-DVB-supported titanium complexes derived from **136-140**. In terms of their structure, the homogeneous models closest in structure to the immobilised diols are those derived from diols **219** and **220**. However, as described above, there is apparently a negative influence from the oxygen atom in the tether on the reactivity of catalysts derived from homogenous analogues **219** and **220**, which probably accounts for their low activity relative to **221**. This effect is likely to be more significant for the solution phase catalysts than the heterogenised

versions due to site-isolation effects in the latter, which makes direct comparison of the results difficult. Site-site interactions of functional groups bound to lightly cross-linked PS-DVB resins will always exist to some degree, depending on the loading (or concentration) of functional groups on the support. This is due to the gel-like nature of the material, which can be described as between solid and liquid, and gives rise to reasonably high mobility of the polymer chains compared to a solid polymer.[22] True site isolation for functionalised resins of the morphology used here, will only occur when there is a very low loading, and hence low concentration, of groups on the support.[33] However, due to the probable decreased extent of "intermolecular" interactions when the diol is bound to the resin relative to in solution phase, caused by the anchoring of the species to the support, comparison with analogue **221** is likely to be more realistic.

4.2.5 Reactivity of PS-DVB-supported titanium catalysts derived from ligands 136-138

The reaction profile with respect to time for the Diels-Alder reaction of methyl

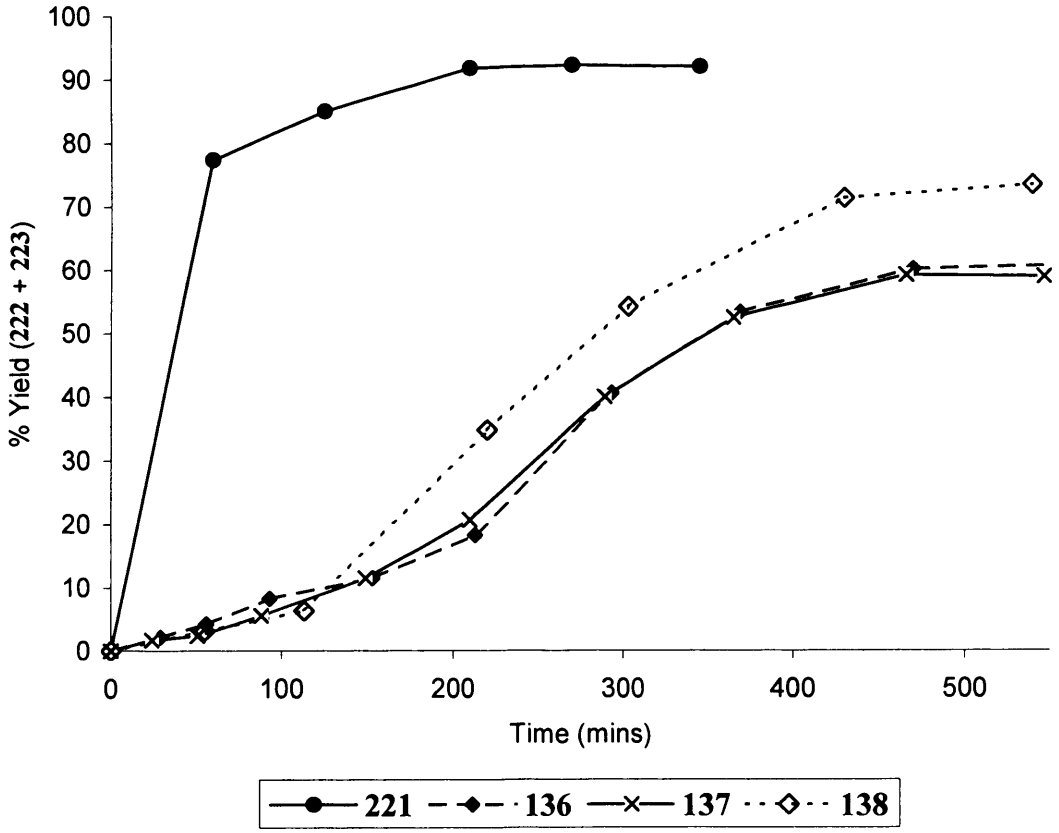
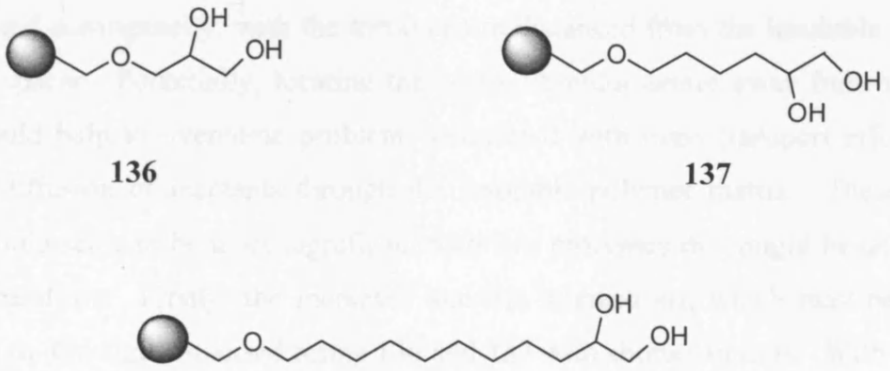


Fig. 39. Reaction of cyclopentadiene and methyl acrylate using 2 mol % Ti catalysts derived from **136-138**.



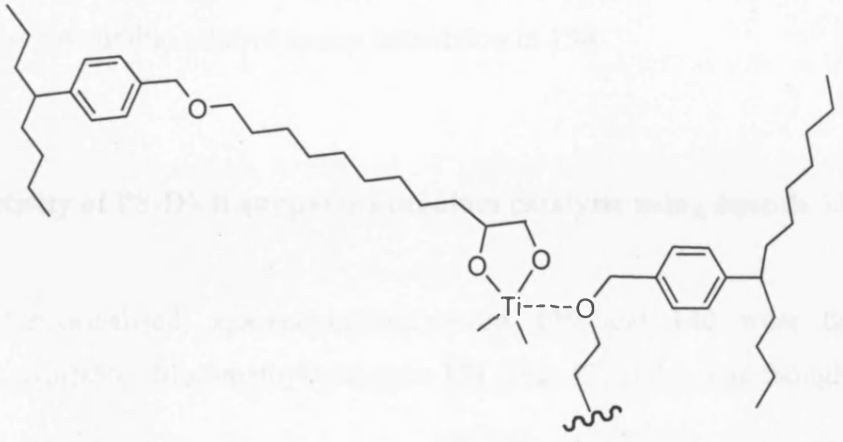
136 **137**

138

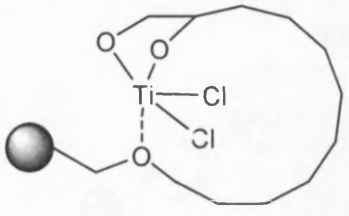
Fig. 40

acrylate with cyclopentadiene catalysed by 2 mol % of titanium dialkoxides derived from polymeric diols **136-138** (Fig. 40) is shown in figure 39. Included for comparison is the reaction employing the homogenous analogue **221**. The results show that there was no difference in activity when ligand **137**, with a four methylene carbon spacer, was used compared to that for diol **136** with only a one methylene carbon spacer. Use of ligand **138**, with an increased spacer length of nine methylene carbon atoms, did however lead to a slightly enhanced catalyst reaction rate and yield.

The improvement observed with catalyst **138** is most likely due to improved



a



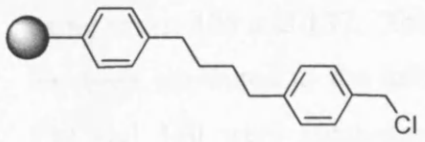
b

Fig. 41. a) Example of site-site interaction of oxygen tether atom to titanium in catalyst derived from resin **138**; b) "Intramolecular" coordination in polymer-bound catalyst.

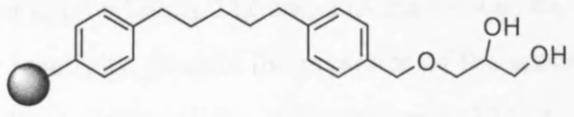
mobility and homogeneity, with the metal centre distanced from the insoluble polymer by the alkyl spacer. Potentially, locating the active titanium centre away from the polymer matrix could help to overcome problems associated with mass transport effects, *i.e.* the hindered diffusion of reactants through the insoluble polymer matrix. These beneficial factors would seem to be more significant than two processes that might be detrimental to efficient catalysis: Firstly, the increased site-site interactions, which may be occurring, compared to diol-functionalised resins **136** and **137** with shorter spacers. With the catalyst on the end of a longer alkyl chain, its improved mobility and the increased distance it reaches into the pores of the polymer matrix, might be expected to increase the likelihood of interactions with another functional site of the resin (Fig. 41a). The second possible negative effect is shown in figure 41b, and is the intramolecular equivalent of the process shown in figure 38b, with interaction of the metal centre with the oxygen donor atom in its own tether. It is this second type of interaction that may explain the similarity in reactivity of catalysts **136** and **137**. It is possible that any positive influence associated with the increased length of the spacer in **137**, is negated by an increase in intramolecular coordination to its tether, resulting in a catalyst with no overall improvement in reactivity. This is consistent with the results obtained for the homogenous analogues **219** and **220**, where it was found that **220** was a poorer ligand for catalysis. It is proposed that the increased spacer length in the catalyst derived from **138** will make this intramolecular interaction less favourable relative to any interaction in **136**.

4.2.6 Reactivity of PS-DVB-supported titanium catalysts using ligands 137-138

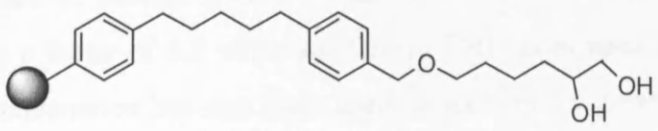
Diol-functionalised, spacer-modified resins **139** and **140** were derived from commercially available chloromethylated resin **131** (Fig. 42) and it was thought they could



131
(chloromethylphenylpentyl)-polystyrene



139



140

Fig. 42

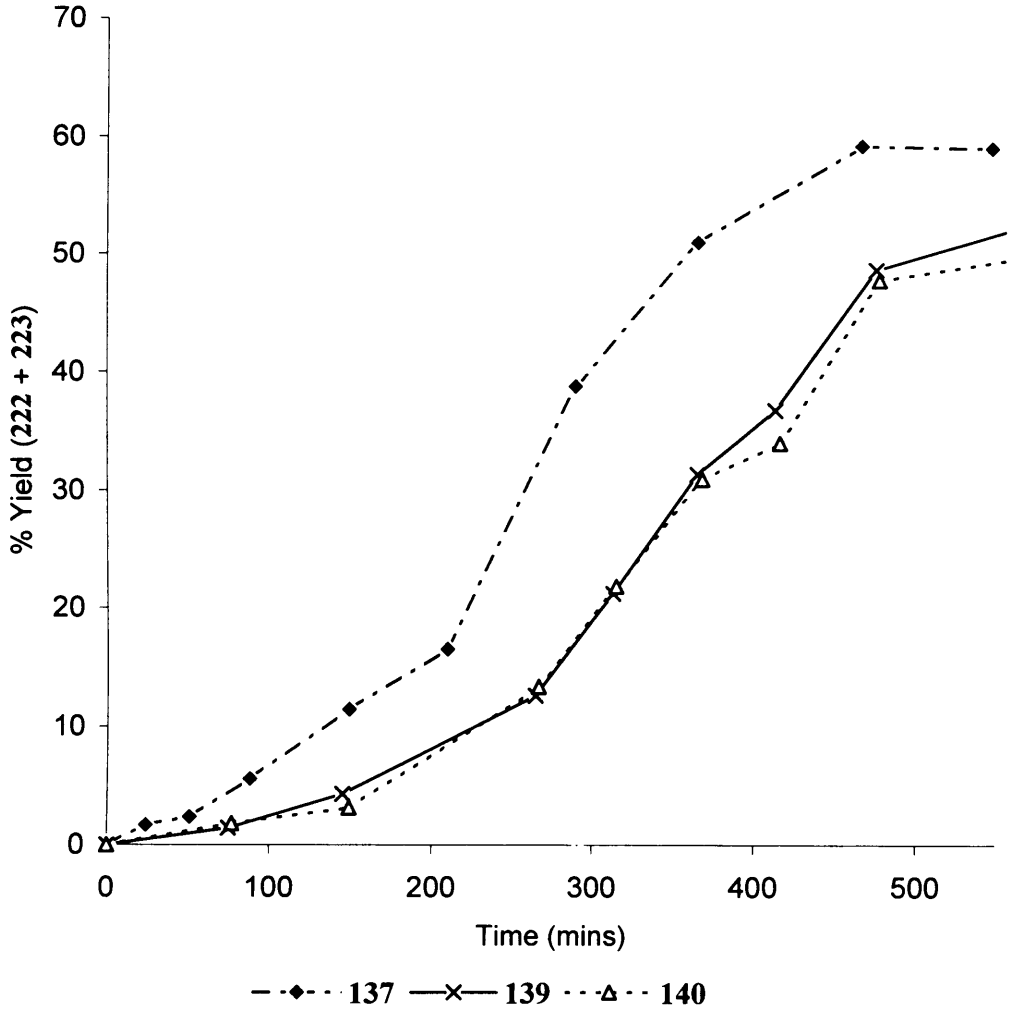


Fig. 43 Reaction of cyclopentadiene and methyl acrylate using 2 mol % Ti catalysts derived from **139-140**.

be considered spacer-modified analogues of resins **136** and **137**, respectively. The application of titanium dialkoxides in the Diels-Alder reaction of methyl acrylate and cyclopentadiene derived from **139** and **140** under our test conditions, gave a reaction profile displayed in figure 43. Included for comparison is the result obtained from **137**.

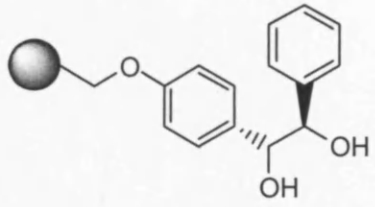
Titanium dialkoxides derived from resins **139** and **140** were found to be less successful catalysts for the formation of cycloadducts **222** and **223** than catalysts obtained using resins **136** and **137**. This poorer reactivity, despite the presence of the spacer group, has been attributed to the inferior swelling ability of the polymer beads **131** from which **139** and **140** were synthesised compared to that for the Merrifield resin used in the synthesis of **136** and **137** (as described in section **2.4.3**). Thus, the bead volume of polymer **131** was shown to increase by a factor of 6.8 when swollen in THF, compared to 8.5 for Avecia Merrifield resin. This explanation has also been used to account for greater difficulty involved in the grafting of alcohols to resin **131** compared to immobilisation reactions undertaken with Merrifield resin. In terms of the catalysis observed, it is

reasonable to suggest that the reduced degree of swelling associated with resin **131** will slow the diffusion of the dienophile and diene through the pores of the polymer matrix resulting in decreased catalyst activity. It would seem that this effect is more significant than any benefit that is produced by the alkyl spacer.

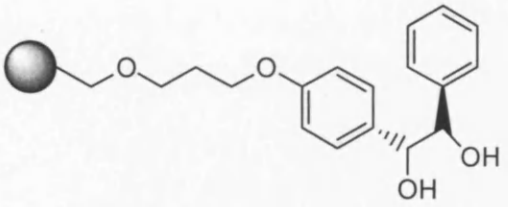
4.3 Asymmetric catalysis using diol-functionalised resins

4.3.1 Introduction

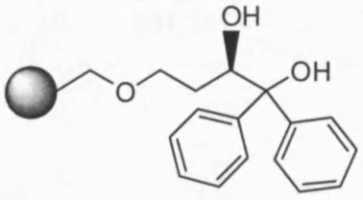
In chapter 3, the synthesis of resins **168-217** (Fig. 44) featuring polymer-bound chiral diols was described. In the following sections, the application of these chiral diols as ligands in asymmetric Lewis acid-catalysed reactions will be discussed. The precedent for using chiral diol ligands in enantioselective Diels-Alder reactions and dialkylzinc additions to aldehydes has been outlined in sections **1.8** and **1.9**, respectively. The substrates employed for these two types of investigation were cyclopentadiene and methacrolein and the addition of diethylzinc to benzaldehyde, respectively. These were chosen as their reactivity is well-established, their transformation to products reliable, and because they are commonly used as test reactions to screen new catalysts, facilitating comparisons with other ligand systems.



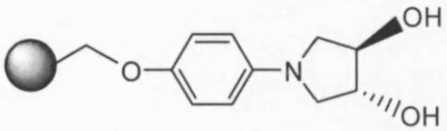
168



173



191



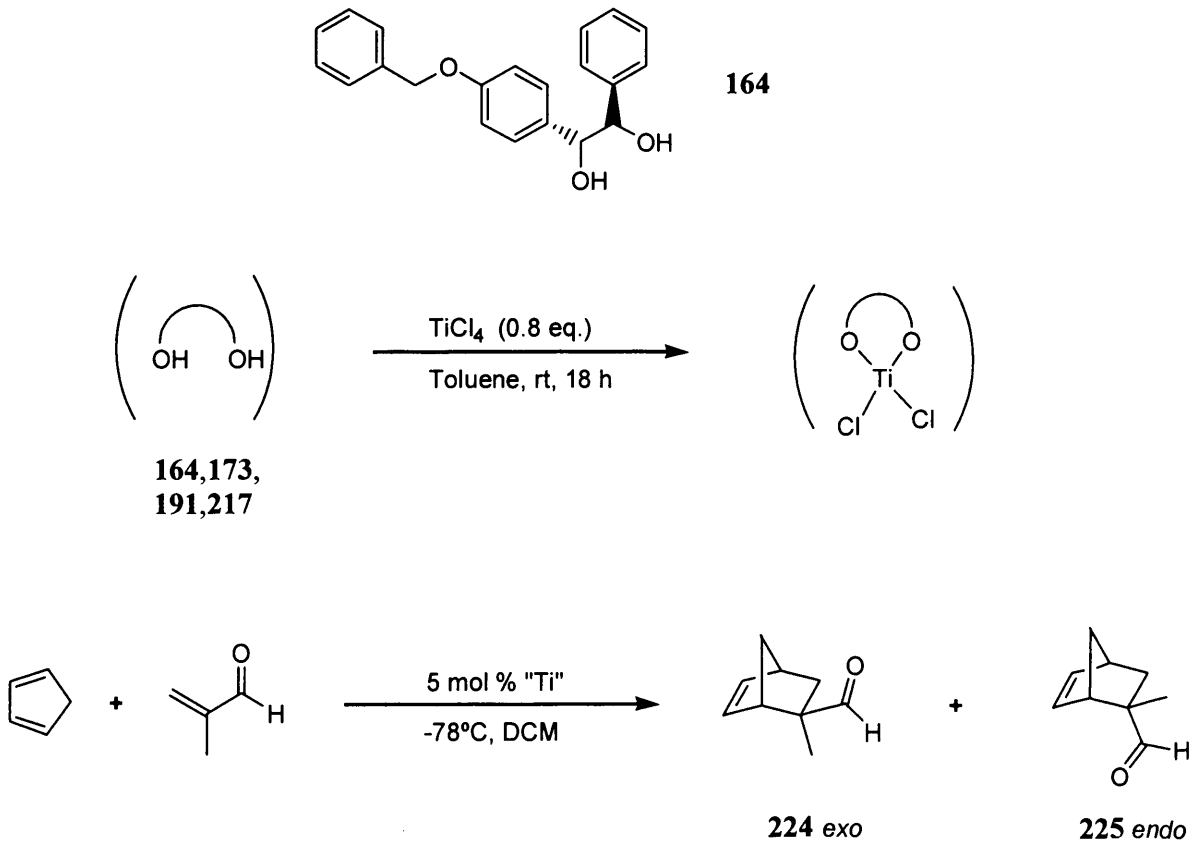
217

Fig. 44

4.3.2 Titanium-catalysed Diels-Alder reaction of methacrolein and cyclopentadiene

Polymeric Diol ligands **173, 191** and **217** (Fig 44) were employed in the titanium-catalysed Diels-Alder reaction of cyclopentadiene and methacrolein (scheme 92). In order to probe the effect of the presence of the polymer matrix itself on catalysis, the homogenous analogue **164** (scheme 92) was also tested. The method of preparation of the heterogeneous catalysts was the same as that outlined in section **4.2.2**, with the diol being treated with a substoichiometric quantity of titanium tetrachloride in order to form the corresponding chelated dialkoxy dichlorides (scheme 92). In reactions involving immobilised ligands **173, 191** and **217**, the beads were treated with solutions of $TiCl_4$ and washed with DCM prior to use and titanium loadings were confirmed by ICP-AE analysis of the combined polymer washings (using a methodology as outlined in section **4.2.2**). The analyses confirmed that uptake of all titanium had been achieved.

The results obtained in reactions using 5 mol % of titanium catalysts generated using diols **164** and **173, 191** and **217** in reactions performed at -78°C in DCM are shown in table 17. Reactions were stirred at -78°C for 8 hours before being allowed to warm to quickly to room temperature at which point they were quenched. In all cases combined



Scheme 92

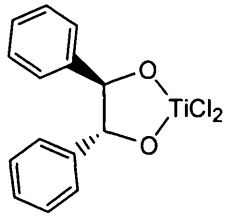
yields of cycloaddition products **224** and **225** obtained were nearly quantitative. Yields and *exo/endo* selectivities were consistent with titanium-based polymer-supported catalysts previously reported.[52,55]

Entry	Ligand	Yield **224** + **226** (%)	*exo/endo* (%)	ee (%)
1	**164**	98	90/10	12
2	**173**	97	91/9	17
3	**191**	98	93/7	35
4	**217**	98	90/10	0

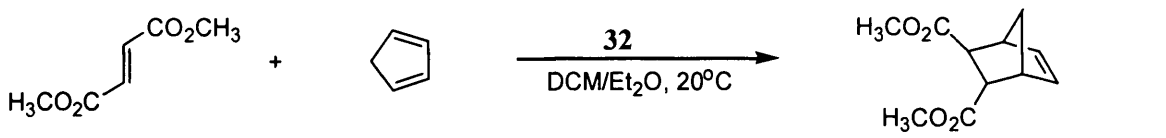
Table 17. Diels-Alder reaction of methacrolein and cyclopentadiene using 5 mol % chiral Ti catalysts.

Enantiomeric excesses observed in the major (*exo*) product, which were determined by ^{1}H NMR spectroscopic analysis of diastereotopic formyl protons in the presence of chiral lanthanide shift reagent, Eu(hfc)$_3$, were found to be low.

The homogenous catalyst derived from **164** and its supported analogue originating from **173** gave similar results, with no significant difference observed in either the *exo/endo* selectivity or enantioselectivity. The most relevant comparison of results obtained from 1,2-diarylethanediol-based ligands **164** and **173** with previously reported systems, is in reactions employing titanium dichloride derivative **32** (scheme 93).[48] This ligand was shown to catalyse the Diels-Alder cycloadditions of various dienes and carboxylic ester dienophiles with ee's of up to 92 % (see section **1.8.1**, table 3). However for this system, high ee's were only observed in reactions employing a stoichiometric quantity of titanium catalyst, at lower loadings, enantioselectivity was found to markedly



32

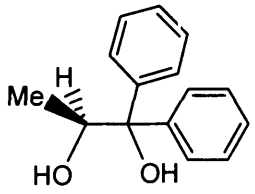


86 %, 80 % ee (1 eq. **32**)
90 %, 16 % ee (0.25 eq. **32**)

Scheme 93

decrease. For example, the Diels-Alder reaction of cyclopentadiene and dimethyl fumarate was reported to proceed in 86 % yield and 80 % ee with one equivalent of **32**, compared to 90 % yield and 16 % ee in the presence of 0.25 equivalents of **32**. From these previously reported results, it could be envisaged that use of titanium catalysts prepared from **164** and **173** at higher catalyst loadings than 5 mol %, or in other Diels-Alder reactions using more sterically challenging substrates, would lead to significantly improved enantioselectivities. Clearly, further investigation into cycloadditions using these ligands is therefore required. In reactions involving polymer-supported diol **173**, the disadvantages of using a higher loading of catalyst may well prove to be negated by the benefits obtained by heterogenisation of the system.

The comparable *exo*/*endo* selectivity and ee obtained using diols **164** and **173** may suggest a similar catalytic activity. This could be due to low activity of the catalyst derived from **164** caused by association of the titanium centre with the benzyloxy-group in an intermolecular manner similar to that described in Fig. 38a. Thus, site-isolation effects in the supported variant derived from **173**, may lead to a catalyst where the expected decrease in activity caused by immobilisation on a polymer-support is cancelled out by an increase in activity due to site-isolation. In order to investigate the relative reaction rates of catalysts derived from **164** and **173**, one method would be to conduct variable-temperature NMR studies into the formation of the reaction products.

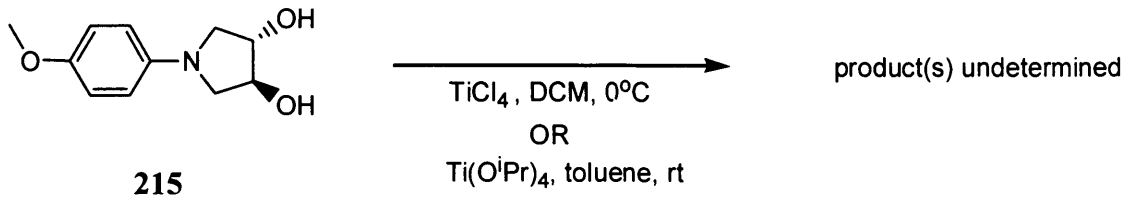


31

Fig. 45

Supported catalyst **191** gave the best enantioselectivity, with an ee of 35 % observed for the *exo* product **224**. Again, use of catalyst loadings higher than 5 mol % may have led to improved selectivity. The use of the homogenous analogue **31** of supported diol **191** (Fig. 45) in the same reaction has previously been shown to give an ee of 73 % in an aluminium-catalysed reaction employing 10 mol % of Lewis acid.[47] No titanium dichloride-based analogues have been reported for comparison.

The results obtained using the catalyst derived from pyrrolidine diol **217** demonstrate the benefits of "site-isolation" (or pseudodilution[56,57]) that are possible when a species is immobilised on a PS-DVB support. Since the novel chiral, C_2-symmetric diol

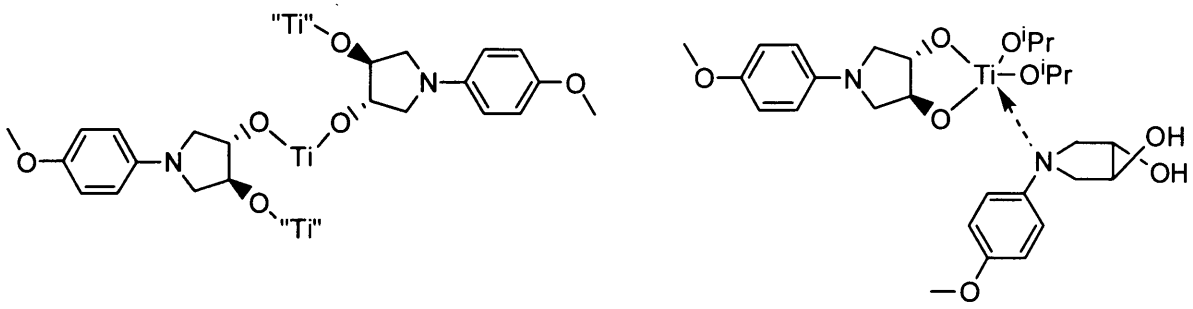


215

Scheme 94

diol **215** could be prepared with comparative ease, it was tempting to prepare a PS DVB resin (**217**) bearing this functionality and to then test its applicability in the asymmetric Diels-Alder reaction.

The homogenous variant of supported diol **217**, **215**, was found to form an insoluble product when treated with one equivalent of titanium tetrachloride in DCM (scheme 94), something that could potentially arise for a number of different reasons. Firstly an insoluble ammonium salt could form, resulting from the reaction of liberated hydrogen chloride with the pyrrolidine nitrogen of the bound ligand. Secondly, formation of alkoxy-titanium-bridged polymers (*e.g.* Fig. 46a) may occur and, thirdly, complexation of the tertiary nitrogen of the pyrrolidine ring to the Lewis acidic centre (Fig. 46b) could also result in polymerisation. Analysis of the insoluble material was unsatisfactory and the structure could not be elucidated.



a b

Fig. 46

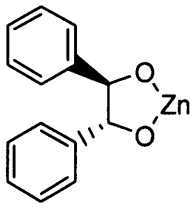
In order to eliminate the possibility of problems arising from ammonium salt formation, **215** was treated with one equivalent of titanium tetraisopropoxide in toluene (scheme 94) in an attempt to form the bis(isopropoxide) derivative through liberation of isopropanol. The resulting product was sparingly soluble in non-coordinating solvents of medium polarity. The ^{1}H NMR spectrum of this material was inconclusive, with free isopropanol detected and broad signals observed for metal-bound isoproxy groups, suggesting possible fluxional behaviour. The product was found to be inactive as a catalyst in the Diels-Alder reaction of methacrolein and cyclopentadiene at -78°C, with no

formation of cycloadducts **224** and **225** being detectable (see scheme 92) after 4 hours, possibly as a result of inter- or intra-molecular donor acceptor interactions blocking substrate binding. Since there was no catalytic activity, no further efforts were made to identify the Ti-containing product.

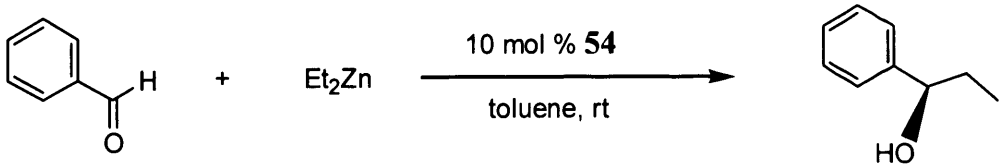
In an attempt to prevent any possible catalyst deactivation resulting from intermolecular association, the resin-bound analogue was prepared with a view to utilising "site isolation" effects in this regard. This strategy proved partially successful, with immobilisation of the diol on PS-DVB beads to give resin **217** (Fig. 44) leading to an active catalyst for an identical Diels-Alder reaction, following addition of $TiCl_4$, with the results displayed in table 17. The activity of the polymer-bound species has been accounted for by prevention of formation of aggregates analogous to those shown in Figs 24 and 36 as envisaged above. This explanation has previously been used to rationalise the improvement in activity of amino alcohols when bound to a polymer-support, compared to in solution phase, in aluminium-catalysed Diels-Alder reactions.[56,57] The absence of any enantioselectivity in the reaction is presumably due to the low steric influence of the chelating diol on the titanium centre. It is possible that the enantioselectivity of this type of system may be improved by introduction of bulky alkyl/aryl substituents to the pyrrolidine ring, but the synthesis of such ligands, however, may prove to be synthetically challenging.

4.3.3 Titanium-catalysed asymmetric diethylzinc addition to benzaldehyde

1,2-Diphenylethanediol has previously been shown to give a good yield (98 %) and ee (89 %) when used as a chelating ligand in a homogeneous zinc dialkoxide (**54**)-



54

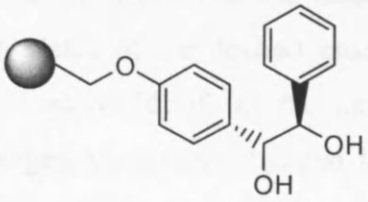


98 %
89 % ee

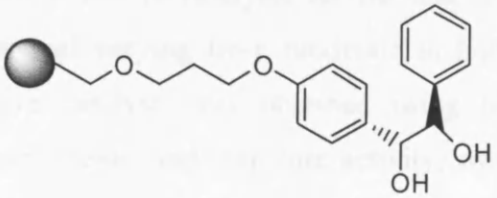
118

Scheme 95

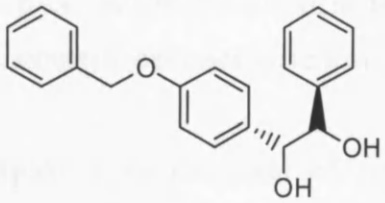
catalysed addition of diethylzinc to benzaldehyde (scheme 95, see also section **1.9.1**).[65] It was hoped that modification of resins **168** and **173** with titanium would lead to new



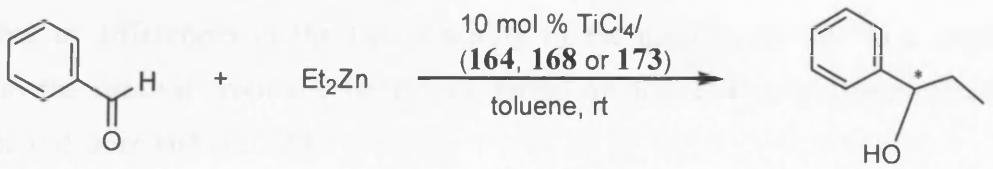
168



173



164



Scheme 96

heterogenised asymmetric catalysts for this reaction. In addition, it was of interest to investigate the effect of the spacer group in resin **173** on the performance of the potential supported catalyst compared to its non-spacer modified analogue **168** and also in comparison with a homogenous variant derived from **164**.

1,2-Diarylethanediol-based ligands **164**, **168** and **173** were screened in the Lewis acid-catalysed addition of diethylzinc to benzaldehyde (scheme 96). The titanium dichloride catalysts were formed by addition of titanium tetrachloride to a solution of diol **164**, or to a suspension of functionalised resins **168** and **173** swollen in toluene, at 0°C. Results from the ICP-AE titanium analyses of washings from resins **168** and **173** following treatment with $TiCl_4$ showed complete uptake of titanium by the resin. At room temperature, benzaldehyde was added to the catalyst (10 mol %) in toluene and after 30 minutes, two equivalents of diethylzinc were added. The mixture was shaken at room temperature for 24 hours before the reaction was quenched and, after workup, the composition of the crude mixture analysed by ^{1}H NMR spectroscopy.

The room temperature addition of diethylzinc to benzaldehyde in toluene has previously been reported to proceed slowly, in the absence of an added catalyst, to give a

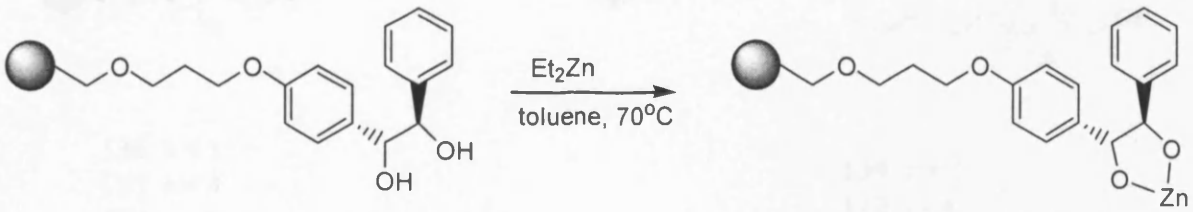
35 % yield of 1-phenylpropanol after 24 hours.[72] The results obtained in alkylation reactions using 10 mol % of catalysts derived from **164-173** are summarised in table 4. The results show that the titanium dialkoxides were effective catalysts for the reaction, with yields of the desired product 1-phenylpropan-1-ol varying from moderate to high. The best yield of 93 %, and hence most active catalyst, was obtained using the homogenous system obtained from diol **164**. Poorer yields, and therefore activity, were observed using supported ligands **168** and **173**. The catalyst produced from resin **173** with a spacer separating the titanium complex from the polymer backbone, proved a more effective catalyst than its non-spacer modified equivalent **168**, giving an improved yield of 83 % compared to 68 %. Enantiomeric excesses were low, however, and were comparable for all three catalyst systems.

In all reactions attempted, both the yield of 1-phenylpropan-1-ol and the ee observed were lower than was previously reported in the reaction employing homogenous zinc-alkoxide catalyst **54** (scheme 95).[64] This difference in activity and selectivity could be due either to differences in the Lewis acidity of the catalyst, or due to a negative influence on the catalyst from the benzyloxy group of diol **164** or polymer-effects in catalysts derived from **168** and **173**.

Entry	Ligand	Lewis acid	Yield 1-phenylpropan-1-ol[a] (%)	ee[b] (%)
1	**164**	Ti	93	34
2	**168**	Ti	68	33
3	**173**	Ti	84	39
4	**173**	Zn	89	35

Table 18. Diethylzinc additions to benzaldehyde; [a] Determined by ^{1}H NMR; [b] Determined by ^{1}H NMR in presence of 0.3 mol eq. $Eu(hfc)_3$.

In order to investigate this, the addition of diethylzinc to benzaldehyde was attempted using the zinc dialkoxide-based analogue of the titanium catalyst derived from **173** (*i.e.* a heterogenised analogue of **54**, scheme 95). Accordingly, diol **173** was heated to



173 **226**

Scheme 97

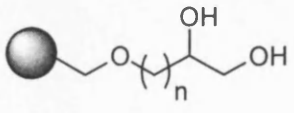
70°C in toluene with diethylzinc in order to form the zinc dialkoxide **226** (scheme 97). This was used immediately in the room temperature addition of diethylzinc to benzaldehyde. The reaction was found to proceed in 89 % yield and 35 % ee, near-identical to the values obtained for the Ti-containing systems. This suggests that the poorer activity of catalysts **164**, **168** and **173** relative to **54** is due primarily to an inhibiting effect either of the benzyloxy group (for catalyst derived from **164**) or of the polymer matrix (catalysts derived from **168** and **173**).

4.4 Summary and conclusions

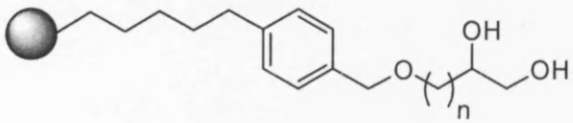
The aim of this chapter was to explore the reactivity of diol-functionalised PS-DVB resins, the syntheses of which were described in chapters 2 and 3, as supports for Lewis acid catalysts. The diols were treated with $TiCl_4$ to form the corresponding supported titanium(IV) dichlorides and employed in reactions chosen for their anticipated convenience in terms of reaction monitoring, reliability and existing literature precedent.

Section **4.2** described an investigation into the use of titanium-functionalised resins derived from functionalised-polymers **136-140** (Fig. 47) as catalysts in the Diels-Alder reaction of methyl acrylate and cyclopentadiene. It was shown the a nine-carbon methylene spacer between the catalyst and polymer matrix (catalyst derived from **138**) may have caused an observed improvement in the activity of the tethered titanium(IV) dichloride species, relative to non-spacer modified analogues derived from diols **136** and **137**. The activity of the catalyst derived from **138** was still poor compared to that of a solution-phase analogue obtained from **221**, however. A significant drop in reactivity was seen in reactions employing catalysts derived from **139** and **140**, when compared to those generated from **136-137** despite the presence of the spacer (in **139** and **140**). This is presumed to be due to the slightly poorer swelling behaviour of these polymer-beads.

Thus, it may be concluded from the observations above, that whilst a spacer group



136 n = 1
137 n = 4
138 n = 9



139 n = 1
140 n = 4

Fig. 47

may improve the performance of an insoluble-polymer-bound catalyst, the morphology of the support remains the major factor in determining its reactivity. The problems associated with diffusion of solution-phase reactants to active sites on an insoluble support mean that if the desire is to truly match the high performance of homogenous catalysts, alternative methods of heterogenisation should be considered. An example is the use of soluble-polymer supports, an area of chemistry which has already been the subject of much attention.[157,158]

In section **4.3** preliminary investigations were reported into the use of PS-DVB resins functionalised with chiral diols as supports for catalysts in the asymmetric Diels-Alder reaction of methacrolein and cyclopentadiene and diethylzinc additions to benzaldehyde. The enantio-selectivities reported are somewhat disappointing, however it is worth noting that no attempt was made to optimise these values, for example by varying the Lewis acid used or loading of catalyst.

In all of the catalytic applications investigated in this chapter, it has been suggested there may be a detrimental effect caused by the presence of a remote, coordinating oxygen atoms in the catalyst "linkers" or tethers. It is believed that these effects are less significant for support-bound catalysts than for their solution phase analogues. Despite this apparent site-isolation effect that is being observed, the performance of support-bound catalysts may still be improved by use of supports of a more inert nature, with no oxygen atoms in the tether; *i.e.* by use of purely hydrocarbon linkers. Alkylation of polystyrene, for example by Suzuki coupling[159-161], has already been reported and may be a strategy worth investigating.

Chapter 5

Experimental

5 Experimental

Air/moisture sensitive operations were conducted under an atmosphere of dry nitrogen using standard Schlenk and cannula techniques. Where necessary, solvents were freshly distilled under nitrogen from sodium/benzophenone (diethyl ether, toluene, THF), from sodium (hexane, 1,4-dioxane), from calcium hydride (acetonitrile, DCM, MeOH) or from P_2O_5 ($CDCl_3$). Molecular sieves were activated by oven drying, then irradiating in a conventional microwave for three 10 minute periods. Where appropriate, liquid reagents were dried, distilled and deoxygenated prior to use.[162] 4-Styryl-phenol was obtained from Acros Organics. Diethylzinc was obtained from Fluka. All other chemicals were purchased from Aldrich. Chloromethylated polystyrene (Merrifield resin, 1 mmol g^{-1} Cl) used was supplied by Avecia and prepared by copolymerisation of styrene, DVB (2%) and 4-vinylbenzyl chloride according to a proprietary procedure. (Chloromethylphenylpentyl)-polystyrene (2 % cross-linked, 1 mmol g^{-1}) was obtained from Aldrich. Cyclopentadiene was obtained from thermal retro-Diels Alder reaction from dicyclopentadiene, by distillation and used immediately.

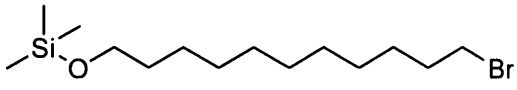
Laboratory coat, safety spectacles and gloves were worn at all times, and all experiments conducted in an efficient fume-hood, following completion of appropriate COSHH assessments. Solvents were disposed of in the appropriate waste solvent recepticles (chlorinated/non-chlorinated), metal containing or organic waste in the appropriate residue vessels.

Routine NMR spectra were collected on a Bruker AM250 or DPX300 at ambient probe temperatures (~290 K) unless stated otherwise. Chemical shifts were referenced to residual protio impurities in the deuterated solvent (^1H), ^{13}C shift of the solvent (^{13}C). Solvent proton shifts (ppm): $CDCl_3$, 7.27 (s); Acetone-d_6, 2.04 (quint); DMSO-d_6, 2.49 (quint); CD_3OD, 3.30 (quint). Solvent carbon shifts (ppm): $CDCl_3$, 77.0 (t); Acetone-d_6, 29.8 (sept), DMSO-d_6, 39.7 (sept), CD_3OD, 49.0 (sept). ^{13}C NMR spectra were assigned with the aid of DEPT 135 experiments and ChemDraw Ultra[163] theoretical shift calculations. Gel-phase ^{13}C NMR spectra of polystyrene resins were obtained on a Bruker ARX 300 machine following a modified literature procedure.[29] Approximately 80 mg of resin was placed in a 5mm NMR tube and 0.6 mL of solvent (carbon tetrachloride/benzene-d6 (4:1) or $CDCl_3$). The resin was given time to swell (10 mins) prior to obtaining spectra. Chemical shifts are reported in ppm and coupling constants in Hz. NMR spectra obtained under CP MAS NMR were acquired by Dr. D. Apperley of the

EPSRC Solid State NMR Service (University of Durham) using an Varian UNITY*Inova* spectrometer.

FAB (3-nitrobenzyl alcohol matrix) and EI mass spectra were recorded on a Kratos Concept 1H instrument and are reported in *(m/z)*. Elemental analyses (for isolated compounds only) were performed by the Warwick Analytical Service Ltd (University of Warwick Science Park, Coventry) or S. Boyer (London Metropolitan University). ICP-AES analyses were obtained by E. Mansley (Department of Geology, University of Leicester). Infrared spectra were collected on a Infrared spectra were collected on a Perkin Elmer 1600 spectrophotometer using KBr discs or a solution cell with KBr windows or on a Perkin Elmer Spectrum1 apparatus fitted with a diamond anvil ATR device. GC-MS were performed using a Perkin-Elmer Autosystem XL GC machine (PE-5MS 30 m coil, internal diameter = 0.25 mm, film thickness = 0.25 μm) coupled to a Perkin-Elmer Turbomass mass spectrometer.

Preparation of (11-bromo-undecyloxy)-trimethyl-silane (73)

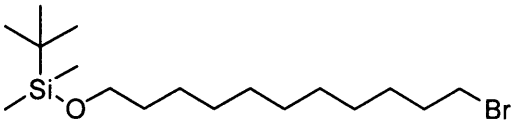


To a stirred solution of 11-bromoundecanol (4.00 g, 15.9 mmol) in THF (50 mL) was added trimethylsilyl chloride (2.08 g, 2.43 mL, 19 mmol) and Et_3N (2.41 g, 3.32 mL, 19 mmol). The mixture was stirred overnight, during which time a white solid precipitated. The mixture was filtered and insoluble components washed with THF (2 x 20 mL). Volatile components were removed from the filtrate and combined washings under reduced pressure to a yellow oil which was purified by vacuum distillation. Silyl ether **73** was obtained as a colourless oil (4.15 g, 81 %) (b.p 125-128°C, 0.5 mmHg, Lit. value = 120-124).[164]

^{1}H (250.13 MHz, $CDCl_3$) δ: 3.62 (2H, t, $^3J_{HH}$ = 7.1, CH_2OSi), 3.46 (2H, t, $^3J_{HH}$ = 6.8, CH_2Br), 1.91-1.80 (2H, m, CH_2CH_2Br), 1.59-1.31 (2H, m, CH_2CH_2Br), 1.26 (s, 14H, $CH_2CH_2CH_2$), 0.10 (9H, s, $SiC(CH_3)_3$).

MS (EI^+): 324$(M)^+$, 322$(M)^+$, 276, 262, 181, 174, 163, 137, 122.

Preparation of (11-bromo-undecyloxy)-t-butyldimethyl-silane (74)



To a stirred solution of 11-bromoundecanol (10.02 g, 39.8 mmol) in THF (200 mL) was added imidazole (3.26 g, 48 mmol) followed by t-butyldimethylsilyl chloride (8.00 g, 53 mmol). The solution was stirred at room temperature for 18 h then quenched with aqueous ammonium chloride (100 mL). The mixture was extracted with ethyl acetate (3 x 50 mL) and the combined organic phases were washed with 1M HCl (2 x 50 mL), aqueous $NaHCO_3$ (2 x 50 mL) and aqueous NaCl (2 x 50 mL) and then dried ($MgSO_4$) and reduced on a rotary evaporator to give a colourless oil. Purification of this oil by chromatography on silica gel {$CHCl_3$/Hexane, 1:4, TLC: R_f 0.64 ($CHCl_3$/Hexane, 1:4)} gave silyl ether **74** (13.96 g, 96 %). Characterisation was consistent with previously reported data[165] and no further purification was undertaken.

^{1}H (250.13 MHz, $CDCl_3$) δ: 3.63 (2H, t, $^3J_{HH}$ = 7.1, CH_2OSi), 3.45 (2H, t, $^3J_{HH}$ = 6.8, CH_2Br), 1.91 (2H, m, CH_2CH_2Br), 1.61-1.40 (2H, m, CH_2CH_2OSi), 1.36 (14H, overlapping m, $CH_2CH_2CH_2$), 0.91 (9H, s, $SiC(CH_3)_3$), 0.10 (6H, s, $SiCH_3$). Consistent with previously reported data.[165]

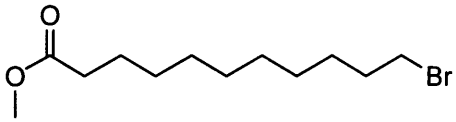
^{13}C (62.90 MHz, $CDCl_3$) δ: 63.7 (CH_2OSi), 34.3 (CH_2Br), 33.3, 33.3, 32.0, 30.0, 29.8, 29.6, 29.2, 28.6 (all CH_2; specific assignment not possible), 26.4 ($SiC(CH_3)_3$), 26.2 (CH_2), 18.7 ($SiC(CH_3)_3$), -4.9 ($SiCH_3$).

MS (EI^+): 366 $(M)^+$, 364$(M)^+$, 294, 276, 262, 153, 122, 102.

Attempted preparation of (12-acetyl-13-oxotetradecyloxy)-t-butyldimethyl-silane (75)

To a stirred solution of **74** (2.00 g, 5.48 mmol) in acetonitrile (30 mL) and DMSO (7.5 mL) was added K_2CO_3 (0.9 g, 7 mmol), Cs_2CO_3 (0.1g) and pentane-2,4-dione (0.55 g, 5.44 mmol). The suspension was stirred at 60°C for 48 h. After 24 h a second 0.55g portion of pentane-2,4-dione was added. The orange mixture was allowed to cool then $CHCl_3$ (200 mL) was added and the organic layer was washed with water (5 x 200 mL). The organic layer was then dried ($MgSO_4$) and reduced on a rotary evaporator to give a yellow oil. The crude product was shown by GC-MS to contain two major products in 69% and 29% yields. The product decomposed upon attempted vacuum distillation.

Preparation of 11-bromo-undecanoic acid methyl ester (77)[166]



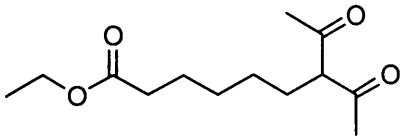
11-bromo-undecanoic acid methyl ester (**77**) was prepared according to a modified literature procedure[166] as follows: 11-bromo-undecanoic acid (20g, 75.4 mmol) was dissolved in methanol (100 cmL) and conc. aqueous H_2SO_4 (2 mL) was added. The mixture was heated at reflux overnight, allowed to cool, then extracted with CH_2Cl_2 (3 x 50 mL). The organic extracts were combined, washed with aqueous $NaHCO_3$ (2 x 50 mL), and water (3 x 50 mL) then dried ($MgSO_4$). Removal of volatile components gave a crude oil that was purified by vacuum distillation. Methyl 11-bromo-undecanoate (b.p 145-148°C, 0.5 mmHg, Lit. value = 154-156°C)[82] was obtained as a colourless oil (20.46 g, 97.0 %).

^{1}H (250.13 MHz, $CDCl_3$) δ: 3.65 (3H, s, CO_2CH_3), 3.40 (2H, t, $^3J_{HH}$ = 6.8, CH_2Br), 2.31 (2H, t, $^3J_{HH}$ = 7.0, $CH_2CO_2CH_3$), 1.85-1.74 (2H, m, CH_2CH_2Br), 1.69-1.51 (m, 2H, $CH_2CH_2CO_2CH_3$), 1.50-1.30 (10H, overlapping m, $CH_2CH_2CH_2$).

^{13}C (62.90 MHz, $CDCl_3$) δ: 174.2 (CO_2CH_3), 51.4 (CO_2CH_3), 34.0 (CH_2CH_2Br), 33.9 ($CH_2CO_2CH_3$), 32.8 (CH_2Br), 29.3, 29.3, 29.1, 29.0, 28.7, 28.1 (all CH_2; specific assignment not possible), 24.9 ($CH_2CH_2CO_2CH_3$).

MS (EI^+): 249, 247, 199, 167, 149, 139, 121, 107, 105, 93, 83.

Preparation of 11-acetyl-12-oxo-tridecanoic acid methyl ester (79)



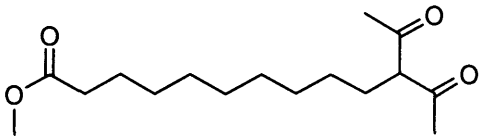
11-Acetyl-12-oxo-tridecanoic acid methyl ester (**79**) was prepared according to a modified literature procedure[81] as follows: To a stirred mixture of methyl 11-bromoundecanoate (**78**) (5 g, 17.9 mmol), acetonitrile (21 mL) and DMSO (6 mL) was added K_2CO_3 (2.00 g, 16 mmol), $CsCO_3$ (0.20 g) and pentane-2,4-dione (1.80 g, 18 mmol). The mixture was stirred for 48 hours at 65°C, then poured onto water (100 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The organic extracts were combined, washed with water (5 x 100 mL) and dried ($MgSO_4$). Removal of CH_2Cl_2 on a rotary evaporator gave a yellow oil. The crude product was dissolved in a mixture of glacial acetic acid (100 mL) and sodium acetate (2.00 g) and heated at reflux temperature overnight. The hot solution was poured into cold water and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were washed with 10 % sodium carbonate (3 x 100 mL) and dried ($MgSO_4$). Removal of CH_2Cl_2 under reduced pressure gave a pale yellow oil. The crude product was purified by high-vacuum distillation (Kügelrohr) to give the product **80** as a white waxy solid (1.34 g, 25 %) (b.p. 175°C, $<10^{-5}$ bar). Characterisation was consistent with previously reported data.[81]

^{1}H (250.13 MHz, $CDCl_3$) δ: 3.65 (3H, s, CO_2CH_3), 3.58 (1H, t, $^3J_{HH}$ = 7.0, $CH_2CH(COCH_3)_2$), 2.29 (2H, t, $^3J_{HH}$ = 6.8, $CH_2CO_2CH_3$), 2.17 (6H, s, $CH(COCH_3)_2$), 1.89-1.79 (2H, m, $CH_2CH(COCH_3)_2$), 1.69-1.53 (2H, m, $CH_2CH_2CO_2$), 1.29 (12H, overlapping m, $CH_2CH_2CH_2$).

^{13}C (62.90 MHz, $CDCl_3$) δ: 204.9 ($COCH_3$), 174.7 (CO_2CH_3), 69.5 ($CH_2CH(COCH_3)_2$), 51.9 (CO_2CH_3), 33.9 ($CH_2CH_2CO_2$), 29.8, 29.7, 29.6, 29.5, 29.4, 28.7, 27.9, 25.3 (all CH_2; specific assignment not possible).

HRMS (EI^+): calcd for $C_{13}H_{22}O_3$: 242.1518; found: 242.1518.

Preparation of 7-acetyl-8-oxo-nonanoic acid ethyl ester (80)



Following the same procedure described for the synthesis of **79**, ethyl 6-bromo-hexanoate (**77**) (10g, 44.8 mmol) was reacted with pentane-2,4-dione (4.50 g, 45 mmol) to give a yellow oil which was purified by vacuum distillation to give the product (**80**) as a pale yellow oil (2.8g, 27 %) (b.p. 123°-126°C, 0.5 mmHg). Characterisation was consistent with previously reported data.[82]

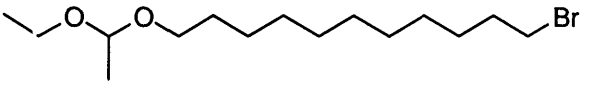
^{1}H (250.13 MHz, $CDCl_3$) δ: 4.01 (2H, q, $^3J_{HH}$ = 7.0, CH_3CH_2O), 3.57 (1H, t, $^3J_{HH}$ = 7.0, $CH_2CH(COCH_3)_2$), 2.28 (2H, t, $^3J_{HH}$ = 7.1, $CH_2CO_2CH_2CH_3$), 2.10 (6H, s, $COCH_3$), 1.90-1.78 (2H, m, $CH_2CH(COCH_3)_2$), 1.39-1.27 (6H, overlapping m, $CH_2CH_2CH_2$), 1.11 (3H, t, $^3J_{HH}$ = 6.9, CH_3CH_2O).

^{13}C (62.90 MHz, $CDCl_3$) δ: 204.6 ($COCH_3$), 173.8 ($CO_2CH_2CH_3$), 69.1 ($CH_2CH(COCH_3)_2$)), 60.5 (CH_3CH_2O), 34.4 ($CH_2CO_2CH_2CH_3$), 30.7 (CH_2; specific assignment not possible), 29.4 ($COCH_3$), 28.3, 27.5, 24.9 (all CH_2; specific assignment not possible), 14.6 (CH_3CH_2O).

MS (EI^+): 265, 187, 155, 137, 109, 95, 91, 81, 67.

HRMS (EI^+): calcd for $C_{17}H_{30}O_3$: 298.2145; found: 298.2144.

Preparation of 1-bromo-11-(1-ethoxy-ethoxy)-undecane (81)

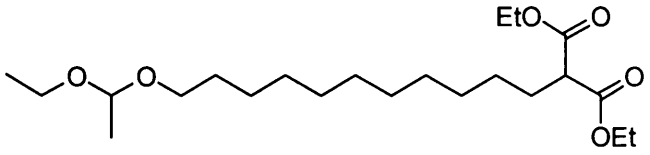


1-bromo-11-(1-ethoxy-ethoxy)-undecane (**81**) was prepared according to a modified literature procedure[83] as follows: 11-bromo-undecanol (25 g, 99.5 mmol) was dissolved in ethyl vinyl ether (50 mL) in a dropping funnel connected to a 3-neck round bottom flask. Approximately 10 mL of this solution was added to the flask and conc. HCl (5 drops) was added with constant stirring. The remaining 11-bromo-undecanol solution was added dropwise and the solution stirred overnight at room temperature. Saturated aqueous $NaHCO_3$ (100 mL) was added, the organic layer separated and the aqueous layer extracted with ether (100 mL). The organic extracts were combined, washed with water (2 x 100 mL) and dried ($MgSO_4$). Removal of volatile components at reduced pressure gave the product as a colourless oil (29.31 g, 92%). Characterisation was consistent with previously reported data[83] and no further purification was undertaken.

^{1}H (250.13 MHz, $CDCl_3$) δ: 4.65 (1H, q, $^3J_{HH}$ = 5.5, C*H*$(OC)_2CH_3$), 3.70-3.40 (4H, overlapping m, OCH_2CH_3 and OCH_2CH_2), 3.39 (2H, t, $^3J_{HH}$ = 7.0, CH_2Br), 1.85 (2H, m, CH_2CH_2Br), 1.61-1.48 (2H, m, CH_2CH_2OC), 1.39-1.27 (17H, overlapping m, CH_3CH and $CH_2CH_2CH_2$), 1.20 (3H, t, $^3J_{HH}$ = 7.0, OCH_2CH_3).

^{13}C (75.78 MHz, $CDCl_3$) δ: 99.5 (*C*H$(OC)_2$), 65.3 (CH_2CH_2OCH), 60.6 (CH_3CH_2OCH), 34.5 (CH_2CH_2Br), 32.10 (CH_2Br), 29.9, 29.6, 29.4, 29.3, 28.6, 28.0, 26.4 (all CH_2; specific assignment not possible), 19.8 ($CH_3CH(OC)_2$), 15.3 (CH_3CH_2OCH).

Preparation of 2-[11-(1-ethoxy-ethoxy)-undecyl]-malonic acid diethyl ester (82)



2-[11-(1-Ethoxy-ethoxy)-undecyl]-malonic acid diethyl ester (**82**) was prepared according to a modified literature procedure[83] as follows: Sodium (1.40 g, 62 mmol) was dissolved in absolute EtOH (30 mL) and the resulting solution then heated to 80°C. Subsequently, diethyl malonate (9.64 g, 60 mmol) was added dropwise with constant stirring. A white precipitate was seen to form. The mixture was heated at reflux for 15 minutes then cooled to 50°C and 1-bromo-11-(1-ethoxy-ethoxy)undecane (**81**) (20.00 g, 61.9 mmol) dissolved in EtOH (100 mL) was added dropwise. The mixture was heated at reflux overnight, resulting in an orange/brown solution. EtOH was removed under reduced pressure and then water (200 mL) was added to the solid residue. Ether (100 mL) was added and the resulting emulsion was broken with aqueous NaCl. The aqueous layer was extracted with ether (3 x 100 mL) and the combined organic extracts were dried ($MgSO_4$) and ether removed *in vacuo* to give the product as a pale yellow oil (23.56 g, 97 %). Characterisation was consistent with previously reported data[83] and no further purification was undertaken.

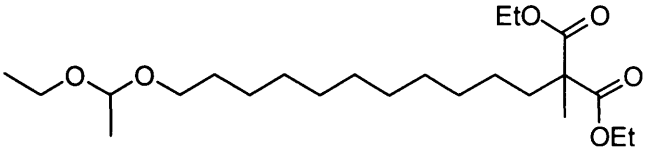
^{1}H (250.13 MHz, $CDCl_3$) δ: 4.65 (1H, q, $^3J_{HH}$ = 5.5, C*H*$(OC)_2CH_3$), 4.15 (4H, q, $^3J_{HH}$ = 7.0, O=COCH_2CH_3), 3.70-3.30 (5H, overlapping m, C*H*$(CO_2)_2$, OCH_2CH_3 and OCH_2CH_2), 1.92-1.80 (2H, m, $CH_2CH_2CH(CO_2)_2$), 1.61-1.50 (2H, m, $CH_2CH_2CH_2OC$), 1.40-1.25 (25H, overlapping m, CH_3CH_2OC=O, $CH_2CH_2CH_2$ and $CH_3CH(OC)_2$), 1.20 (3H, t, $^3J_{HH}$ = 7.0, CH_3CH_2OCH).

^{13}C (62.90 MHz, $CDCl_3$) δ: 169.56 (*C*=O), 99.5 (*C*H$(OC)_2$), 65.3 (CH_2CH_2OCH), 61.2 (CH_3CH_2OC=O), 60.6 (CH_3CH_2OCH), 52.1 (*C*H$(CO_2)_2$), 29.9, 29.5, 29.4, 29.3, 29.2, 28.7,

28.1, 27.3, 26.2 (all CH_2; specific assignment not possible), 19.8 ($CH_3CH(OC)_2$), 15.3 (CH_3CH_2OCH), 14.0 ($CH_3CH_2OC{=}O$).

MS (EI^+): 425 $(MNa)^+$, 374, 357, 313, 220, 180, 161, 122.

Preparation of 2-[11-(1-ethoxy-ethoxy)-undecyl]-2-methyl-malonic acid diethyl ester (83)



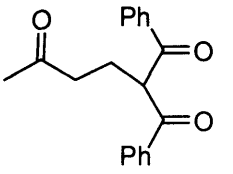
Following an identical procedure to that described for the synthesis of **82**, diethyl methyl malonate (12.8 g, 74 mmol) was reacted with 1-bromo-11-(1-ethoxyethoxy)undecane (**81**) (20.05 g, 62 mmol) to give the β-disubstituted malonate **83** as a yellow oil (4.93g, 98%, greater than 92% purity as shown by GC-MS). The crude oil was used directly in the next step.

^{1}H (250.13 MHz, $CDCl_3$) δ: 4.66 (1H, q, $^3J_{HH}$ = 5.5, $CH(OC)_2CH_3$), 4.17 (4H, q, $^3J_{HH}$ = 7.0, $CH_3CH_2OC{=}O$), 3.67-3.33 (4H, overlapping m, OCH_2CH_3 and OCH_2CH_2), 1.87-1.77 (2H, t, $CH_2CH_2C(CO_2)_2$), 1.67-1.52 (2H, m, $CH_2CH_2CH_2OC$), 1.45 (3H, s, $CH_3C(CO_2CH_2CH_3)$), 1.42-1.15 (28H, overlapping m, $CH_3CH(OC)_2$, $CH_2CH_2CH_2$, $CH_3CH_2OC{=}O$, OCH_2CH_3 and $CH_3CH(OC)_2$).

^{13}C (62.90 MHz, $CDCl_3$) δ: 172.5 ($C{=}O$), 99.5 ($CH(OC)_2$), 65.2 (CH_2CH_2OCH), 61.0 ($CH_3CH_2OC{=}O$), 60.6 (CH_3CH_2OCH), 53.6 ($C(CO_2)_2$), 35.4 ($CH_2C(CO_2)_2$), 29.9, 29.8, 29.5, 29.5, 29.3, 26.2, 25.6, 24.2 (all CH_2; specific assignment not possible), 19.8 ($CH_3CH(OC)_2$), 19.8 ($CH_3C(CO_2)_2$), 15.3 (CH_3CH_2OCH), 14.0 ($CH_3CH_2OC{=}O$).

MS (EI^+): 434, 388, 371 $(M\text{-}CH_3CH_2O)^+$, 357, 345, 327, 238.

Preparation of 2-benzoyl-1-phenyl-hexane-1,5-dione (86)



2-Benzoyl-1-phenyl-hexane-1,5-dione was prepared according to a modified literature procedure[88] as follows: A solution of 1,3-diphenyl-propane-1,3-dione (5.00 g, 22.23 mmol), methyl vinyl ketone (1.85 mL, 22.22 mmol) and $FeCl_3.6H_2O$ (0.32 g, 1.19 mmol) in $CHCl_3$ (10 mL) was stirred at room temperature for 24 hours, during which time it turned dark brown. The crude mixture was transferred directly to a short silica column

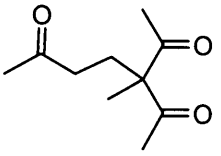
(10 cm) where it was purified by chromatography {Et_2O/hexane, 5:1, TLC: R_f 0.40 (Et_2O/hexane, 5:1)} to give the product as a white solid (6.40 g, 98 %).

^{1}H (250.13, $CDCl_3$) δ: 8.05-8.03 (4H, m, *o*-C_6H_5), 7.60-7.55 (2H, m, *p*-C_6H_5), 7.49-7.43 (4H, m, *m*-C_6H_5), 5.49 (1H, t, $^3J_{HH}$ = 6.6, $CH(COC_6H_5)_2$), 2.71 (2H, t, $^3J_{HH}$ = 6.4, CH_2COCH_3), 2.32 (2H, q, $^3J_{HH}$ = 6.6, CH_2CH_2CH), 2.13 (3H, s, CH_3CO).

^{13}C (62.90, $CDCl_3$) δ: 208.6 (CH_3CO), 196.2 (C_6H_5CO), 135.8 (*i*-C_6H_5), 133.5 (*p*-C_6H_5), 128.8 (*o*-C_6H_5), 128.6 (*m*-C_6H_5), 54.7 ($CH(COC_6H_5)_2$), 40.6 (CH_2COCH_3), 29.9 (CH_3), 23.1 (CH_2CH_2CH).

M.p.: 66-68°C (Lit. Value = 60).[88]

Preparation of 3-acetyl-3-methyl-heptane-2,6-dione (87)



Following an identical procedure to that described for the synthesis of compound **86**, 3-methyl-pentane-2,4-dione (5.10 g, 44.7 mmol) was reacted with methyl vinyl ketone to give the product as a colourless oil (3.60 g, 66 %) after purification by chromatography on silica gel{EtOAc/hexane, 1:2, TLC: R_f 0.30 (EtOAc/hexane,1:2)}. Characterisation was consistent with previously reported data.[88]

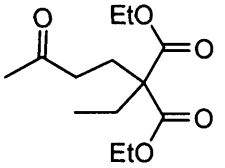
^{1}H (250.13, $CDCl_3$) δ: 2.32 (2H, t, $^3J_{HH}$ = 7.0, CH_2COCH_3), 2.11-2.04 (11H, overlapping m, CH_3CO and $CH_2CH_2C(COCH_3)_2$), 1.27 (3H, s, $CH_3C(COCH_3)_2$).

^{13}C (62.90, $CDCl_3$) δ: 207.1 (*C*O), 65.1 *C*$(COCH_3)_2$, 38.2 (CH_2COCH_3), 29.8 (CH_3COCH_2), 27.5 ($CH_2CH_2C(COCH_3)_2$), 26.4 ($C(COCH_3)_2$), 18.4 ($CH_3C(COCH_3)_2$).

MS (EI^+): 185 $(M)^+$, 167, 159, 141, 125, 115, 89.

HRMS (EI^+): calcd for $C_{10}H_{16}O_3$: 184.1099; found: 184.1099.

Preparation of 2-ethyl-2-(3-oxo-butyl)-malonic acid diethyl ester (88)



Following an identical procedure to that described for the synthesis of compound **86**, with the exception of an increased reaction time of 4 days, 2-ethyl-malonic acid diethyl ester (10.00 g, 53 mmol) was reacted with methyl vinyl ketone to give a crude product which was purified by vacuum distillation (b.p 42-45°C, 0.1 mmHg, Lit. Value = 52-54)[167] affording **88** as a colourless oil (3.30 g, 25 %).

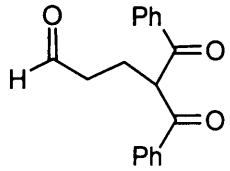
^{1}H (250.13, $CDCl_3$) δ: 4.12 (4H, q, $^3J_{HH}$ = 6.8), 2.44 (2H, t, $^3J_{HH}$ = 7.0, CH_2COCH_3), 2.18-2.05 (5H, overlapping m, CH_3COCH_2 and $CH_2CH_2C(CO_2C)_2$), 1.95-1.81 (2H, q, $^3J_{HH}$ = 6.8, $CH_3CH_2C(CO_2)_2$), 1.20 (6H, t, $^3J_{HH}$ = 6.9, CH_3CH_2O), 0.89 (3H, t, $^3J_{HH}$ = 7.0).

^{13}C (75.75, $CDCl_3$) δ: 207.5 (CH_3CO), 171.4 (CO_2), 61.4 (CH_3CH_2O), 57.0 ($C(CO_2C)_2$), 38.6 (CH_2COCH_3), 29.9 (CH_3COCH_2), 26.2, 25.7 (both CH_2, specific assignment not possible), 14.0 (CH_3CH_2O), 8.4 (CH_3CH_2C).

MS (EI^+): 259 $(M)^+$, 231, 213, 185, 159, 141, 89.

HRMS (EI^+): calcd for $C_{13}H_{22}O_5$: 258.1467; found 248.1467.

Preparation of 4-benzoyl-5-oxo-5-phenyl-pentanal (89)



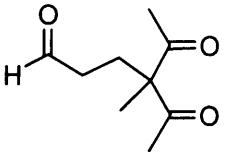
4-benzoyl-5-oxo-5-phenyl-pentanal (89) was prepared according to a modified literature procedure[89] as follows: A solution of 1,3-diphenyl-propane-1,3-dione (2.00 g, 8.91 mmol), acrolein (0.65 mL, 9.80 mmol), $CeCl_3.7H_2O$ (0.66 g, 1.78 mmol) and NaI (0.13 g, 0.89 mmol) in MeCN (2 mL) was stirred at room temperature overnight. DCM (50 mL) was added to the orange/brown mixture, which was then filtered and the filtrate concentrated under reduced pressure to leave a viscous brown oil. The crude product was purified by chromatography on silica gel {EtOAc/hexane, 1:2, TLC: R_f 0.35 (EtOAc/hexane,1:2)}to give the product as a white solid (1.20 g, 48 %).

^{1}H (250.13, $CDCl_3$) δ: 9.78 (1H, s, *H*C=O), 8.07-8.02 (4H, m, *o*-C_6H_5), 7.61-7.55 (2H, m, *p*-C_6H_5), 7.48-7.40 (4H, m, *m*-C_6H_5), 5.49 (1H, t, $^3J_{HH}$ = 6.6, $CH(COC_6H_5)_2$), 2.68 (2H, t, $^3J_{HH}$ = 6.4, CH_2COH), 2.37 (2H, q, $^3J_{HH}$ = 6.6, CH_2CH_2CH).

^{13}C (62.90, $CDCl_3$) δ: 201.6 (HC=O), 195.9 (C_6H_5CO), 135.8 (*i*-C_6H_5), 133.6 (*p*-C_6H_5), 128.8 (*o*-C_6H_5), 128.5 (*m*-C_6H_5), 54.7 ($CH(COC_6H_5)_2$), 41.5 ($CH_2C(O)H$), 21.7 (CH_2CH_2CH).

MS (EI^+): 281 $(M)^+$, 225, 200, 159.

Preparation of 4-Acetyl-4-methyl-5-oxo-hexanal (90)



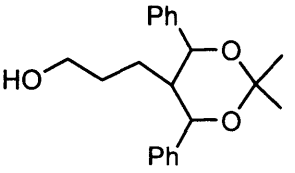
Following an identical procedure to that described for the synthesis of compound **89**,

3-methyl-pentane-2,4-dione (1.00 g, 8.77 mmol) was reacted with acrolein to give the product as a white solid (0.38 g, 25 %) after purification by chromatography on silica gel {EtOAc/hexane, 1:2, TLC: R_f 0.35 (EtOAc/hexane,1:2)}.

^{1}H (301.24, $CDCl_3$) δ: 9.72 (1H, s, *H*C=O), 2.40 (2H, t, $^3J_{HH}$ = 6.7), 2.11-2.03 (8H, overlapping m, C*H*$_3$CO and $CH_2CH_2C(COCH_3)_2$), 1.40 (3H, s, *C*H$_3$C(COCH$_3$)$_2$).

^{13}C (75.47, $CDCl_3$) δ: 207.0 (CH_3CO), 200.7 (H*C*=O), 65.3 *C*(COCH$_3$)$_2$, 39.0 (*C*H$_2$C(O)H), 26.5 ($CH_2CH_2C(COCH_3)_2$), 25.9 (C(CO*C*H$_3$)$_2$), 18.4 (*C*H$_3$C(COCH$_3$)$_2$).

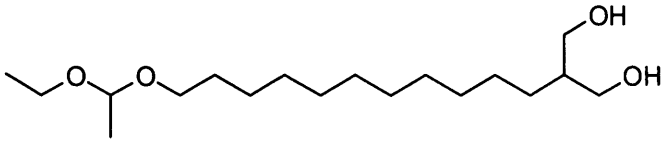
Preparation of 3-(2,2-Dimethyl-4,6-diphenyl-[1,3]dioxan-5-yl)-propan-1-ol (91)



To a cooled (0°C) solution of 4-benzoyl-5-oxo-5-phenyl-pentanal (**89**) (3.70 g, 12.57 mmol) in ether (50 mL), in a 250 mL, 3-neck round bottom flask, fitted with a reflux condenser and pressure-equalising dropping funnel, was added $LiAlH_4$ (1M solution in ether, 37 mL, 37 mmol) dropwise *via* the pressure-equalising dropping funnel. Formation of a white precipitate was observed upon addition. The mixture was allowed to warm to room temperature and then refluxed overnight. Non-dried ether was added (30 mL), followed by successive addition of water (5 mL), 15 % aqueous NaOH (5 mL) and water (20 mL). The mixture was filtered and the white precipitate washed with ether (2 x 50 mL). The filtrate was washed with water (50 mL) and the organic layer separated, dried ($MgSO_4$) and solvent removed under reduced pressure to give a yellow oil. The oil was dissolved in DCM (30 mL) and DMP (2 mL) was added followed by *p*-TsOH (50 mg). The light brown solution was stirred overnight then diluted with saturated aqueous $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic fractions were dried ($MgSO_4$) and volatile components removed *in vacuo* to leave a brown oil which was purified by chromatography on silica gel {EtOAc/hexane, 1:2, TLC: R_f 0.35 (EtOAc/hexane, 1:2)} to give a white solid found to be a mixture of diastereoisomers which were not separated (0.400 g ,10.4 %).

^{1}H (250.13 MHz, $CDCl_3$) δ: 7.51-7.28 (10H, overlapping m, *o,m,p*-C$_6$*H*$_5$), 4.72 (2H, d, $^3J_{HH}$ = 8.0, C*H*C$_6$H$_5$), 3.05 (2H, t, $^3J_{HH}$ = 6.9, C*H*$_2$OH), 1.91-1.84 (3H, overlapping m, C*H*(CHOC)$_2$ and C*H*$_2$CH$_2$OH), 1.69 (3H, s, C*H*$_3$), 1.57 (3H, s, C*H*$_3$), 1.20 (2H, m, C*H*$_2$CH(CHOC)$_2$).

Preparation of 2-[11-(1-ethoxy-ethoxy)-undecyl]-propane-1,3-diol (96)



To a cooled (0°C), stirred solution of 2-[11-(1-ethoxy-ethoxy)-undecyl]-malonic acid diethyl ester (**82**) (5.00 g, 12.4 mmol) in ether (100 mL), in a 250 mL, 3-neck round bottom flask, fitted with a reflux condenser and pressure-equalising dropping funnel, was added $LiAlH_4$ (1M solution in ether, 42 mL, 42 mmol) dropwise, *via* the pressure-equalising dropping funnel, over 20 minutes. Effervescence and formation of a white precipitate was observed upon addition. When addition was complete, the mixture was heated at reflux for 12 hours. Non-dried ether was added (30 mL), followed by successive addition of water (5 mL), 15 % aqueous NaOH (5 mL) and water (20 mL). The mixture was filtered and the white precipitate washed with ether (2 x 50 mL). The filtrate was washed with water (50mL) and the organic layer separated, dried ($MgSO_4$) and solvent removed under reduced pressure to give the product as a low-melting waxy solid (3.62 g, 93.0 %).

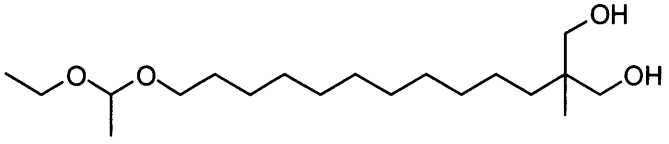
^{1}H (250.13 MHz, $CDCl_3$) δ: 4.65 (1H, q, $^3J_{HH}$ = 5.5, C*H*$(OC)_2CH_3$); 3.82-3.35 (8H, overlapping m, CH_3CH_2OC, CH_2CH_2OC and CH_2OH), 2.70 (2H, br s, v½ = 15 Hz, O*H*), 1.81-1.70 (1H, m, C*H*$(CH_2OH)_2$), 1.62-1.49 (2H, m, CH_2CH_2OC), 1.40-1.25 (21H, overlapping m, $CH_2CH_2CH_2$ and $CH_3CH(OC)_2$), 1.20 (3H, t, $^3J_{HH}$ = 7.0, CH_3CH_2OC).

^{13}C (62.90 MHz, $CDCl_3$) δ: 99.5 (*C*H$(OC)_2$), 66.6 (*C*H_2OH), 65.3 (CH_2CH_2OCH), 60.7 (CH_3CH_2OC), 41.9 (*C*H$(CH_2OH)_2$), 29.8, 29.5, 29.4, 29.4, 27.7, 27.2, 26.2 (all *C*H_2; specific assignment not possible), 19.8 (*C*H_3CH$(OC)_2$), 15.3 (*C*H_3CH_2OC).

MS (EI^+): 341 $(MNa)^+$, 283 $(M\text{-}2H_2O)^+$, 255, 227, 199, 183, 146, 117.

M.p.: 35-37°C.

Preparation of 2-[11-(1-ethoxy-ethoxy)-undecyl]-2-methyl-propane-1,3-diol (97)



Following an identical procedure to that described for the synthesis of **96**, 2-[11-(1-ethoxy-ethoxy)-undecyl]-2-methyl-malonic acid diethyl ester (**83**) (5.01 g, 12 mmol) was reduced with $LiAlH_4$ (1M solution in ether, 36 mL, 36 mmol) to give the desired product as a waxy solid (3.74 g, 96 %).

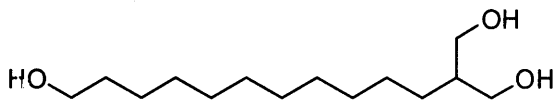
^{1}H (250.13 MHz, $CDCl_3$) δ: 4.65 (1H, q, $^3J_{HH}$ = 5.5, C*H*$(OC)_2CH_3$); 3.75-3.37 (8H, overlapping m, CH_3CH_2OC, CH_2CH_2OC and CH_2OH), 2.15 (2H, br s, ν½ = 7.5 Hz, O*H*), 1.63-1.49 (2H, m, CH_2CH_2OC), 1.41-1.23 (24H, overlapping m, $CH_3C(CH_2OH)_2$, $CH_2CH_2CH_2$, CH_3CH_2OC and $CH_3CH(OC)_2$ and $CH_2CH_2C(CH_2OH)_2$), 0.81 (3H, s, $CH_3C(CH_2OH)_2$).

MS (EI^+): 313 $(M-H_2O)^+$, 287, 269, 225, 207, 165, 151, 137, 123, 109, 95, 81, 67.

Attempted preparation of ketal 101 *via* selective deprotection of (98)

2-[11-(1-Ethoxy-ethoxy)-undecyl]-propane-1,3-diol (**96**) (2.5 g, 7.88 mmol) was dissolved in DMF (100 mL) and dimethoxypropane (1.64 g, 15mmol) and *p*-toluene sulfonic acid (0.09 g, 0.47 mmol) were added. The mixture was stirred at room temperature overnight. Water (100 mL) was added, the organic layer separated and the aqueous layer extracted with ether (3 x 100 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated to give ketal **98** as a clear oil (2.81 g, 99 %) that was used directly in the next step. Ketal **98** was dissolved in THF (50 mL) and pyridinium *p*-toluene sulfonate (0.05 eq, 0.086 g) added. The mixture was stirred at room temperature for 24 hours. Water (50 mL) was added, the organic layer separated and the aqueous layer extracted with CH_2Cl_2 (3 x 50 mL). The organic layers were combined, dried ($MgSO_4$) and volatile components removed under reduced pressure to give a pale yellow oil that solidified on standing. GC-MS analysis revealed a mixture of products. Ether (10 mL) was added and the insoluble white solid subsequently formed, which was collected by filtration. Triol **99** was obtained as a white solid (0.79 g, 41 %). (For characterisation see below).

Preparation of 2-hydroxymethyl-tridecane-1,13-diol (99)



To a solution of **96** (2.5 g, 7.85 mmol) in THF (50 mL) was added HCl (5 mL, 0.5M) and the mixture stirred at room temperature overnight. Saturated aqueous $NaHCO_3$ (30 mL) was added, the organic layer was separated and then dried ($MgSO_4$). Removal of THF under reduced pressure gave an oil that solidified at room temperature. Addition of cold ether (10 mL) followed by filtration gave pure **99** as a white solid (0.73 g, 38 %).

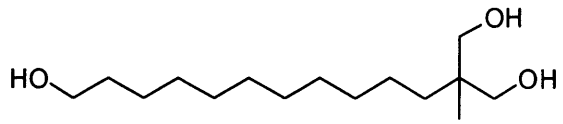
^{1}H (250.13 MHz, CD_3OD) δ: 3.78-3.67 (6H, overlapping m, C*H*$_2$OH), 1.84-1.72 (3H, overlapping m, C*H*$(CH_2OH)_2$ and C*H*$_2CH_2OH$), 1.25 (18H, overlapping m, $CH_2CH_2CH_2$ and C*H*$_2CH(CH_2OH)_2$).

^{13}C (62.90 MHz, CD_3OD) δ: 64.3 ($CHCH_2OH$), 63.4 (CH_2CH_2OH), 44.8 (*C*$H(CH_2OH)_2$), 34.1 (*C*H_2CH_2OH), 31.6, 31.2, 31.6, 31.0, 29.4, 28.7, 27.4 (all CH_2; specific assignment not possible).

MS (EI^+): 269 $(MNa)^+$, 247 $(MH)^+$, 229 $(M-H_2O)^+$, 211 $(M-2H_2O)^+$, 193 $(-3H_2O)^+$, 181, 137, 123, 109, 95, 81.

M.p.: 38-40°C.

Preparation of 2-hydroxymethyl-2-methyl-tridecane-1,13-diol (100)



Following an identical procedure to that described for the synthesis of **99**, 2-[11-(1-ethoxy-ethoxy)-undecyl]-2-methyl-propane-1,3-diol (**97**) (2.0 g, 6 mmol) was deprotected to give the diol product as a white solid (1.05 g, 66.8 %).

^{1}H (250.13 MHz, CD_3OD) δ: 3.51 (2H, t, $^3J_{HH}$ = 6.9, CH_2CH_2OH), 3.36 (4H, s, CCH_2OH), 1.61-1.43 (2H, m, CH_2CH_2OH), 1.41-1.20 (18H, overlapping m, $CH_2CH_2CH_2$ and $CH_2CH_2C(CH_2OH)_2$), 0.80 (3H, s, $CH_3C(CH_2OH)_2$).

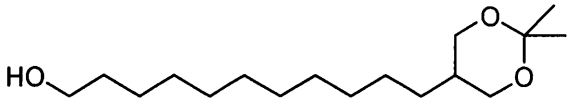
^{13}C (62.90 MHz, CD_3OD) δ: 68.6 ($C(CH_2OH)_2$), 63.4 (CH_2CH_2OH), 40.7 ($C(CH_2OH)_2$), 35.5, 34.1, 32.2, 31.2, 31.0, 27.4, 24.7 (all CH_2; specific assignment not possible), 19.5 (CH_3).

IR (ATR): 3187, 2915, 2871, 2848, 14681376, 1073, 1054, 1043 cm^{-1}.

MS (EI^+): 283 $(MNa)^+$, 261 $(MH)^+$, 207 $(M-3H_2O)^+$, 137, 123, 109, 95, 81, 67.

M.p.: 56-57°C.

Preparation of 11-(2,2-dimethyl-[1,3]dioxan-5-yl)-undecan-1-ol (101)



To a stirred solution of 2-hydroxymethyl-tridecane-1,13-diol (**99**) (0.60 g, 2.43 mmol) in acetone (50 mL) was added sodium sulphate (1.00 g) and HCl in ether (1M, 2 mL, 2mmol) and the reaction stirred overnight at room temperature. The mixture was diluted with saturated aqueous $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (3 x 50 mL).

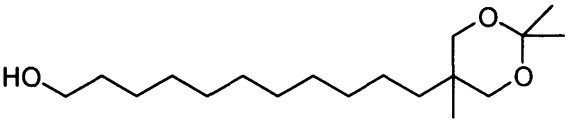
The combined organic fractions were dried ($MgSO_4$) and volatile components removed *in vacuo* to leave an oil that solidified. The residue was purified by chromatography on silica gel {EtOAc/hexane, 1:2, TLC: R_f 0.30 (EtOAc/hexane, 1:2)} to give the product as a colourless oil 0.52 g (74%).

^{1}H (250.13 MHz, $CDCl_3$) δ: 3.81 (2H, dd, $^2J_{HH}$ = 12.1, $^3J_{HH}$ = 2.9, ($CH_{2ax}OC)_2$), 3.61 (2H, t, $^3J_{HH}$ = 6.9, CH_2OH), 3.52 (2H, dd, $^2J_{HH}$ = 12.1, $^3J_{HH}$ = 1.0, ($CH_{2eq}OC)_2$), 2.16 (1H, bs, O*H*), 1.90-1.72 (1H, m, $CH(CH_2OC)_2$), 1.63-1.48 (2H, m, CH_2CH_2OH), 1.42 (3H, s, CH_3) 1.40, (3H, s, CH_3), 1.40-1.10 (18H, overlapping m, $CH_2CH_2CH_2$ and CH_2CH_2CH).

^{13}C (62.90 MHz, $CDCl_3$) δ: 97.7 ($C(OC)_2$), 65.0 (($CH_2OC)_2$), 63.0 (CH_2OH), 34.1 ($CH(CH_2OC)_2$), 32.8, 29.7, 29.5, 29.4, 28.6 (all CH_2; specific assignment not possible), 27.6 (CH_3), 26.4 (CH_2), 25.7 (CH_2), 20.2 (CH_3).

MS (EI^+): 309 $(MNa)^+$, 291, 269 $(M\text{-}H_2O)^+$, 109, 95, 91, 81.

Preparation of 11-(2,2,5-trimethyl-[1,3]dioxan-5-yl)-undecan-1-ol (102)



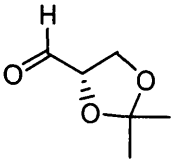
Following an identical procedure to that described for the synthesis of **101**, 2-hydroxymethyl-2-methyl-tridecane-1,13-diol (**100**) (0.90 g, 3.4 mmol) was protected, affording the product as a colourless oil (0.92 g, 88.6 %).

^{1}H (250.13, $CDCl_3$) δ: 3.61 (2H, t, $^3J_{HH}$ = 6.9, CH_2OH), 3.57-3.32 (4H, m, $(CH_2OC)_2$), 2.16 (1H, b, O*H*), 1.63-1.48 (2H, m, CH_2CH_2OH), 1.42 (3H, s, CH_3) 1.40, (3H, s, CH_3), 1.40-1.10 (18H, overlapping m, $CH_2CH_2CH_2$ and $CH_2CH_2C(CH_3)$), 0.85 (3H, s, $CH_3C(CH_2O)_2$).

^{13}C (62.90, $CDCl_3$) δ: 97.8 ($C(OC)_2$), 69.5 (CH_2OC), 62.9 (CH_2OH), 38.7 ($C(CH_2OC)_2$), 35.5, 32.7, 32.5, 30.5, 30.4, 29.5, 29.4, 25.7 (all CH_2; specific assignment not possible), 24.0 ($OCCH_3$), 23.5 ($OCCH_3$), 23.2 (CH_2), 23.0 (CH_2), 19.6 ($CH_3C(CH_2OC)_2$).

MS (EI^+): 283 $(M\text{-}H_2O)^+$, 261, 207, 177, 151, 137, 123, 109, 95, 81.

Preparation of (*R*)-2,2-dimethyl-[1,3]dioxolane-4-carbaldehyde (105)

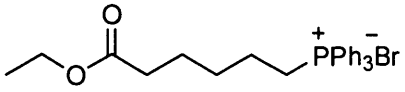


(*R*)-2,2-dimethyl-[1,3]dioxolane-4-carbaldehyde (**105**) was prepared according to a modified literature procedure[168] as follows: 1,2:5,6-di-*O*-isopropylidene-D-mannitol (2.60 g, 9.88 mmol) was dissolved in DCM (30 mL) and $NaIO_3$ (4.23 g, 20 mmol) was added

followed by H_2O (1.5 mL) to the vigorously stirred solution. The mixture was stirred for 1 hour then $MgSO_4$ (5.00 g) was added. The mixture was stirred for a further 15 minutes then filtered, the solid washed with DCM (2 x 10 mL) and the filtrate concentrated at reduced pressure to give a clear oil which was used directly in the next step (2.49 g, 96.8 %) without further purification.

^{1}H (250.13 MHz, $CDCl_3$) δ: 9.72 (1H, s, O=C*H*), 4.47-4.39 (1H, m, C*H*OC), 4.23-4.10 (2H, m, CH_2OC), 1.52 (3H, s, CH_3), 1.45 (3H, s, CH_3).

Preparation of ethyl 6-(phosphoniumbromide)hexanoate (106)



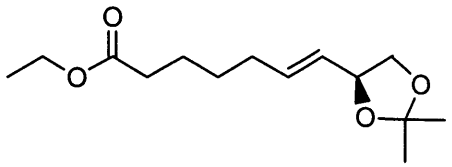
A 100mL 3-neck, round bottom flask, fitted with a reflux condenser, was charged with ethyl 6-bromohexanoate (10.00 g, 45 mmol), triphenylphosphine (11.78 g, 45 mmol) and $CHCl_3$ (25 mL) and the stirred mixture was heated to 90°C for 60 hours. $CHCl_3$ was removed at reduced pressure and the residue was washed with hexane (3 x 50 mL) by stirring/decanting. Traces of hexane were removed *in vacuo* to leave the product as a viscous oil (21.23 g, 97.2 %).

^{1}H (250.13 MHz, $CDCl_3$) δ: 7.87-7.59 (15H, m, *o,m,p*-C_6H_5), 4.00 (2H, q, $^3J_{HH}$ = 6.9, CH_3CH_2OC=O), 3.77-3.63 (2H, m, CH_2CH_2CP), 2.20 (2H, t, $^3J_{HH}$ = 6.8, O=CCH_2CH_2), 1.76-1.48 (6H, m, $CH_2CH_2CH_2$), 1.15 (3H, t, $^3J_{HH}$ = 6.9, CH_3CH_2OC=O).

^{31}P (101.26 MHz, $CDCl_3$) δ: 23.7.

MS (EI^+): 405 $(M)^+$, 377, 291.

Preparation of (*S*)-7-(2,2-dimethyl-[1,3]dioxolan-4-yl)-hept-6-enoic acid ethyl ester (107)



A 250mL, 3-neck round bottom flask, fitted with a reflux condenser, was charged with phosphonium salt **106** (10.00 g, 20.6 mmol) and dried *in vacuo*. After backfilling with N_2, THF (60 mL) was added and the stirred solution was cooled to 0°C. Potassium *tert*-butoxide (2.60 g, 23.2 mmol) was added in small portions with the solution turning dark brown immediately. After stirring at 0°C for 30 mins, the solution was cooled to -40°C and a solution of freshly prepared 2,2-dimethyl-[1,3]dioxolane-4-carbaldehyde (**105**) (2.60 g, 19.8 mmol) in THF (30 mL) was added. The mixture was stirred at -40°C for 1

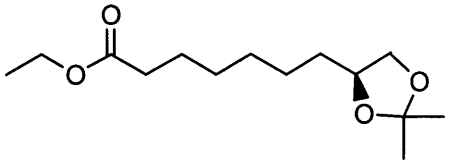
hour then allowed to warm to room temperature and stirred overnight. A second equivalent of potassium *tert*-butoxide (2.60 g, 23.2 mmol) and 2,2-dimethyl-[1,3]dioxolane-4-carbaldehyde (**105**) (2.60 g, 19.8 mmol) were added and the mixture was stirred for a further 72 hours. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl (100 mL) then the organic layer was separated and the aqueous layer extracted with pet. ether 40-60 (3 x 30 mL). The organic extracts were combined, dried ($MgSO_4$) and volatile components were removed under reduced pressure to give a viscous dark oil. The residue was purified by chromatography on silica gel {Pet. ether/EtOAc, 12:1 TLC: R_f 0.30 (Pet. ether/EtOAc, 12:1)} to give the product, contaminated with the *cis* isomer, as a pale orange oil (2.40 g, 45.4 %). No further purification was undertaken. NMR data is reported for the major (*trans*) isomer:

^{1}H (301.24 MHz, $CDCl_3$) δ: 5.67-5.59 (1H, m, CH_2CH=CHCHOC), 5.45-5.38 (1H, m, CH_2CH=C*H*CHOC), 4.83 (1H, m, CH_2CH=CHC*H*OC), 4.17-4.03 (4H, overlapping m, CH_2COC and CH_3CH_2OC=O), 2.29 (2H, t, $^3J_{HH}$ = 6.8, O=CCH_2CH_2), 2.22-2.04 (2H, m, CH_2CH=CHCHOC), 1.72-1.56 (2H, m, O=CCH_2CH_2), 1.46-1.30 (8H, overlapping m, CCH_3 and $CH_2CH_2CH_2$), 1.21 (3H, t, $^3J_{HH}$ = 6.9, CH_3CH_2OC=O).

^{13}C (75.76 MHz, $CDCl_3$) δ: 173.6 (*C*=O), 134.5 (CH_2CH=CHCHOC), 127.4 (CH_2CH=*C*HCHOC), 109.0 (*C*$(OC)_2$), 71.9 (*C*HOC), 69.4 (CH_2OC), 60.2 (CH_3CH_2OC=O), 34.1 (CH_2CH=CHCHOC), 29.0 (O=C*C*H2), 27.3 (CH_2CH_2CH=CH), 26.7 (CCH_3), 26.0 (CCH_3), 24.4 (O=CCH_2CH_2), 14.2 (CH_3CH_2OC=O).

MS (EI^+): 279 $(MNa)^+$, 230, 181, 153, 146, 135, 123, 107, 93, 87.

Preparation of (*S*)-7-(2,2-dimethyl-[1,3]dioxolan-4-yl)-heptanoic acid ethyl ester



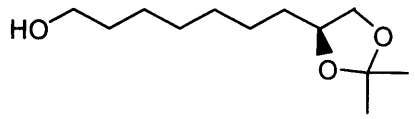
In a 100mL, round bottom flask, 7-(2,2-dimethyl-[1,3]dioxolan-4-yl)-hept-6-enoic acid ethyl ester (**107**) (2.00 g, 7.87 mmol) was dissolved in EtOH (30 mL) and under an atmosphere of N_2, 10% Pd-C (0.50 g) was added. The mixture was stirred vigorously under an atmosphere of H_2 overnight, then the catalyst was removed by filtration and the filtrate concentrated under reduced pressure to leave the product as a colourless oil (1.96 g, 97.3 %).

^{1}H (250.13 MHz, $CDCl_3$) δ: 4.09-3.92 (4H, overlapping m, CH_3CH_2OC=O and CH_2OC), 3.51-3.40 (1H, m, CHOC), 2.20 (2H, t, $^3J_{HH}$ = 6.8, O=CCH_2), 1.68-1.45 (4H, overlapping

m, O=CCH$_2$C*H*$_2$ and CH$_2$C*H*$_2$CHOC), 1.43-1.20 (12H, overlapping m, CH$_2$C*H*$_2$CH$_2$ and (CO)$_2$C(C*H*$_3$)$_2$), 1.17 (3H, t, $^3J_{HH}$ = 6.9, C*H*$_3$CH$_2$OC=O).

^{13}**C** (75.76 MHz, $CDCl_3$) δ: 173.8 (*C*=O), 108.6 (*C*(OC)$_2$), 76.0 (*C*HOC), 69.5 (*C*H$_2$OC), 60.2 (CH$_3$*C*H$_2$OC=O), 34.3, 34.3, 30.3, 29.2 (all *C*H$_2$; specific assignment not possible), 28.1 ((CO)$_2$C*C*H$_3$), 26.9 ((CO)$_2$C*C*H$_3$), 25.7 (*C*H$_2$; specific assignment not possible), 25.6 (*C*H$_2$; specific assignment not possible), 14.2 (*C*H$_3$CH$_2$OC=O).

Preparation of (*S*)-7-(2,2-dimethyl-[1,3]dioxolan-4-yl)-heptan-1-ol (109)



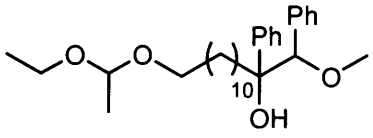
Following an identical procedure to that described in the synthesis of **96**, (2,2-dimethyl-[1,3]dioxolan-4-yl)-heptanoic acid ethyl ester (1.00 g, 3.9 mmol) was reduced with $LiAlH_4$ (1M solution in ether, 4 mL, 4 mmol) to give the pale yellow oil upon work up. The residue was purified by chromatography on silica gel {EtOAc/hexane, 1:2, TLC: Rf 0.30 (EtOAc/hexane, 1:2)} to give the product as a colourless oil (0.81 g, 96 %).

^{1}**H** (250.13 MHz, $CDCl_3$) δ: 4.03-3.92 (2H, m, C*H*$_2$OC), 3.59 (2H, t, $^3J_{HH}$ = 6.2, C*H*$_2$OH), 3.46 (1H, m, C*H*OC), 1.64 (1H, br s, $\nu_{1/2}$ = 12.5 Hz, O*H*), 1.60-1.20 (18H, overlapping m, CH$_2$C*H*$_2$CH$_2$, C*H*$_2$CHOC and CC*H*$_3$).

^{13}**C** (75.76 MHz, $CDCl_3$) δ: 108.6 (*C*(OC)$_2$), 76.1 (*C*HOC), 69.4 (*C*H$_2$OC), 63.0 (*C*H$_2$OH), 33.5, 32.7, 29.5, 29.2 (all *C*H$_2$; specific assignment not possible), 26.9 (C*C*H$_3$), 25.7 (C*C*H$_3$), 25.6, 25.6 (both *C*H$_2$; specific assignment not possible).

HRMS (EI$^+$): calcd for $C_{12}H_{23}O_3$: 215.1648; found: 215.1647.

Preparation of 13-(1-Ethoxy-ethoxy)-1-methoxy-1,2-diphenyl-tridecan-2-ol (112)



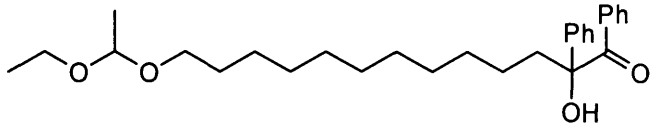
In a 250mL, 3-neck round bottom flask, fitted with a reflux condenser and pressure-equalising dropping funnel magnesium (0.30 g, 12 mmol) was dried *in vacuo*. After backfilling with N_2, Et_2O (5 mL) was added, followed by dropwise addition of a solution of 1-bromo-11-(1-ethoxy-ethoxy)-undecane (3.69 g, 11.5 mmol) in Et_2O (10 mL), *via* the pressure equalising dropping funnel, at such a rate so as to initiate and maintain Grignard formation. The stirred mixture was then heated at reflux for 2 hours resulting in a grey/black solution. After cooling to room temperature, a solution of benzoin methyl ether (2.00 g, 9.42 mmol) dissolved in Et_2O (20 mL) was added dropwise during which time the

reaction mixture turned orange. The mixture was refluxed overnight then allowed to cool. H_2O (10 mL) was added followed by saturated aqueous ammonium chloride solution (50 mL). The organic layer was separated, then the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$), then volatile components were removed under reduced pressure to leave a pale orange oil which was not purified and used directly in the next step(4.23 g, 78.1 %).

^{1}H (250.13 MHz, $CDCl_3$) δ: 7.53-7.29 (10H, overlapping m, *o,m,p*-C_6H_5), 4.64 (1H, q, $^3J_{HH}$ = 5.6, C*H*$(OC)_2$), 4.05 (1H, s, C*H*OCH_3), 3.67-3.31 (4H, overlapping m, CH_3CH_2OC and CH_2CH_2OC), 2.05-1.88 (2H, t, $^3J_{HH}$ = 6.8, CH_2CH_2COH), 1.61-1.45 (2H, m, $OCH_2CH_2CH_2$), 1.30-1.10 (19H, overlapping m, $CH_2CH_2CH_2$ and $CH_3CH(OC)_2$).

^{13}C (62.90 MHz, $CDCl_3$) δ: 142.4, 137.3, 130.6, 128.9, 128.8, 127.9, 127.8, 127.7, 99.9 (*C*H$(OC)_2$), 91.0 (*C*OCH_3), 79.4 (*C*OH), 65.7 (CH_3CH_2O), 61.0 (CH_2OC), 57.8 ($COCH_3$), 38.6, 32.3, 30.6, 30.3, 30.0, 26.6, 26.1, 23.6 (all CH_2, specific assignment not possible) 20.3 ($CH_3CH(OC)_2$), 15.7 (CH_3CH_2O).

Preparation of 13-(1-ethoxy-ethoxy)-2-hydroxy-1,2-diphenyl-tridecan-1-one (114)



In a 250mL, 3-neck round bottom flask, fitted with a reflux condenser and pressure-equalising dropping funnel, anhydrous cadmium chloride $CdCl_2$ was prepared by heating powdered cadmium chloride hemipentahydrate (0.71 g, 3.11 mmol) *in vacuo* at 180°C for 18 hours. After backfilling with N_2, Et_2O (40 mL) was added and the suspension stirred. A separate 100mL, 3-neck round bottom flask, fitted with a reflux condenser and pressure equalising dropping funnel, was charged with magnesium turnings (0.151 g, 6.21 mmol) and placed under vacuum. After backfilling with N_2, Et_2O (5 mL) was added, followed by dropwise addition of a solution of 1-bromo-11-(1-ethoxy-ethoxy)-undecane (2.01 g, 6.19 mmol) in Et_2O (10 mL), *via* the pressure equalising dropping funnel, at such a rate so as to initiate and maintain Grignard formation. The stirred mixture was then heated at reflux for 3 hours resulting in a grey/black solution. The cooled solution was transferred *via* cannula to the $CdCl_2$ suspension and the mixture stirred at room temperature overnight. To the suspension was added a solution of benzil (1.70 g, 8.09 mmol) in Et_2O (30 mL) dropwise and the mixture was stirred at room temperature for two hours, then heated at reflux for 12 hours. The cooled reaction mixture was quenched by cautious addition of HCl (aq) (1M, 30 mL). The organic phase was separated and the

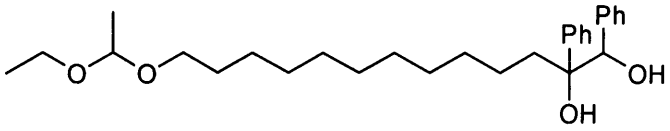
aqueous phase extracted with Et_2O (3 x 30mL). The organic extracts were combined and washed with first saturated aqueous $NaHCO_3$ solution (2 x 100 mL) then saturated aqueous NaCl solution (2 x 100 mL), then dried ($MgSO_4$) before volatile components removed under reduced pressure to leave a bright yellow oil/solid mixture. The residue was purified by chromatography on silica gel {EtOAc/hexane, 1:2, TLC: R_f 0.50 (EtOAc/hexane, 1:2)} to give the product as a pale yellow oil (2.25 g, 80 %).

^{1}H (250.13 MHz, $CDCl_3$) δ: 7.89-7.81 (2H, m, *o*-C_6H_5C=O), 7.60-7.52 (3H, m, *m,p*-C_6H_5C=O), 7.40-7.13 (5H, m, C_6H_5COH), 4.60 (1H, q, $^3J_{HH}$ = 5.5, $CH(OC)_2$), 3.62-3.31 (4H, overlapping m, CH_3CH_2OC and CH_2CH_2OC), 2.28 (2H, t, $^3J_{HH}$ = 7.0, CH_2COH), 1.53-1.41 (2H, m, CH_2CH_2OC), 1.35-1.05 (22H, overlapping m, $CH_2CH_2CH_2$, $CH_3CH(OC)_2$ and CH_3CH_2OC).

^{13}C (62.90 MHz, $CDCl_3$) δ: 202.1 (*C*=O), 142.3 (*i*-C_6H_5COH), 134.8 (*i*-C_6H_5C=O), 132.8 (*p*-C_6H_5C=O), 129.9, 129.8, 129.0, 128.8, (all aromatic *C*H; specific assignment not possible), 126.2 (*p*-C_6H_5COH), 99.5 ($CH(OC)_2$), 81.6 (*C*OH), 65.3 (CH_2CH_2OCH), 60.6 (CH_3CH_2OCH), 37.8 (CH_2COH), 29.9, 29.8, 29.7, 29.6, 29.5, 29.2, 26.2 (all CH_2; specific assignment not possible), 22.9 (CH_2CH_2COH), 19.9 ($CH_3CH(OC)_2$), 15.3 (CH_3CH_2OC).

MS (EI^+): 477 $(MNa)^+$, 426, 365, 347, 197, 105.

Preparation of 13-(1-ethoxy-ethoxy)-1,2-diphenyl-tridecane-1,2-diol (116)



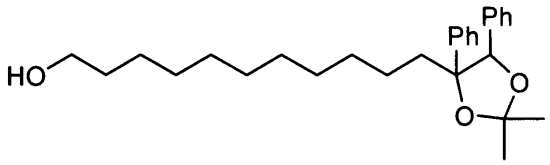
In a 100mL, 3-neck round bottom flask, fitted with a reflux condenser and pressure equalising dropping funnel, 12-(1-ethoxy-ethoxy)-2-hydroxy-1,2-diphenyl-tridecan-1-one (**114**) (2.00 g, 4.4 mmol) was dissolved in Et_2O (30 mL). The stirred solution was cooled to 0°C and $LiAlH_4$ (1M solution in Et_2O, 6 mL, 6 mmol) was added dropwise. The mixture was allowed to warm to room temperature and then stirred for one hour before the reaction was quenched with H_2O (1 mL), aqueous NaOH solution (15 %, 1 mL) and finally H_2O (5 mL). The white precipitate was removed by filtration and washed with Et_2O (2 x 10mL). The combined filtrate was washed with aqueous NaCl solution (40 mL) then the organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give the product as a clear oil (1.96 g, 98 %), which was used directly in the next step without further purification.

^{1}H (250.13 MHz, $CDCl_3$) δ: 7.32-7.02 (10H, overlapping m, *o,m,p*-C_6H_5), 4.78 and 4.69 (1H, 2s, diastereotopic *C*HOH), 4.66 (1H, q, $^3J_{HH}$ = 5.5, $CH_3CH(OC)_2$), 3.63-3.35 (4H,

overlapping m, CH_3CH_2OC and CH_2CH_2OC), 2.45 (2H, br s, $\nu\frac{1}{2}$ = 17.5 Hz, O*H*), 2.00-1.91 (2H, m, CH_2CH_2COH), 1.75-1.58 (2H, m, $CH_2CH_2CH_2OC$), 1.52-1.39 (2H, m, CH_2CH_2COH), 1.32-1.00 (20H, $CH_2CH_2CH_2$, $CH_3CH(OC)_2$ and CH_3CH_2OC).

MS (EI^+): 351, 310, 269, 228, 187, 146, 105

Preparation of 11-(2,2-dimethyl-4,5-diphenyl-[1,3]dioxolan-4-yl)-undecan-1-ol (118)



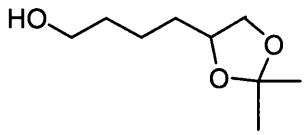
Crude 12-(1-ethoxy-ethoxy)-1,2-diphenyl-dodecane-1,2-diol (**116**) (1.90 g, 4.16 mmol) was dissolved in THF (30 mL) and to the stirred solution was added HCl (1M, 10 mL). The solution was stirred overnight then aqueous saturated $NaHCO_3$ solution (20 mL) was added and the mixture extracted with DCM (3 x 50 mL). The organic extracts were combined, dried ($MgSO_4$) and volatile components were removed under reduced pressure to leave **117** as a waxy solid. The solid was dissolved in dry DCM (30 mL) then 2,2-dimethoxypropane (1.69 g, 2 mL, 16 mmol) was added followed by *p*-toluene sulphonic acid monohydrate (30 mg, 0.16 mmol). The solution was stirred at room temperature for 36 hours then saturated aqueous $NaHCO_3$ solution (10mL) was added. The organic layer was separated and the aqueous layer extracted with DCM (2 x 10 mL). The organic fractions were combined, washed with NaCl(aq) (20 mL), H_2O (20 mL) then dried ($MgSO_4$) and volatile components removed *in vacuo* to give a colourless oil. The residue was purified by chromatography on silica gel {EtOAc/hexane, 1:2, TLC: R_f 0.30 (EtOAc/hexane, 1:2)} to give the product as a colourless oil and mixture of diastereoisomers, which were not separated (0.85 g, 48.3 %).

^{1}H (250.13 MHz, $CDCl_3$) δ: 7.43-7.01 (10H, m, *o,m,p*-C_6H_5), 5.34 and 5.25 (2s, 1H, diastereotopic C*H*OH), 3.58 (2H, t, $^3J_{HH}$ = 6.2, CH_2OH), 1.89-1.85 (2H, m, $CH_2CH_2CHOCPh$), 1.84-1.70 (2H, m, $CH_2CH_2CH_2OH$), 1.64 (3H, s), 1.56 (3H, s), 1.36-1.09 (14H, m).

^{13}C (62.90 MHz, $CDCl_3$) δ: 142.4 (*C*), 141.2 (*C*), 136.3 (*C*), 135.3(*C*), 128.2, 127.9, 127.8, 127.8, 127.6, 127.3, 127.3, 126.9, 126.7, 125.9, 125.8 (all aromatic *C*H), 108.0 (*C*), 107.8 (*C*), 88.9 (*C*), 87.7 (*C*H), 87.1 (*C*), 86.6 (*C*H), 63.0 (CH_2), 41.2, 34.4, 32.7, 30.0, 29.5, 29.4, 29.3 (all CH_2), 28.6 (CH_3), 27.3 (CH_3), 26.5 (CH_3), 25.7 (CH_2), 24.2 (CH_2), 23.0 (CH_2).

MS (EI^+): 447 $(MNa)^+$, 407 $(M\text{-}H_2O)^+$, 367 $(M\text{-}CH_3COCH_3)^+$, 349, 311, 204, 186, 167, 150, 135, 118, 102.

Preparation of 4-(2,2-dimethyl-[1,3]dioxolan-4-yl)-butan-1-ol (120)



To a stirred solution of hexane-1,2,6-triol (6.65 g, 6.0 mL, 49.6 mmol) in acetone (50 mL) was added sodium sulphate (3.6 g) and 1M HCl in ether (12 mL, 12mmol). The mixture was stirred overnight at room temperature then diluted with saturated aqueous $NaHCO_3$ (100 mL) and the product extracted with DCM (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to leave a yellow oil. The residue was purified by chromatography on silica gel {EtOAc/hexane, 1:2, TLC: R_f 0.50 (EtOH/toluene, 1:5)} to give the product as a colourless oil (7.69 g, 89%). Characterisation was consistent with previously reported data.[169]

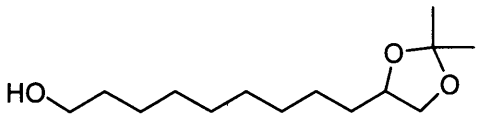
^{1}H (250.13 MHz, $CDCl_3$) δ: 4.00-4.10 (2H, m, C*H*$_2$OC), 3.65 (2H, t, $^3J_{HH}$ = 6.2, C*H*$_2$OH), 3.50 (1H, m, C*H*OC), 2.10 (1H, br s, ν½ = 7.5 Hz, O*H*), 1.70-1.40 (6H, overlapping m, C*H*$_2$CH$_2$OH, CH$_2$C*H*$_2$CH$_2$ and C*H*$_2$CHOC), 1.41 (3H, s, C*H*$_3$), 1.32 (3H, s, C*H*$_3$).

^{13}C (75.48 MHz, $CDCl_3$) δ: 108.0 (*C*(OC)$_2$), 75.7 (*C*HOC), 69.0 (*C*H$_2$OC), 61.8 (*C*H$_2$OH), 32.9 (*C*H$_2$CH$_2$OH), 32.2 (*C*H$_2$CHOC), 26.6 (*C*H$_3$), 25.4 (*C*H$_3$), 21.7 (CH$_2$*C*H$_2$CH$_2$).

MS (EI$^+$): 197 (MNa)$^+$, 175 (MH)$^+$, 157(M-H_2O)$^+$.

HRMS (EI$^+$): calcd for $C_9H_{17}O_3$: 173.1178; found: 173.1178.

Preparation of 9-(2,2-dimethyl-[1,3]dioxolan-4-yl)-nonan-1-ol (121)



To a solution of 1,2,11-undecanetriol (0.85 g, 4.17mmol) in DCM (20 mL), was added 2,2-dimethoxypropane (4.24 g, 5 mL, 40 mmol) and *p*-toluene sulfonic acid monohydrate (5 mol %, 40 mg, 0.21 mmol). The solution was stirred at room temperature overnight then saturated aqueous $NaHCO_3$ solution (20mL) was added. The organic layer was separated and the aqueous layer extracted with DCM (2 x 10 mL). The organic layers were combined, washed with aqueous saturated NaCl solution (20 mL), H_2O (20 mL) then dried ($MgSO_4$) and volatile components removed *in vacuo* to give a pale yellow oil. The residue was purified by chromatography on silica gel {EtOAc/hexane, 1:2, TLC: R_f 0.30 (EtOAc/hexane, 1:2)} to give the product as a colourless oil (0.95 g, 93 %).

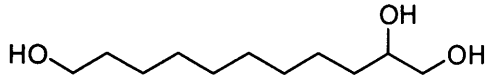
^{1}H (250.13 MHz, $CDCl_3$) δ: 4.03-3.92 (2H, m, C*H*$_2$OC), 3.59 (2H, t, $^3J_{HH}$ = 6.2, C*H*$_2$OH), 3.47 (1H, m, C*H*OC), 1.62-1.20 (22H, overlapping m, $CH_2CH_2CH_2$, CH_2CH_2CHOH and CH_3).

^{13}C (62.90 MHz, $CDCl_3$) δ: 108.6 (*C*(OC)$_2$), 76.1 (*C*HOC), 69.5 (*C*H$_2$OC), 63.0 (*C*H$_2$OH), 33.6, 32.7, 30.9, 29.6, 29.4, 29.3 (all *C*H$_2$; specific assignment not possible), 26.9 (*C*H$_3$), 25.7 (*C*H$_3$), 25.7 (*C*H$_2$).

MS (EI$^+$): 267 (MNa)$^+$, 245 (MH)$^+$, 227 (M-H_2O)$^+$, 201, 187 (M-CH_3COCH_3), 169, 151, 123, 109, 95.

HRMS (EI$^+$): calcd for $C_{14}H_{21}O_3$: 243.1961; found: 243.1960.

Preparation of undecane-1,2,11-triol (122)[31]



Undecane-1,2,11-triol (**122**) was prepared according to a modified literature procedure[31] as follows: AD-mix-β (10g) was dissolved in ^{t}BuOH/H_2O (1:1 mixture, 70 mL) and the stirred yellow solution was cooled to 0°C. 10-Undecen-1-ol (1.22 g, 7.14 mmol) was added and the mixture stirred vigorously at 4°C for 24 hours. The reaction was quenched by addition of Na_2SO_3 (14 g, 111 mmol) then the mixture was extracted with DCM (3 x 50 mL). The organic extracts were combined, dried ($MgSO_4$) and volatile components removed under reduce pressure to give a yellow solid, which was washed with cold hexane (3 x 10 mL) to leave the product as a white solid (1.22 g, 79%).

^{1}H (250.13 MHz, DMSO-d_6) δ: 4.38 (1H, t, $^3J_{HH}$ = 5.6, CH_2CH_2OH), 4.29-4.21 (2H, overlapping m, CHO*H* and $CHCH_2OH$), 3.40-3.27 (3H, overlapping m, C*H*OH and $CHCH_2OH$), 3.24-3.15 (2H, m, CH_2CH_2OH), 1.45-1.32 (4H, overlapping m, CH_2CH_2OH and CH_2CHOH), 1.32-1.25 (12H, overlapping m, $CH_2CH_2CH_2$).

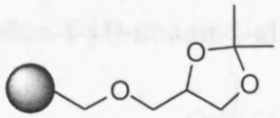
^{13}C (62.90 MHz, DMSO-d_6) δ: 71.5 (*C*HOH), 66.4 ($CHCH_2OH$), 61.1 (CH_2CH_2OH), 33.8, 32.9, 31.6, 29.7, 29.5, 29.3, 25.9, 25.5 (all *C*H$_2$; specific assignment not possible).

IR (ATR): 3321 (br), 2919, 2848, 1469, 1067, 1049 cm^{-1}.

MS (EI$^+$): 227 (MNa)$^+$, 169 (M-2H_2O)$^+$, 117, 85

M.p: 67-69°C (Lit. Value = 74-75).[31]

Preparation of polystyrene-bound (2,2-dimethyl-[1,3]dioxolan-4-yl)-methanol (124)

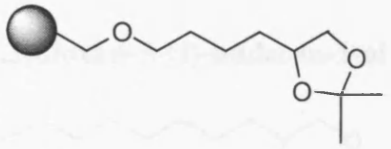


Following the procedure used for the preparation of resin **125**, (2,2-dimethyl-[1,3]dioxolan-4-yl)-methanol (**119**) (2.60 g, 20 mmol) was reacted with chloromethylated polystyrene (4.00 g, 1mmol g^{-1} Cl) to give the product as pale yellow beads (4.32 g). Characterisation was consistent with previously reported data.[98]

^{13}C CP MAS (75.43 MHz, $CDCl_3$) δ: 109.2 ($C(OC)_2$), 74.6 ($CHOC$), 73.3 ($C_6H_5CH_2O$), 70.8 ($CHCH_2OC$), 66.8 ($C_6H_5CH_2OCH_2$), 26.7 (CCH_3), 25.4 (CCH_3).

Elemental analysis: Expected Cl 0 %; Found Cl <0.30 %

Preparation of polystyrene-bound 4-(2,2-dimethyl-[1,3]dioxolan-4-yl)-butan-1-ol (125)



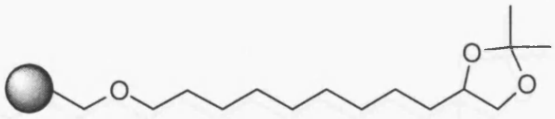
The synthesis of resin **125** is illustrative of the procedure used for grafting alcohols **101-102** and **118-121** to Avecia Merrifield resin and (chloromethylphenylpentyl)-polystyrene (**131**): A 100mL, 3-neck round bottom flask, fitted with a reflux condenser and an overhead stirrer, was charged with sodium hydride (60% dispersion in mineral oil, 5 eq, 0.4 g, 10 mmol). The solid was washed with hexane (3 x 10 mL) and then THF (30 mL) was added. Alcohol **120** (5 eq, 1.75 g, 10 mmol) was then added cautiously, followed by 15-crown-5 (0.16 g, 0.6 mmol). The mixture was stirred for 30 minutes then chloromethylated polystyrene (2g, 1mmol g^{-1} Cl) was added and the mixture was heated to 60°C for 5 days. The resulting orange mixture was allowed to cool then quenched by cautious addition of H_2O (5mL). The polymer beads were collected by filtration, washed with 3 cycles of THF, THF/H_2O (1:1), EtOH, H_2O (100 mL of each), washed with acetone (3 x 100 mL) and finally dried *in vacuo* for 24 hours at 70°C to give pale yellow beads (2.07g)

^{13}C CP MAS (75.43 MHz, $CDCl_3$) δ: 108.6 ($C(OC)_2$), 76.0 ($CHOC$), 72.9 ($C_6H_5CH_2O$), 69.9 ($CH_2CH_2OCH_2$), 69.5 (CH_2OC), 33.5 (CH_2CHOC), 29. ($CH_2CH_2OCH_2$), 27.0 (CCH_3), 25.8 (CCH_3), 22.5 ($CH_2CH_2CH_2$).

IR (CCl_4): 1369, 1217, 1062 cm^{-1}

Elemental analysis: Expected Cl 0 %; Found Cl <0.30 %

Preparation of polystyrene-bound 9-(2,2-dimethyl-[1,3]dioxolan-4-yl)-nonan-1-ol (127)

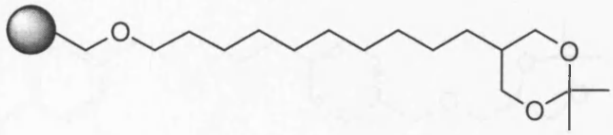


Following the general procedure used for the preparation of resin **125**, 9-(2,2-dimethyl-[1,3]dioxolan-4-yl)-nonan-1-ol (**121**) (1.20 g, 4.91 mmol) was reacted with chloromethylated polystyrene (1.00 g, 1mmol g^{-1} Cl) to give the product as white beads (1.15 g).

^{13}C CP MAS (75.43 MHz, $CDCl_3$) δ: 108.3 ($C(OC)_2$), 75.9 ($CHOC$), 72.6 ($C_6H_5CH_2O$), 70.0 (CH_2CH_2OC), 69.3 ($CHCH_2OC$), 33.4 (OCH_2CH_2), 29.3 ($CH_2CH_2CH_2$), 26.9 (CH_2), 26.1 ($C(OC)_2$), 25.8 ($C(OC)_2$), 25.6 (CH_2).

Elemental analysis: Expected Cl 0 %; Found Cl 0.44 %

Preparation of polystyrene-bound 11-(2,2-dimethyl-[1,3]dioxan-5-yl)-undecan-1-ol (128)

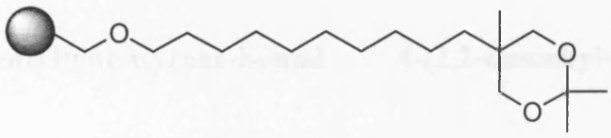


Following the general procedure used for the preparation of resin **125**, 11-(2,2-dimethyl-[1,3]dioxan-5-yl)-undecan-1-ol (**101**) (0.80 g, 2.79 mmol) was reacted with chloromethylated polystyrene (0.60 g, 1mmol g^{-1} Cl) to give the product as white beads (0.59 g).

^{13}C CP MAS (75.43 MHz, $CDCl_3$) δ: 64.96 ($CH(CH_2OC)_2$), 34.17 ($CH(CH_2OC)_2$), 29.56 (CH_2), 27.57 (CCH_3), 20.43 (CCH_3).

Elemental analysis: Expected Cl 0 %; Found Cl 2.20 %

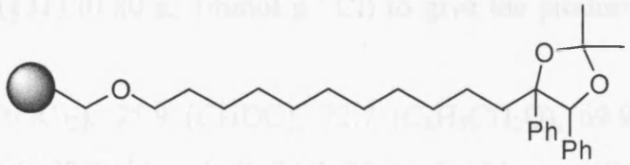
Preparation of polystyrene-bound 11-(2,2,5-trimethyl-[1,3]dioxan-5-yl)-undecan-1-ol (129)



Following the general procedure used for the preparation of resin **125**, 11-(2,2,5-trimethyl-[1,3]dioxan-5-yl)-undecan-1-ol (**102**), (0.80 g, 2.66 mmol) was reacted with chloromethylated polystyrene (0.50 g, 1mmol g^{-1} Cl) to give the product as white beads (0.50 g).

Elemental analysis: Expected Cl 0 %; Found Cl 2.44 %

Preparation of polystyrene-bound 11-(2,2-dimethyl-4,5-diphenyl-[1,3]dioxolan-4-yl)-undecan-1-ol (130)

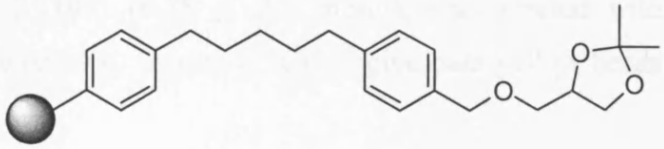


Following the general procedure used for the preparation of resin **125**, 11-(2,2-dimethyl-4,5-diphenyl-[1,3]dioxolan-4-yl)-undecan-1-ol (**118**) (0.75 g, 1.77 mmol) was reacted with chloromethylated polystyrene (0.35 g, 1mmol g^{-1} Cl) to give the product as white beads (0.34 g).

^{13}C CP MAS (75.43 MHz, $CDCl_3$) δ: 108.1 (*C*$(OC)_2$), 89.0-88.5 (C_6H_5*C*OC), 69.3 (O*C*H_2CH_2), 32.2 (CH_2*C*H_2COC), 29.2 (*C*H_2), 26.6 (*C*H_3), 24.0 (*C*H_2).

Elemental analysis: Expected Cl 0 %; Found Cl 3.06 %

Preparation of (methylphenylpentyl)polystyrene-bound (2,2-dimethyl-[1,3]dioxolan-4-yl)-methanol (132)

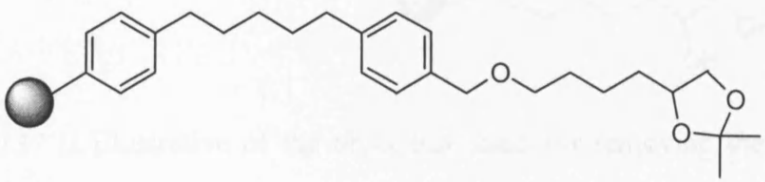


Following the general procedure used for the preparation of resin (**125**), (2,2-dimethyl-[1,3]dioxolan-4-yl)-methanol (**119**) (0.46 g, 3.5 mmol) was reacted with (chloromethylphenylpentyl)-polystyrene (**131**) (0.70 g, 1mmol g^{-1} Cl) to give the product as pale yellow beads (0.74 g).

^{13}C (75.76 MHz, $CDCl_3$) δ: 74.7 (*C*HOC), 73.4 (C_6H_5*C*H_2O), 71.0 (CH*C*H_2OC), 66.9 ($C_6H_5CH_2$O*C*H_2), 36.0 (overlapping *C*$H_2C_6H_4$), 31.4, 29.1 (both *C*H_2; specific assignment not possible), 26.8 (CCH_3), 25.4 (C*C*H_3).

Elemental analysis: Expected Cl 0 %; Found Cl 0.70 %

Preparation of (methylphenylpentyl)polystyrene-bound 4-(2,2-dimethyl-[1,3]dioxolan-4-yl)-butan-1-ol (133)

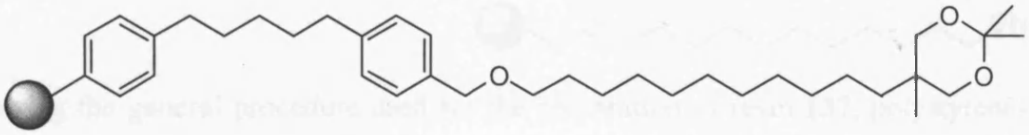


Following the general procedure used for the preparation of resin **125**, 4-(2,2-dimethyl-[1,3]dioxolan-4-yl)-butan-1-ol (**120**) (0.70 g, 4 mmol), was reacted with (chloromethylphenylpentyl)-polystyrene (**131**) (0.80 g, 1mmol g^{-1} Cl) to give the product as pale yellow beads (0.91 g).

^{13}**C** (75.76 MHz, $CDCl_3$) δ: 108.5 (*C*$(OC)_2$), 75.9 (*C*HOC), 72.7 ($C_6H_5CH_2O$), 69.9 ($CH_2CH_2OCH_2$), 69.4 (CH_2OC), 35.8, 35.6, 33.4, 31.3, 29.9, 29.7, 29.0 (all CH_2; specific assignment not possible), 26.9 (CH_3), 25.7 (CH_3), 22.5 (CH_2).

Elemental analysis: Expected Cl 0 %; Found Cl 0.38 %

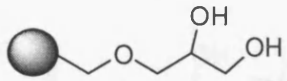
Preparation of polystyrene-bound 11-(2,2,5-trimethyl-[1,3]dioxan-5-yl)-undecan-1-ol (134)



Following the general procedure used for the preparation of resin **125**, 11-(2,2,5-trimethyl-[1,3]dioxan-5-yl)-undecan-1-ol (**101**) (0.75 g, 2.5 mmol), was reacted with (chloromethylphenylpentyl)-polystyrene (0.50 g, 1mmol g^{-1} Cl) to give pale yellow beads (0.72 g).

Elemental analysis: Expected Cl 0 %; Found Cl 3.72 %

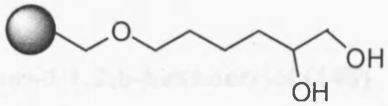
Preparation of polymer-bound glycerol (136)



Following the general procedure used for the preparation of resin **137**, polystyrene-bound (2,2-Dimethyl-[1,3]dioxolan-4-yl)-methanol (**124**) (3.00 g, 1 mmol g^{-1}) was deprotected to give resin **136** (2.95 g).

^{13}**C** (75.76 MHz, $CDCl_3$) δ: 73.6 ($C_6H_4CH_2O$), 72.1 (br, OCH_2CHOH and OCH_2CHOH), 67.2 (CH_2OH).

Deprotection of ketal-functionalised resins: Preparation of polymer-bound 1,2,6-hexanetriol (137)



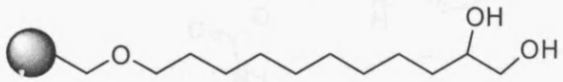
The synthesis of resin **137** is illustrative of the procedure used for removing the ketal protecting group from resins **124-130**: To resin **125** (1.5 g) was added 1,4-dioxane (40 mL) and HCl (1M, 10 mL). The mixture was stirred (overhead stirrer) for 24 hours at

70°C. After being allowed to cool, the mixture was filtered and the polymer beads were washed with 3 cycles of THF, THF/H_2O (1:1), EtOH, H_2O (100 mL of each) then washed with acetone (2 x 100 mL). Removal of volatile components *in vacuo* for 18h at 70°C gave pale yellow beads (1.35 g).

^{13}C CP MAS (75.43 MHz, $CDCl_3$) δ: 72.9 ($C_6H_5CH_2O$), 72.1 (*C*HOH), 70.0 ($CH_2CH_2OCH_2$), 66.7 (CH_2OH), 33.0 (CH_2CHOH), 29.7 ($CH_2CH_2OCH_2$), 22.4 ($CH_2CH_2CH_2$).

IR (CCl_4): 3401 (br), 1360, 1102, 1062, 1025 cm^{-1}

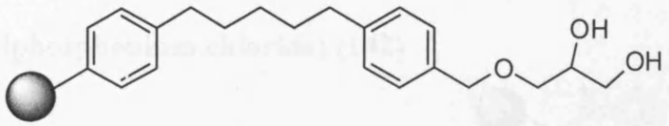
Preparation of polymer-bound 1,2,11-undecanetriol (138)



Following the general procedure used for the preparation of resin **137**, polystyrene-bound 9-(2,2-dimethyl-[1,3]dioxolan-4-yl)-nonan-1-ol (**127**) (0.80 g, 1 mmol g^{-1}) was deprotected to give resin **138** (0.76 g).

^{13}C CP MAS (75.43 MHz, $CDCl_3$) δ: 72.5 ($C_6H_4CH_2O$), 72.2 (*C*HOH), 70.3 (OCH_2CH_2), 66.7 ($CHCH_2OH$), 33.2 ($CH_2CHOHCH_2OH$), 30.8, 29.7, 26.3, 25.6 (all CH_2; specific assignment not possible).

Preparation of (chloromethylphenylpentyl)polystyrene-bound glycerol (139)

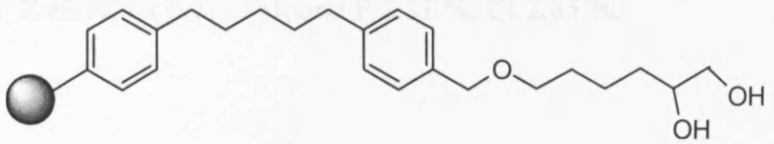


Following the general procedure used for the preparation of resin **137**, (methylphenylpentyl)polystyrene-bound (2,2-dimethyl-[1,3]dioxolan-4-yl)-methanol (**132**) (0.60 g, 1 mmol g^{-1}) was deprotected to give resin **139** (0.56 g).

^{13}C (75.76 MHz, $CDCl_3$) δ: 73.4 ($C_6H_4CH_2O$), 72.0 (br, OCH_2CHOH and OCH_2CHOH), 67.4 (CH_2OH), 35.7, 29.5, 22.5 (all CH_2, specific assignment not possible).

IR (CCl_4): 3408 (br), 1365, 1181, 1066, 1029 cm^{-1}.

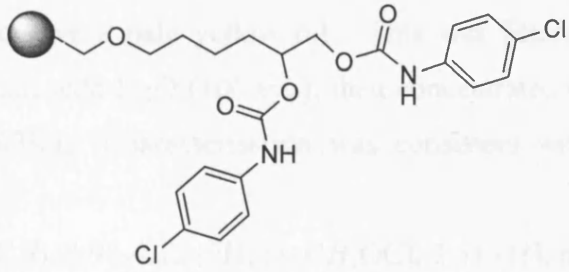
Preparation of (chloromethylphenylpentyl)polystyrene-bound 1,2,6-hexanetriol (140)



Following the general procedure used for the preparation of resin **137**, (methylphenylpentyl)polystyrene-bound 4-(2,2-dimethyl-[1,3]dioxolan-4-yl)-butan-1-ol (**133**) (0.60 g, 1 mmol g^{-1}) was deprotected to give resin **140** (0.57 g).

^{13}C (75.76 MHz, $CDCl_3$) δ: 73.0 ($C_6H_5CH_2O$), 72.1 (*C*HOH), 69.9 ($CH_2CH_2OCH_2$), 66.8 (CH_2OH), 35.8, 33.0, 29.7, 29.0 (all CH_2; specific assignment not possible), 22.4 ($CH_2CH_2CH_2$).

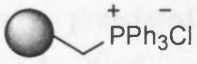
Derivatisation of diol functionalised resin 125 with *p*-chlorophenyl isocyanate: Preparation of resin 141



To resin **137** (0.1 g) was added THF (10 mL), *p*-chlorophenyl isocyanate (0.05 g, 0.3 mmol) and Et_3N (0.05 mL). The mixture was stirred at reflux temperature overnight and, after cooling, the polymer beads were collected by filtration and continuously washed (Soxhlet) with THF for 24h. After removal of solvent *in vacuo* at 70°C for 6 hours, pale yellow beads were obtained (0.11 g).

Elemental analysis: Expected N 2.00 %, Cl 5.05 %; Found N 1.35 %, Cl 3.57 %.

Preparation of poly-(styrenediphenylphosphonium chloride) (142)

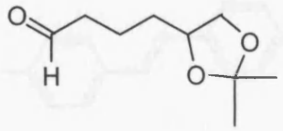


Poly-(styrenediphenylphosphonium chloride) (**142**) was prepared according to a modified to literature procedure[103] as follows: Chloromethylated polystyrene (10 g, 1 mmol g^{-1} Cl) was swollen in 1,4-dioxane (100 mL) and triphenylphosphine (12 g, 46 mmol) was added. The mixture was stirred (overhead stirrer) and heated at reflux for 1 week. The resin beads were collected by filtration and washed with hot toluene (4 x 50 mL), ether (3 x 50 mL) then dried under vacuum at 50°C to give white beads (12.68 g).

^{31}P (101.26 MHz, $CDCl_3$) δ: 22.65.

Elemental analysis: expected P 2.42 %, Cl 2.77 %; found P 2.51 %, Cl 2.85 %.

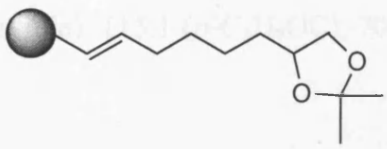
Preparation of 4-(2,2-dimethyl-[1,3]dioxolan-4-yl)-butyraldehyde (143)



To a cold solution of 4-(2,2-dimethyl-[1,3]dioxolan-4-yl)-butan-1-ol (**120**) (2.08 g, 11.9 mmol) in DCM (30 mL) was added activated 4Å molecular sieves (3 g) and pyridinium chlorochromate (4.95 g, 23 mmol). The solution was stirred for 30 minutes with a colour change to purple/brown taking place. The mixture was immediately transferred to a 10 cm long silica gel column and eluted with Et_2O (300 mL). The eluent was concentrated under reduced pressure to give a pale yellow oil. This was filtered through a second 10 cm long silica gel column with Et_2O (100 mL), then concentrated to give the product as a yellow oil(1.23 g, 60%). Characterisation was consistent with previously reported data.[170]

^{1}H (250.13 MHz, $CDCl_3$) δ: 9.86 (1H, s, O=C*H*), 3.98-4.12 (2H, m, CH_2OC), 3.51 (1H, m, C*H*OC), 2.52 (2H, dt, $^3J_{HH}$ = 7.1, $^3J_{HH}$ = 2.1, O=CHCH_2), 1.45-1.80 (4H, overlapping m, $CH_2CH_2CH_2$ and CH_2CH_2CHOC), 1.41(3H, s, CH_3), 1.33 (3H, s, CH_3).

Preparation of polystyrene-bound 2,2-Dimethyl-4-(6-phenyl-hex-5-enyl)-[1,3]dioxolane (144)

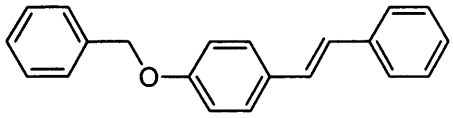


2,2-Dimethyl-4-(6-phenyl-hex-5-enyl)-[1,3]dioxolane (**144**) was prepdared according to a modified literature procedure[103] as follows: To a stirred (overhead stirrer) mixture of 4-(2,2-dimethyl-[1,3]dioxolan-4-yl)-butyraldehyde (**143**) (0.62 g, 3.5 mmol), DCM (8 mL) and 50% aqueous NaOH (10 mL) was added resin (**142**) (1.5 g) and cetyltrimethylammonium bromide (0.15 g). The mixture was stirred at room temperature for 72 hours, turning orange after 30 minutes. The polymer beads were collected by filtration and washed with THF/H_2O (1:1, 2 x 50 mL), THF (4 x 50 mL) and ether (5 x 50 mL). The polymer beads were then extracted (Soxhlet) with THF for 18 hours and finally solvent was removed *in vacuo* for 18 hours at 60°C to leave off-white beads (0.86 g).

^{13}C ((Leicester) 75.75 MHz, $CDCl_3$) δ: 108.7 (*C*$(OC)_2$), 76.0 (*C*HOC), 69.7 (CH_2OC), 33.6, 27.6 (CH_3), 26.3 (CH_3).

Elemental analysis: Expected Cl 0 %, P 0 %; Found Cl <0.30 %, P 0.04 %.

Preparation of 1-benzyloxy-4-styryl-benzene (163)



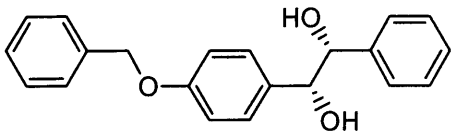
A 250mL, 3-neck round bottom flask, fitted with a reflux condenser, was charged with 4-styryl-phenol (4.00 g, 20.4 mmol). The solid was dissolved in acetone (70 mL) then a mixture of anhydrous K_2CO_3 (3.92 g, 30.6 mmol) and Cs_2CO_3 (0.100 g, 0.31 mmol) was added. The mixture was stirred at room temperature for 30 minutes after which time it had turned yellow. Benzyl bromide (4.18 g, 2.92 mL, 24.5 mmol) was added and the mixture was stirred at 60°C for 18 hours. The vessel was allowed to cool and diluted with Et_2O (100 mL). The resulting precipitate was removed by filtration and volatile components were removed from the filtrate under reduced pressure to leave an off-white solid. The residue was washed with Et_2O (3 x 40 mL) to leave the product as a fluffy white solid (3.60 g, 61.7 %).

^{1}H (250.13 MHz, $CDCl_3$) δ: 7.46-7.12 (12H, overlapping m, *o,m,p*-$C_6H_5CH_2$, *o,m,p*-C_6H_5CH=C and *o*-C_6H_4(CH=CH)OC), 7.00-6.81 (4H, overlapping m, C*H*=C*H* and *m*-C_6H_4(CH=CH)OC), 5.02 (2H, s, CH_2).

^{13}C (62.90 MHz, $CDCl_3$) δ: 158.5 ($C_6H_5CH_2OC$), 137.6 (*i*-$C_6H_5CH_2$), 136.9 (*i*-C_6H_5CH=CH), 130.4 (C_6H_5CH=CH*C*), 128.6, 128.6, 128.2, 128.0, 127.7, 127.4, 127.2, 126.8, 126.3 (all aromatic *C*H; specific assignment not possible), 115.1 (*o*-C_6H_4OC), 70.1 ($C_6H_5CH_2OC$).

M.p: 166-168 (Lit. Value = 168-169).[171]

Preparation of (*R*),(*R*)-1-(4-benzyloxy-phenyl)-2-phenyl-ethane-1,2-diol (164)



AD-mix-β (10.26 g) was dissolved in ^{t}BuOH/H_2O (1:1 mixture, 100 mL) and the stirred yellow solution was cooled to 0°C. Methane sulphonamide (0.70 g, 7.33 mmol) was added followed by 1-benzyloxy-4-styryl-benzene (**163**) (2.10 g, 7.33 mmol). The resulting suspension was stirred vigorously at 4°C for 48 hours then Na_2SO_3 (11.06 g, 87.7 mmol) was added and the stirred mixture was allowed to warm to room temperature. The mixture was diluted with H_2O (50 mL) then extracted with DCM (4 x 50 mL). The organic extracts were combined, dried ($MgSO_4$) and volatile components were removed under

reduced pressure to leave a yellow solid. The solid residue was washed with Et_2O (3 x 30 mL) to leave the product as a white solid (1.96 g, 83.6 %).

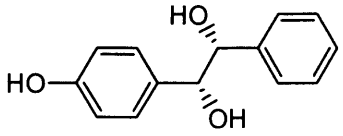
^{1}H (250.13 MHz, $CDCl_3$) δ: 7.50-7.21 (10H, overlapping m, *o,m,p*-$C_6H_5CH_2O$ and *o,m,p*-C_6H_5CHOH), 7.15 (2H, d, *o*-C_6H_4CHOH), 6.91 (2H, d, *m*-C_6H_4CHOH), 5.08 (2H, s, $C_6H_5CH_2O$), 4.76 (1H, d, $^3J_{HH}$ = 7.4, C*H*OH), 4.74 (1H, d, $^3J_{HH}$ = 7.4, C*H*OH) 2.48 (2H, bs, $\nu½$ = 62 Hz , O*H*).

^{13}C (62.90 MHz, DMSO-d_6) δ: 157.3 ($C_6H_5CH_2OC$), 142.5 (*i*-C_6H_5CHOH), 137.4 (*i*-$C_6H_5CH_2$), 134.7 ($C_6H_5CHOHCHOHC$)), 128.5, 128.4, 127.9, 127.8, 127.4, 127.4, 126.8 (all aromatic *C*H; specific assignment not possible), 113.8 (*o*-C_6H_4OC), 77.9 (*C*HOH), 77.4 (*C*HOH), 69.2 ($C_6H_5CH_2O$).

IR (ATR): 3505, 3404, 2895, 1608, 1583, 1510, 1497, 1455, 1242, 1174, 1040 cm^{-1}.

M.p.: 158-159°C.

Preparation of 1-(4-hydroxy-phenyl)-2-phenyl-ethane-1,2-diol (167)



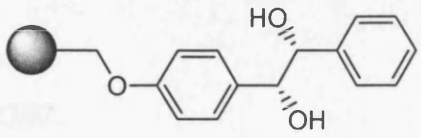
Under an atmosphere of N_2, a 100mL, 3-neck round bottom flask, was charged with 1-(4-benzyloxy-phenyl)-2-phenyl-ethane-1,2-diol (**164**) (0.60 g, 1.87 mmol) and absolute EtOH (25 mL) was added. Pd-C (10 %, 0.105g) was added to the stirred solution and a balloon of H_2 gas was fitted to the apparatus. The mixture was stirred vigorously for 18 hours, until TLC showed all starting material had been consumed, and was then filtered and volatile components removed *in vacuo* to leave a white solid. The solid was washed with Et_2O (2 x 10 mL) to leave the product as a white powder (0.43 g, 57.8 %).

^{1}H (250.13 MHz, Acetone-d_6) δ: 8.11 (1H, s, *H*OC_6H_4)), 7.21-7.04 (5H, overlapping m, C_6H_5CHOH), 6.94 (2H, d, $^3J_{HH}$ = 8.5, *o*-C_6H_4CHOH), 6.62 (2H, d, $^3J_{HH}$ = 8.5, *m*-C_6H_4CHOH), 4.57 (1H, d, $^3J_{HH}$ = 7.6, C*H*OH), 4.50 (1H, d, $^3J_{HH}$ = 7.6, C*H*OH), 4.45 (1H, s, CHO*H*), 4.37 (1H, s, CHO*H*).

^{13}C (62.90 MHz, Acetone-d_6) δ: 157.19 (HO*C*), 142.30 (*i*-C_6H_5CHOH), 132.65 ($C_6H_5CHOHCHOHC$), 129.08, 128.17, 127.99, 127.68 (all aromatic *C*H; specific assignment not possible), 115.03 (*o*-C_6H_4OH), 79.45 (*C*HOH), 79.13 (*C*HOH).

MS (EI^+): 253 $(MNa)^+$, 213 $(M\text{-}H_2O)^+$, 197, 155, 130, 127, 109.

Preparation of polystyrene-bound (4-Hydroxy-phenyl)-2-phenyl-ethane-1,2-diol (168)

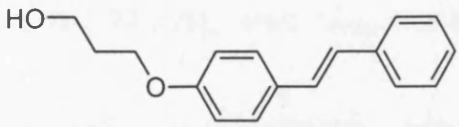


A 100mL, 3-neck round bottom flask, fitted with a reflux condenser and an overhead stirrer, was charged with Merrifield resin (0.30 g, 1 mmol g^{-1} Cl) and (4-hydroxy-phenyl)-2-phenyl-ethane-1,2-diol (**167**) (0.20 g, 0.86 mmol). DMF (20 mL) was added and the mixture stirred for 10 minutes then K_2CO_3 (0.20 g, 1.56 mmol) and Cs_2CO_3 (0.050 g, 0.154 mmol) were added and the mixture stirred at 80°C for 72 hours, during which time it turned yellow. The mixture was allowed to cool and the polymer beads collected by filtration then washed with THF, THF/H_2O (1:1), EtOH, H_2O (100 mL of each, 3 cycles) then washed with acetone (2 x 100 mL) and dried *in vacuo* at 70°C for 18 hours. The product was obtained as pale yellow beads (0.32 g).

^{13}**C** (75.48 MHz, $CDCl_3$) δ: 114.40 (*o*-C_6H_4OH), 78.75 (b, *C*HOH), 70.03 ($CH_2OC_6H_4$).

Elemental analysis: Expected Cl 0 %; Found Cl 0.59 %

Preparation of 3-(4-styryl-phenoxy)-propan-1-ol (169)



A 250mL, 3-neck round bottom flask, fitted with a reflux condenser, was charged with 4-styryl-phenol (5.00 g, 25.5 mmol). The solid was dissolved in acetone (100 mL) then a mixture of anhydrous K_2CO_3 (3.60 g, 28.0 mmol) and Cs_2CO_3 (0.100 g, 0.31 mmol) was added. The mixture was stirred at room temperature for 30 minutes over which time it turned yellow. 3-Bromo-propan-1-ol (3.61 g, 2.35 mL, 26 mmol) was added by syringe and the mixture was stirred at 60°C for 18 hours. The vessel was allowed to cool and diluted with Et_2O (100 mL). The resulting precipitate was removed by filtration and the filtrate was concentrated under reduced pressure to leave an off-white solid (6.30 g, 97.1 %).

^{1}**H** (300.13 MHz, $CDCl_3$) δ: 7.48-7.10 (7H, overlapping m, *o,m,p*-C_6H_5 and *o*-C_6H_4CH=CH), 7.00-6.72 (4H, overlapping m, C*H*=C*H* and *m*-C_6H_4CH=CH), 4.08 (2H, t, $^3J_{HH}$ = 6.2, $CH_2CH_2OC_6H_4$), 3.81 (2H, t, $^3J_{HH}$ = 6.2, CH_2OH), 2.06-1.94 (2H, m, $CH_2CH_2CH_2$), 1.70 (1H, b s, O*H*).

^{13}**C** (75.48 MHz, DMSO-d_6) δ: 159.74 (CH_2OC), 138.74 (*i*-C_6H_5CH=CHC_6H_4), 130.88 (C_6H_5CH=*C*HC), 129.45, 129.09, 128.71, 128.59, 127.93, 127.09, 127.06 (all aromatic

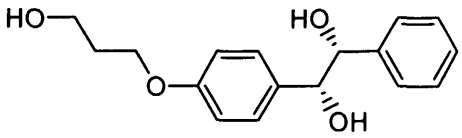
*C*H; specific assignment not possible), 115.53 (*o*-C_6H_4OC), 65.67 (CH_2CH_2OC), 59.00 (CH_2OH), 33.32 (CH_2CH_2OH).

MS (EI^+): 276 $(MNa)^+$, 234 $(M\text{-}H_2O)^+$, 190, 181, 178, 149.

HRMS (EI^+): calcd for $C_{17}H_{18}O_2$: 254.1307; found: 254.1307.

M.p: 152-153°C.

Preparation of 1-[4-(3-hydroxy-propoxy)-phenyl]-2-phenyl-ethane-1,2-diol (170)



Following an identical procedure to that described for the synthesis of compound **164**, 3-(4-styryl-phenoxy)-propan-1-ol (**169**) (2.50 g, 9.83 mmol) was dihydroxylated with AD-mix-β (13.75 g) to give compound **170** as a white solid (2.79 g, 97.8 %).

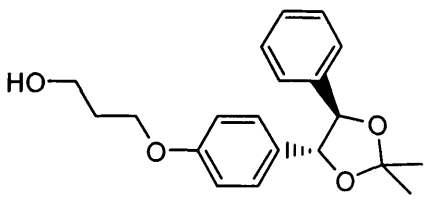
^{1}H (300.13 MHz, DMSO-d_6) δ: 7.33-7.04 (5H, overlapping m, *o,m,p*-C_6H_5), 6.98 (2H, d, $^3J_{HH}$ = 8.6, *o*-C_6H_4CHOH), 6.70 (2H, d, $^3J_{HH}$ = 8.6, *m*-C_6H_4CHOH), 5.30 (1H, d, $^3J_{HH}$ = 3.5, CHO*H*), 5.22 (1H, d, $^3J_{HH}$ = 3.5, CHO*H*), 4.55-4.46 (2H, overlapping m, C_6H_5CHOH and $C_6H_5CHOHCHOH$), 3.96 (2H, t, $^3J_{HH}$ = 6.4, $CH_2CH_2OC_6H_4$), 3.55 (2H, dt, $^3J_{HH}$ = 5.3, $^3J_{HH}$ = 6.2, CH_2CH_2OH), 2.95 (1H, bs, CH_2OH), 1.91-1.77 (2H, sept, $^3J_{HH}$ = 6.2, $CH_2CH_2CH_2$).

^{13}C (75.48 MHz, DMSO-d_6) δ: 157.7 (CH_2OC), 142.6 (*i*-C_6H_5CHOH), 134.3 ($C_6H_5CHOHCHOHC$), 128.4, 127.5, 127.4, 126.8 (all aromatic *C*H; specific assignment not possible), 113.4 (*o*-C_6H_4OC), 78.0 (*C*HOH), 77.5 (*C*HOH), 64.5 ($CH_2OC_6H_4$), 57.5 (CH_2OH), 32.3 ($CH_2CH_2CH_2$).

IR (ATR): 3499, 3322 (br), 3244 (br), 2920, 2849, 1610, 1512, 1469, 1245, 1048, 1008 cm^{-1}.

MS (EI^+): 311 $(MNa)^+$, 271 $(M\text{-}H_2O)^+$, 253 $(M\text{-}2H_2O)^+$, 213, 191, 181, 167, 161, 149, 105, 91.

Preparation of 3-[4-(2,2-dimethyl-5-phenyl-[1,3]dioxolan-4-yl)-phenoxy]-propan-1-ol (171)



Following an identical procedure to that described in for the synthesis of compound **121**, 1-[4-(3-hydroxy-propoxy)-phenyl]-2-phenyl-ethane-1,2-diol (**170**) (2.00 g, 6.94

mmol) was protected to give compound **171** (1.56 g, 68.5 %) as a white solid, after purification by chromatography on silica gel {hexane/EtOAc, 2:1, TLC: R_f 0.20 (hexane/EtOAc, 2:1)}.

^{1}H (300.13 MHz, $CDCl_3$) δ: 7.33-7.20 (5H, m, *o,m,*p-C_6H_5), 7.17 (2H, d, $^3J_{HH}$ = 8.7, *o*-C_6H_4CHOH), 6.87 (2H, d, $^3J_{HH}$ = 8.7, *o*-C_6H_4CHOH), 4.74 (1H, d, $^3J_{HH}$ = 8.7, C*H*OC), 4.69 (1H, d, $^3J_{HH}$ = 8.4, C*H*OH), 4.11 (2H, t, $^3J_{HH}$ = 6.0, $CH_2CH_2OC_6H_4$), 3.86 (2H, t, $^3J_{HH}$ = 6.0, CH_2OH), 2.09-1.98 (2H, m, $CH_2CH_2CH_2$), 1.87 (1H, bs, O*H*), 1.66 (6H, s, CCH_3).

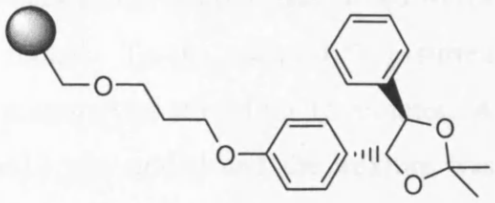
^{13}C (75.48 MHz, $CDCl_3$) δ: 158.8 (CH_2OC), 136.8 (*i*-C_6H_5CHOC), 128.8 (C_6H_5CH(OC)CH(OC)*C*), 128.3, 128.1, 126.6 (all aromatic *C*H; specific assignment not possible), 114.4 (*o*-C_6H_4OC), 109.1 ($C(OC)_2$), 85.3 (*C*HOC), 85.2 (*C*HOC), 65.6 ($CH_2OC_6H_4$), 60.4 (CH_2OH), 31.9 ($CH_2CH_2CH_2$), 27.2 (CH_3), 27.1 (CH_3).

IR (CCl_4): 3510, 2950, 2932, 2881, 1614, 1516, 1372, 1230, 1164, 1061, 1028, 995 cm^{-1}.

HRMS (EI^+): calcd for $C_{20}H_{24}O_4$: 328.1675; found: 328.1675.

M.p.: 64-65°C.

Polystyrene-bound 3-[4-(2,2-dimethyl-5-phenyl-[1,3]dioxolan-4-yl)-phenoxy]-propan-1-ol (172)

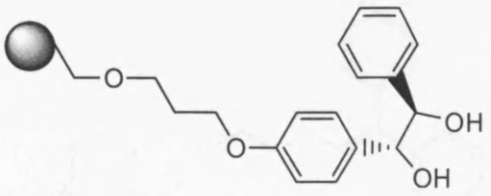


Following the general procedure used for the preparation of resin **125**, 3-[4-(2,2-dimethyl-5-phenyl-[1,3]dioxolan-4-yl)-phenoxy]-propan-1-ol (**171**) (0.92 g, 2.80 mmol), was reacted with Merrifield resin (0.70 g, 1 mmol g^{-1} Cl) to give the product as pale yellow beads (0.86 g).

^{13}C ((Durham) 75.43 MHz, $CDCl_3$) δ: 114.4 (*o*-C_6H_4OC), 85.3 (b, *C*HOC$(CH_3)_2$), 73.0 ($C_6H_4CH_2OCH_2$), 66.7 ($CH_2CH_2OC_6H_4$), 64.9 ($CH_2CH_2OCH_2$), 29.8 ($CH_2CH_2CH_2$), 27.3 (CH_3).

Elemental analysis: Expected Cl 0 %; Found Cl 0.25 %

Polystyrene bound 1-[4-(3-hydroxy-propoxy)-phenyl]-2-phenyl-ethane-1,2-diol (173)

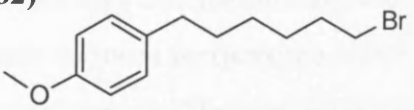


Following general procedure used for the preparation of resin **137**, polystyrene-bound 3-[4-(2,2-dimethyl-5-phenyl-[1,3]dioxolan-4-yl)-phenoxy]-propan-1-ol (**172**) (0.50 g, 1 mmol g^{-1}) was deprotected to give resin (**173**) (0.46 g).

^{13}C (75.48 MHz, $CDCl_3$) δ: 114.2 (*o*-C_6H_4OC), 78.5 (b, *C*HOH), 73.1 ($C_6H_4CH_2OCH_2$), 66.2 ($CH_2CH_2OC_6H_4$), 64.9 ($CH_2CH_2OCH_2$), 29.8 ($CH_2CH_2CH_2$).

IR (CCl_4): 3347 (br), 1369, 1243, 1172, 1054, 1028, 907 cm^{-1}.

Preparation of 1-(6-bromo-hexyl)-4-methoxy-benzene (182)



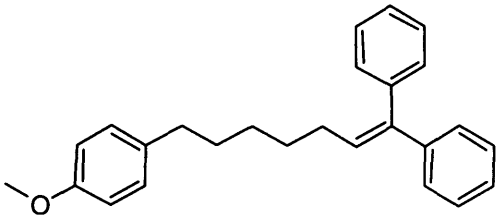
Under an atmosphere of N_2, a solution of 6-bromohexanoyl chloride (10.00 g, 46.8 mmol) in DCM (50 mL) was prepared in a 250mL, 3-neck round bottom flask, fitted with a reflux condenser and pressure equalising dropping funnel. To the cooled (0°C), stirred solution was added $AlCl_3$ (5.33 g, 40 mmol) and the mixture was stirred for 15 minutes. A solution of anisole (4.10, 38 mmol) in DCM (20 mL) was added and the mixture was allowed to warm to room temperature and stirred for 1 hour. Triethylsilane (15 mL, 94.6 mmol) was added and the mixture stirred for. The crude product was used directly in the next step without removal of high-boiling silyl bi-products. Characterisation of the crude product was consistent with previously reported data.[172]

^{1}H (300.13 MHz, $CDCl_3$) δ: 7.10 (2H, d, $^{3}J_{HH}$ = 8.8, *m*-$C_6H_4OCH_3$), 6.83 (2H, d, $^{3}J_{HH}$ = 8.8, *o*-$C_6H_4OCH_3$), 3.80 (3H, s, OCH_3), 3.41 (2H, t, $^{3}J_{HH}$ = 6.7, CH_2Br), 2.56 (2H, t, $^{3}J_{HH}$ = 7.6, $C_6H_4CH_2CH_2$), 1.85-1.69 (2H, m, CH_2CH_2Br), 1.48-1.23 (6H, overlapping m, $CH_2CH_2CH_2$).

^{13}C (75.48 MHz, $CDCl_3$) δ: 157.6 (CH_3OC), 134.6 (*p*-$C_6H_4OCH_3$), 129.2 (*m*-$C_6H_4OCH_3$), 113.6 (*o*-$C_6H_4OCH_3$), 55.2 (OCH_3), 34.8 ($C_6H_4CH_2CH_2$), 34.0 (CH_2Br), 32.7 (CH_2CH_2Br), 31.5 ($C_6H_4CH_2CH_2$), 28.3, 28.0 (both CH_2; specific assignment not possible).

MS (EI^+): 190 $(M\text{-}HBr)^+$, 181, 167, 149, 135, 113, 88, 71.

Preparation of 1-(7,7-diphenyl-hept-6-enyl)-4-methoxy-benzene (184)



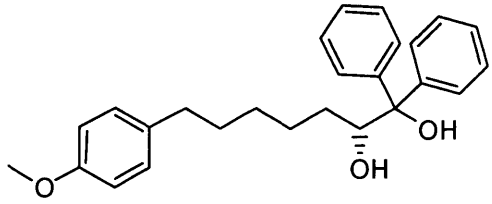
A stirred mixture of crude 1-(6-bromo-hexyl)-4-methoxy-benzene (**182**) and triphenylphosphine (11.00g, 41.9 mmol) was heated to 110°C overnight, then allowed to cool and washed by stirring the mixture with Et_2O (5 x 50 mL) and decantation. The resulting viscous oil was transferred to a 500mL, 3-neck round bottom flask, fitted with a reflux condenser and pressure equalising dropping funnel, and dried *in vacuo*. After backfilling with N_2, THF (150 mL) was added and the stirred solution was cooled to -78°C. *n*-Buli (1.6 M in hexanes, 34.5 mmol, 21.6 mL) was added cautiously and the mixture was stirred at -78°C for 30 minutes before being allowed to warm to room temperature. The mixture was stirred at room temperature for 4 hours, turning deep red/brown, prior to addition of a solution of benzophenone (6.28 g, 34.5 mmol) in THF (30 mL). The mixture was stirred at room temperature overnight, with a colour change to green/blue being observed, and was then cooled to 0°C and quenched by the cautious addition of H_2O (50 mL). The mixture was extracted with DCM (4 x 50 mL), the organic extracts were combined, washed with H_2O (100 mL), dried ($MgSO_4$) and volatile components removed *in vacuo* to give an orange oil. The residue was purified by chromatography on silica gel {Hexane/EtOAc, 2:1, TLC: R_f 0.25 (Hexane/EtOAc, 2:1)} to give the product as a colourless oil (3.41 g, 20.4 %).

^{1}H (300.13 MHz, $CDCl_3$) δ: 7.39-7.14 (10H, m, *o,m,p*-C_6H_5), 7.05 (2H, d, $^3J_{HH}$ = 7.2, *m*-$C_6H_4OCH_3$), 6.81 (2H, d, $^3J_{HH}$ = 7.2, *o*-$C_6H_4OCH_3$), 6.06 (1H, t, $^3J_{HH}$ = 7.6, CH_2CH=C), 3.75 (3H, s, OCH_3), 2.50 (2H, t, $^3J_{HH}$ = 7.6, $C_6H_4CH_2CH_2$), 2.10 (2H, dt, $^3J_{HH}$ = 7.6, $^3J_{HH}$ = 6.0, CH_2CH_2CH=C), 1.58-1.25 (6H, overlapping m, $CH_2CH_2CH_2$).

^{13}C (75.48 MHz, $CDCl_3$) δ: 157.6 (CH_3OC), 142.8 ($(C_6H_5)_2C$=CH), 141.4 (aromatic *C*; specific assignment not possible), 140.3 (aromatic *C*; specific assignment not possible), 134.8 (*p*-$C_6H_4OCH_3$), 130.1, 129.9, 129.2, 128.2, 128.1, 127.2, 126.8, 126.7 (all aromatic *C*H; specific assignment not possible), 113.6 (*o*-$C_6H_4OCH_3$), 55.2 (OCH_3), 34.9 ($C_6H_4CH_2CH_2$), 31.5 ($C_6H_4CH_2CH_2$), 29.7, 29.6, 28.8 (all CH_2; specific assignment not possible).

MS (EI^+): 380 $(MNa)^+$, 302, 260, 245, 176, 124, 98.

Preparation of 7-(4-methoxy-phenyl)-1,1-diphenyl-heptane-1,2-diol (185)



Following an identical procedure to that described for the synthesis of compound **164**, 1-(7,7-diphenyl-hept-6-enyl)-4-methoxy-benzene (**184**) (2.72 g, 7.34 mmol) was dihydroxylated with AD-mix-β (10.27 g) to give (**185**) as a white solid (2.84 g, 95.2 %).

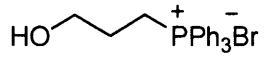
^{1}H (300.13 MHz, $CDCl_3$) δ: 7.51-7.15 (10H, m, *o,m,p*-C_6H_5), 7.05 (2H, d, $^3J_{HH}$ = 7.5, *m*-$C_6H_4OCH_3$), 6.81 (2H, d, $^3J_{HH}$ = 7.5, *o*-$C_6H_4OCH_3$), 4.53 (1H, t, $^3J_{HH}$ = 6.8, CH_2CHOH), 3.76 (3H, s, OCH_3), 3.05 (1H, s, $(C_6H_5)_2COH$), 2.49 (2H, t, $^3J_{HH}$ = 7.6, $C_6H_4CH_2CH_2$), 2.02 (1H, s, O*H*), 1.60-1.41 (4H, overlapping m, $C_6H_4CH_2CH_2$ and CH_2CHOH), 1.38-1.20 (4H, overlapping m, $CH_2CH_2CH_2$).

^{13}C (75.48 MHz, $CDCl_3$) δ: 157.6 (CH_3OC), 145.8 (aromatic *C*; specific assignment not possible), 143.9 (aromatic *C*; specific assignment not possible), 134.9 (*p*-$C_6H_4OCH_3$), 129.2, 128.5, 128.1, 127.1, 126.7, 126.1, 125.5 (all aromatic *C*H; specific assignment not possible), 113.6 (*o*-$C_6H_4OCH_3$), 80.1 ($(C_6H_5)_2COH$), 75.6 (*C*HOH), 55.2 (OCH_3), 34.9 ($C_6H_4CH_2CH_2$), 31.7 ($C_6H_4CH_2CH_2$), 30.1 ($C_6H_4CH_2CH_2CH_2$), 29.0 (CH_2CH_2CHOH) 26.3 (CH_2CH_2CHOH).

MS (EI^+): 413 $(MNa)^+$, 392 $(MH)^+$, 373 $(M\text{-}H_2O)^+$, 205, 185, 167, 144, 121, 105, 91.

IR (ATR): 3570, 3499, 3239, 2924, 2854, 1611, 1512, 1447, 1246, 1173, 1032.

Preparation of 3-(triphenylphosphoniumbromide)-propan-1-ol (187)



A 100mL round-bottom flask, fitted with a reflux condenser, was charged with 3-bromo-propan-1-ol (10.05 g, 71.9 mmol), triphenylphsophine (18.90 g, 72.1 mmol) and DMF (15 mL) and the stirred mixture was heated to 100°C for 18 hours. The mixture was allowed to cool and the resulting solid was collected by filtration and washed with Et_2O (3 x 50 mL) to leave the product as a white solid (27.23 g, 94.4 %).

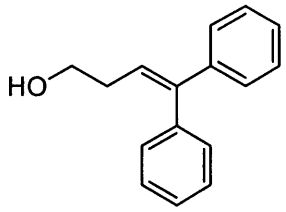
^{1}H (250.13 MHz, MeOH-d_4) δ: 8.00-7.68 (15H, m, *o,m,p*-C_6H_5), 3.81-3.68 (2H, m, CH_2CH_2P), 3.59-3.40 (2H, m, CH_2OH), 2.10 (1H, bs, O*H*), 2.02-1.76 (2H, m, $CH_2CH_2CH_2$).

^{31}P (101.26 MHz, MeOH-d_4) δ: 24.13.

MS (EI^+): 321 $(M\text{-}Br)^+$.

M.p.: 226-230°C (Lit. Value = 229-230)[173]

Preparation of 4,4-diphenyl-but-3-en-1-ol (188)[174]



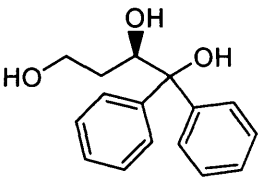
A 250mL, 3-neck round bottom flask, fitted with a reflux condenser and pressure equalising dropping funnel, was charged with 3-(triphenylphosphoniumbromide)-propan-1-ol (**187**) (10.00 g, 24.9 mmol) and the apparatus dried *in vacuo*. After backfilling with N_2, dry THF (80 mL) was added and the stirred solution was cooled to -78°C. *n*-BuLi (1.6 M in hexanes, 50 mmol, 31.25 mL) was added cautiously and the mixture was stirred at -78°C for 30 minutes then allowed to warm to room temperature. The mixture was stirred at room temperature for 4 hours, turning deep red/brown and then a solution of benzophenone (5.00 g, 27.8 mmol) in THF (30 mL) was added. The mixture was stirred at room temperature overnight, with a colour change to green/blue observed, and was then cooled to 0°C and quenched by the cautious addition of H_2O (50 mL). The mixture was extracted with Et_2O (4 x 50 mL), the organic extracts were combined, washed with H_2O (100 mL), dried ($MgSO_4$) and volatile components removed under reduced pressure to give an orange oil. The residue was purified by chromatography on silica gel {Hexane/EtOAc, 10:1, TLC: R_f 0.30 (Hexane/EtOAc, 10:1)} to give the product as a colourless oil (5.36 g, 96.0 %). Characterisation was consistent with previously reported data.[174]

^{1}H (250.13 MHz, $CDCl_3$) δ: 7.39-7.17 (10H, m, *o,m,p*-C_6H_5), 6.12 (1H, t, $^3J_{HH}$ = 7.5, CH_2CH=C), 3.70 (2H, t, $^3J_{HH}$ = 6.7, CH_2OH), 2.40 (2H, dt, $^3J_{HH}$ = 7.5, $^3J_{HH}$ = 6.7, CH_2CH_2CH=C), 1.56 (1H, br s, $\nu_{½}$ = 12.5 Hz O*H*).

^{13}C (62.90 MHz, $CDCl_3$) δ: 144.2 (($C_6H_5)_2C$=C), 142.4 (aromatic *C*; specific assignment not possible), 139.8 (aromatic *C*; specific assignment not possible), 130.0, 129.8, 128.2, 128.1, 127.2, 127.1 (all aromatic *C*H; specific assignment not possible), 125.2 (*C*H=C($C_6H_5)_2$), 62.6 (CH_2OH), 33.3 (CH_2CH_2CH).

HRMS (EI^+): calcd for $C_{16}H_{16}O$: 224.1202; found: 224.1201.

Preparation of 1,1-diphenyl-butane-1,2,4-triol (189)



Following an identical procedure to that described for the synthesis of compound **164**, 4,4-diphenyl-but-3-en-1-ol (**188**) (3.20 g, 14.3 mmol) was dihydroxylated with AD-mix-β (20.00 g) to give (**189**) as a white solid (3.41 g, 92.3 %).

^{1}H (250.13 MHz, DMSO-d_6) δ: 7.51 (2H, d, $^3J_{HH}$ = 6.8, specific assignment not possible), 7.41 (2H, d, $^3J_{HH}$ = 6.8, specific assignment not possible), 7.24-7.15 (4H, m, specific assignment not possible), 7.14-7.03 (2H, m, specific assignment not possible), 5.17 (1H, s, $(C_6H_5)_2CO\mathit{H}$), 4.59 (1H, dt, $^3J_{HH}$ = 6.9, $^3J_{HH}$ = 3.0, $CH_2C\mathit{H}OH$), 4.39 (1H, d, $^3J_{HH}$ = 3.0, $CHO\mathit{H}$), 4.32 (1H, t, $^3J_{HH}$ = 6.1, $CH_2O\mathit{H}$), 3.55-3.43 (2H, m, $C\mathit{H}_2OH$), 1.51-1.37 (2H, m, $CH_2C\mathit{H}_2CHOH$).

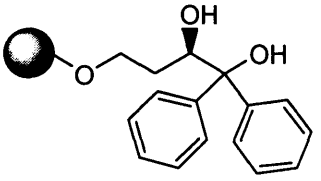
^{13}C (62.90 MHz, DMSO-d_6) δ: 147.3, 146.6 (both aromatic *C*; specific assignment not possible), 127.8, 127.5, 127.0, 126.1 (all aromatic *C*H; specific assignment not possible), 79.7 ($(C_6H_5)_2\mathit{C}OH$), 72.1 ($CH_2\mathit{C}HOH$), 58.8 ($\mathit{C}H_2OH$), 34.6 ($CH_2\mathit{C}H_2CHOH$).

IR (ATR): 3432 (br), 1589, 1497, 1143, 1068 cm^{-1}.

MS (EI^+): 281 $(MNa)^+$, 223 $(M\text{-}2H_2O)^+$, 199, 167, 139, 102, 83.

M.p.: 164°C.

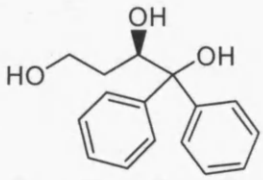
Preparation of polystyrene-bound 1,1-diphenyl-butane-1,2,4-triol (191)



A 100mL, 3-neck round bottom flask, fitted with a reflux condenser and an overhead stirrer, was charged with 1,1-diphenyl-butane-1,2,4-triol (**189**) (1.00 g, 3.87 mmol) and dried *in vacuo*. After backfilling with N_2, THF (20 mL) was added and the stirred suspension was cooled to 0°C. A solution of NaO^tBu (0.336 g, 3.5 mmol) in THF (5 mL) was added and the mixture stirred at 0°C for 1 hour then allowed to warm to room temperature and stirred for a further 2 hours. Merrifield resin (0.80 g, 1 mmol g^{-1}) was added and the mixture was heated at 60°C for 72 hours. The mixture was allowed to cool and the polymer beads collected by filtration then washed with THF, THF/H_2O (1:1), EtOH, H_2O (100 mL of each, 3 cycles) then washed with acetone (2 x 100 mL) and dried *in vacuo* at 70°C for 18 hours. The product was obtained as white beads (0.79 g).

Elemental analysis: Expected Cl 0 %; Found Cl 2.95 %

Preparation of 1,1-diphenyl-butane-1,2,4-triol (189)



Following an identical procedure to that described for the synthesis of compound **164**, 4,4-diphenyl-but-3-en-1-ol (**188**) (3.20 g, 14.3 mmol) was dihydroxylated with AD-mix-β (20.00 g) to give (**189**) as a white solid (3.41 g, 92.3 %).

^{1}H (250.13 MHz, DMSO-d_6) δ: 7.51 (2H, d, $^3J_{HH}$ = 6.8, specific assignment not possible), 7.41 (2H, d, $^3J_{HH}$ = 6.8, specific assignment not possible), 7.24-7.15 (4H, m, specific assignment not possible), 7.14-7.03 (2H, m, specific assignment not possible), 5.17 (1H, s, $(C_6H_5)_2CO\mathit{H}$), 4.59 (1H, dt, $^3J_{HH}$ = 6.9, $^3J_{HH}$ = 3.0, $CH_2C\mathit{H}OH$), 4.39 (1H, d, $^3J_{HH}$ = 3.0, $CHO\mathit{H}$), 4.32 (1H, t, $^3J_{HH}$ = 6.1, $CH_2O\mathit{H}$), 3.55-3.43 (2H, m, $C\mathit{H}_2OH$), 1.51-1.37 (2H, m, $CH_2C\mathit{H}_2CHOH$).

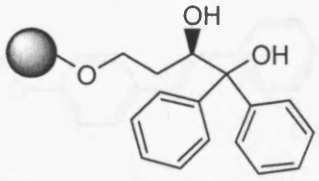
^{13}C (62.90 MHz, DMSO-d_6) δ: 147.3, 146.6 (both aromatic *C*; specific assignment not possible), 127.8, 127.5, 127.0, 126.1 (all aromatic *C*H; specific assignment not possible), 79.7 ($(C_6H_5)_2\mathit{C}OH$), 72.1 ($CH_2\mathit{C}HOH$), 58.8 ($\mathit{C}H_2OH$), 34.6 ($CH_2\mathit{C}H_2CHOH$).

IR (ATR): 3432 (br), 1589, 1497, 1143, 1068 cm^{-1}.

MS (EI^+): 281 $(MNa)^+$, 223 $(M\text{-}2H_2O)^+$, 199, 167, 139, 102, 83.

M.p.: 164°C.

Preparation of polystyrene-bound 1,1-diphenyl-butane-1,2,4-triol (191)

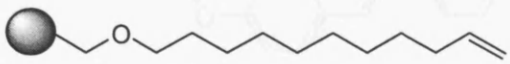


A 100mL, 3-neck round bottom flask, fitted with a reflux condenser and an overhead stirrer, was charged with 1,1-diphenyl-butane-1,2,4-triol (**189**) (1.00 g, 3.87 mmol) and dried *in vacuo*. After backfilling with N_2, THF (20 mL) was added and the stirred suspension was cooled to 0°C. A solution of NaO^tBu (0.336 g, 3.5 mmol) in THF (5 mL) was added and the mixture stirred at 0°C for 1 hour then allowed to warm to room temperature and stirred for a further 2 hours. Merrifield resin (0.80 g, 1 mmol g^{-1}) was added and the mixture was heated at 60°C for 72 hours. The mixture was allowed to cool and the polymer beads collected by filtration then washed with THF, THF/H_2O (1:1), EtOH, H_2O (100 mL of each, 3 cycles) then washed with acetone (2 x 100 mL) and dried *in vacuo* at 70°C for 18 hours. The product was obtained as white beads (0.79 g).

Elemental analysis: Expected Cl 0 %; Found Cl 2.95 %

IR (CCl_4): 3702, 1265, 1069, 1028 cm^{-1}

Preparation of polystyrene-bound undecen-1-ol (200)

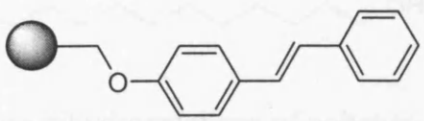


In a 100mL, 3-neck round bottom flask, fitted with a reflux condenser and an overhead stirrer, NaH (60 % dispersion in mineral oil, 0.70 g, 8.1 mmol) was washed with hexane (3 x 20 mL). THF (50 mL) was added followed by undecen-1-ol (1.36 g, 8 mmol) and 18-crown-6 (0.35 g, 1.3 mmol). After stirring at room temperature for 30 minutes, chloromethylated polystyrene (4 g, 1mmol g^{-1} Cl) was added and the mixture was heated at reflux for 72 h, with the mixture turning pale pink after 24 h. The polymer beads were recovered by filtration then washed with H_2O, H_2O:THF (1:1), THF (50 mL of each, 3 cycles) then acetone (2 x 50 mL) and finally dried at 70°C for 18 h under vacuum. 4.48 g of partially-functionalised polystyrene beads were obtained. Characterisation was consistent with previously reported data.[99]

^{13}C CP MAS (75.43 MHz, $CDCl_3$)δ: 139.1 (CH=CH_2), 114.1 (CH=CH_2), 72.8 ($C_6H_4CH_2O$), 70.3 (OCH_2CH_2), 33.8 (CH_2CH=CH_2), 29.8, 29.5, 29.3, 29.1, 28.9, 26.3 (all CH_2; specific assignment not possible).

Elemental analysis: Expected Cl 0 %; Found Cl 0.46 %

Preparation of polystyrene-bound 4-styryl-phenol (201)

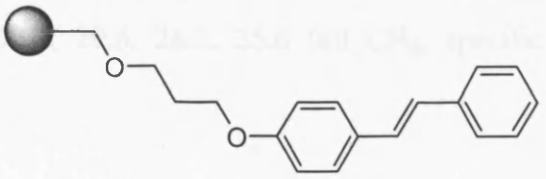


In a 100mL, 3-neck round bottom flask, fitted with a reflux condenser and an overhead stirrer, Merrifield resin (2.00 g, 1mmol g^{-1} Cl) was swollen in DMF (30 mL). To the stirred mixture was added 4-styryl-phenol (1.60 g, 8.15 mmol) followed by a mixture of K_2CO_3 (2.15 g, 16.80 mmol) and Cs_2CO_3 (0.10 g, 0.31 mmol). The mixture was stirred at 80°C for 48 hours then, after cooling, the polymer beads were recovered by filtration then washed with H_2O, H_2O/THF (1:1), THF (50 mL of each, 3 cycles) then acetone (2 x 50 mL) and finally dried at 70°C for 24 hours under vacuum. The product was obtained as off-white beads (2.26 g).

^{13}C (75.58 MHz, $CDCl_3$) δ: 115.0 (*o*-C_6H_4OC), 70.0 ($C_6H_4CH_2O$).

Elemental analysis: Expected Cl 0 %; Found Cl 0.01 %

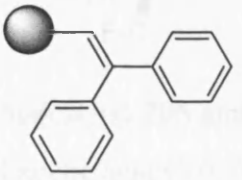
Preparation of polystyrene-bound 3-(4-styryl-phenoxy)-propan-1-ol (202)



Following general procedure used for the preparation of resin **125**, 3-(4-styryl-phenoxy)-propan-1-ol (**169**) (1.00 g, 3.93 mmol), was reacted with Merrifield resin (1.00 g, 1 mmol g^{-1} Cl) to give the product as off-white beads (1.18 g).

Elemental analysis: Expected Cl 0 %; Found Cl 0.0 %

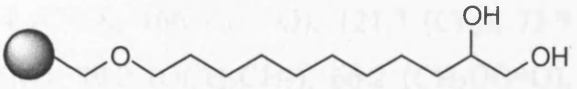
Preparation of polystryene-bound triphenylethene (203)



Following an identical procedure to that described in the synthesis of resin **144**, benzophenone (1.16 g, 7.3 mmol) was reacted with poly-(styrenediphenylphosphonium chloride) (**142**) (4.00 g) to give the product as pale orange beads (3.05 g).

Elemental analysis: Expected Cl 0 %, P 0 %; Found Cl 0.09 %, P 0.19 %

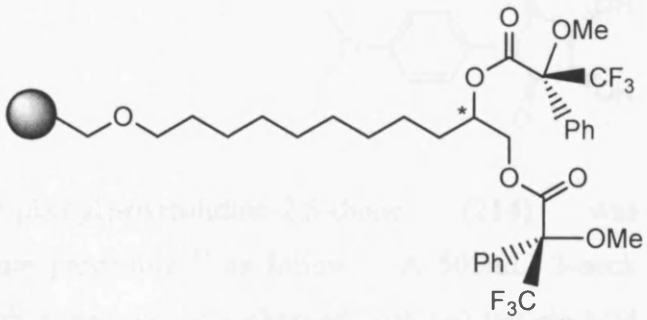
Dihydroxylation of polymer-bound olefins: Preparation of diol-functionalised resin 204



The following procedure was used in the solid-phase dihydroxylations of polymer-bound olefins **200-202**. AD-mix-β (1.40 g) was mixed with either DCM/^{t}BuOH/H_2O (2:1:0.05, 10 mL) or THF/H_2O (2:1) to which methyl sulphonamide (0.095 g, 1 mmol) was added in both cases. At this stage, Et_4NBr (0.020 g, 0.095 mmol) and 4-methylmorpholine *N*–oxide (0.117 g, 1 mmol) were added and the mixture shaken at room temperature for 10 minutes. Undecenyloxymethylated polystyrene (1.00 g, 1 mmol g^{-1} olefin) was added and the mixture was shaken vigorously at room temperature for 5 days. The beads were collected by filtration and washed with THF, THF/H_2O, H_2O (50 mL of each, 3 cycles) then washed with DCM (3 x 50 mL) and acetone (3 x 50 mL) before being dried *in vacuo* at 70°C for 18 hours. The product was obtained as off-white beads (0.98 g).

^{13}C CP MAS (75.43 MHz, $CDCl_3$) δ: 72.6 ($C_6H_4CH_2O$), 72.3 (*C*HOH), 70.3 (OCH_2CH_2), 66.8 ($CHCH_2OH$), 33.2 ($CH_2CHOHCH_2OH$), 30.9, 29.6, 26.2, 25.6 (all CH_2; specific assignment not possible).

General procedure for the attempted solid-phase preparation of bis(Mosher's) esters: Analysis of resin 204



The following procedure was used in the attempted synthesis of bis(esters) **205** and **209-210**: In a small vial, (R)-(+)-α-methoxy- α-(trifluoromethyl)phenyl acetic acid (0.050 g, 0.214 mmol) was dissolved in DCM (1 mL) and 1,3-dicyclohexylcarbodiimide (0.074 g, 0.359 mmol), 4-dimethylaminopyridine (0.003 g, 0.025 mmol) and diol functionalised resin **204** (0.100 g) were added. The vial was shaken vigorously for 5 days then the polymer beads were collected by filtration, washed with DCM (5 x 30 mL) and dried *in vacuo* at 70°C to give the product as white beads (0.115 g). Polymer-beads functionalised with a mixture of the mono- and bis- esters were obtained.

^{13}C CP MAS (75.43 MHz, $CDCl_3$) δ: 166.4 (*C*=O), 166.3 (*C*=O), 121.3 (CF_3), 73.9 (*C*HOC=O), 73.7 (*C*HOC=O), 72.7 ($C_6H_4CH_2O$), 70.2 (OCH_2CH_2), 66.2 (CH_2OC=O), 65.8 (CH_2OC=O), 55.4 (OCH_3), 33.8, 33.2, 30.4, 30.2, 29.8, 29.5, 29.1, 28.9, 26.2, 25.2, 24.9, 24.5 (all CH_2, specific assigment not possible).

Elemental analysis: Expected F 6.30 %; Found 5.49 %

Analysis of resin 207: attempted solid-phase preparation of bis(Mosher's) ester 209

Following the general procedure described for the analysis of resin **204**, resin **207** was converted to product **209**.

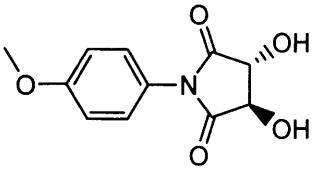
Elemental analysis: Found 1.30 %

Analysis of resin 208: attempted solid-phase preparation of bis(Mosher's) ester 210

Following the general procedure described for the analysis of resin **204**, resin **208** was converted to product **210**.

Elemental analysis: Found 4.57 %

Preparation of (*R*),(*R*)-3,4-dihydroxy-1-(4-methoxy-phenyl)-pyrrolidine-2,5-dione (214)



(*R*),(*R*)-3,4-dihydroxy-1-(4-methoxy-phenyl)-pyrrolidine-2,5-dione (**214**) was prepared according to a modified literature procedure[149] as follows: A 500mL, 3-neck round bottom flask, fitted with Dean-Stark apparatus, was charged with (+)-tartaric acid (10.00 g, 66 mmol), *p*-anisidine (8.20 g, 66.6 mmol) and xylenes (200 mL). The refluxing solution was azeotropically dehydrated for 4 hours, with 2.2 mL H_2O collected. The mixture was allowed to cool and the resulting purple/brown precipitate was collected by filtration and washed with Et_2O (2 x 30 mL) to give the product as a brown powder (15.1 g, 96.4 %).

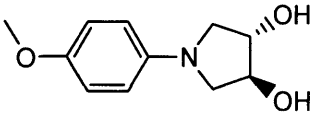
^{1}H (301.24 MHz, DMSO-d_6) δ: 7.23 (2H, d, $^3J_{HH}$ = 9.0, *o*-$C_6H_4OCH_3$), 7.01 (2H, d, $^3J_{HH}$ = 9.0, *m*-$C_6H_4OCH_3$), 6.40 (2H, d, O*H*), 4.56 (2H, d, $^3J_{HH}$ = 4.1, C*H*OH), 3.79 (3H, s, OCH_3).

^{13}C (75.76 MHz, DMSO-d_6) δ: 174.5 (*C*=O), 159.2 (CH_3OC), 128.5 (*m*-$C_6H_4OCH_3$), 124.8 (*p*-$C_6H_4OCH_3$), 114.4 (*o*-$C_6H_4OCH_3$), 74.7 (*C*HOH), 55.7 (OCH_3).

MS (EI^+): 238 $(M)^+$, 210 $(M\text{-}CO)^+$, 192, 181, 165, 150, 134, 124, 122, 109, 91, 74.

HRMS (EI^+): calcd for $C_{11}H_{12}O_5N$: 238.0716; found: 238.0716.

Preparation of (*S*),(*S*)-1-(4-methoxy-phenyl)-pyrrolidine-3,4-diol (215)



(*S*),(*S*)-1-(4-methoxy-phenyl)-pyrrolidine-3,4-diol (**215**) was prepared according to a modified literature procedure[149] as follows: A 250mL, 3-neck round bottom flask, fitted with a reflux condenser and pressure equalising dropping funnel, was charged with $NaBH_4$ (3.98 g, 10.5 mmol) and dried *in vacuo*. After backfilling with N_2, THF (60 mL) was added. To the stirred, cooled (0°C) suspension was added (*R*),(*R*)-3,4-dihydroxy-1-(4-methoxy-phenyl)-pyrrolidine-2,5-dione (**214**) (5.00 g, 21.1 mmol) cautiously in small

portions. The mixture was allowed to warm to room temperature then a solution of iodine (12.85 g, 51 mmol) in THF (100 mL) was added dropwise over a period of 90 minutes. The iodine colour was consumed in an exothermic reaction. The mixture was heated at reflux overnight, allowed to cool then quenched by cautious addition of HCl (3M, 20 mL). The mixture was neutralized by addition of NaOH (3M, *ca.* 30 mL) then the organic layer was separated and the aqueous layer extracted with Et_2O (3 x 50 mL) and DCM (3 x 50 mL). The organic extracts were combined, washed with aqueous NaCl solution (100 mL), H_2O (100 mL) then dried ($MgSO_4$) and all volatile components were removed *in vacuo* to give a brown slurry. A cycle of dissolving the residue in MeOH (30 mL), adding conc. HCl solution (5 mL) and removing MeOH at reduced pressure, was repeated 5 times. To the resulting residue was added a solution of KOH (1.00 g) in MeOH (50 mL) and anhydrous K_2CO_3 (25.00 g). MeOH was removed *in vacuo* to leave a brown solid, which was extracted (Soxhlet) overnight with DCM. Concentration of the DCM filtrate at reduced pressure gave a brown solid that was recrystallised from hot EtOH to give the product (3.20 g, 72.6 %).

^{1}H (250.13 MHz, DMSO-d_6) δ: 6.83 (2H, d, $^3J_{HH}$ = 7.5, *o*-$C_6H_4OCH_3$), 6.51 (2H, d, $^3J_{HH}$ = 7.5, *m*-$C_6H_4OCH_3$), 5.08 (2H, s, O*H*), 4.07 (2H, s, C*H*OH), 3.70 (3H, s, OCH_3), 3.51 (2H, dd, $^2J_{HH}$ = 11.7, $^3J_{HH}$ = 2.5 Hz, NC*H*2CH), 3.08 (2H, dd, $^2J_{HH}$ = 11.7, $^3J_{HH}$ = 1.5 Hz NCH_2CH).

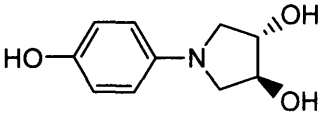
^{13}C (75.75 MHz, DMSO-d_6) δ: 150.3 (*i*-$C_6H_4OCH_3$), 142.9 (*p*-$C_6H_4OCH_3$), 115.0 (aromatic *C*H; specific assignment not possible), 112.0 (aromatic *C*H; specific assignment not possible), 75.2 (*C*HOH), 55.6 (O*C*H$_3$), 54.2 (N*C*H$_2$CHOH).

IR (ATR): 3381, 3244, 2962, 2856, 1511, 1446, 1240, 1180, 1099, 1081, 1050, 1030 cm^{-1}

MS (EI$^+$): 210 (MH)$^+$, 192 (M-H_2O)$^+$, 174 (M-H_2O)$^+$, 142, 124.

HRMS (EI$^+$): calcd for $C_{11}H_{15}O_3N$: 209.1052; found: 209.1052.

Preparation of (*S*),(*S*)-1-(4-hydroxy-phenyl)-pyrrolidine-3,4-diol (216)



Under an atmosphere of N_2, a solution of (*S*),(*S*)-1-(4-methoxy-phenyl)-pyrrolidine-3,4-diol (**215**) (0.50 g, 2.42 mmol) in DCM (30 mL) was cooled to 0°C and to which was added, by syringe, BBr_3 (1M solution in DCM, 9.00 mL, 9.00 mmol). The solution was stirred overnight at room temperature then cooled to 0°C and quenched by cautious addition of HCl (1M, 25 mL). The red aqueous layer was separated, neutralized by

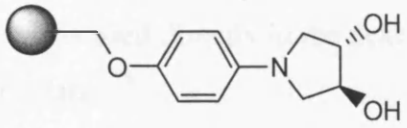
addition of 1M NaOH and concentrated by heating to a volume of 5 mL. MeOH (20 mL) was added followed by conc. HCl (1 mL) and MeOH was removed under reduced pressure. The cycle was repeated 3 times then the residue dissolved in acetone (30 mL), dried ($CuSO_4$) and concentrated under reduced pressure to give the product as a viscous brown oil (0.40 g, 84.8 %).

^{1}H (250.13 MHz, MeOH-d_4) δ: 7.54 (2H, d, $^3J_{HH}$ = 7.5, *o*-C_6H_4OH), 6.90 (2H, d, $^3J_{HH}$ = 7.5, *m*-C_6H_4OH), 4.43 (2H, s, C*H*OH), 4.01 (2H, d, $^2J_{HH}$ = 11.6, NCH_2CH), 3.67 (2H, d, $^2J_{HH}$ = 11.6, NCH_2CH).

^{13}C (62.90 MHz, MeOH-d_4) δ: 159.56 (*i*-C_6H_4OH), 134.93 (*p*-C_6H_4OH), 124.13 (aromatic *C*H; specific assignment not possible), 117.57 (aromatic *C*H; specific assignment not possible), 76.29 (*C*HOH), 66.49 (NCH_2).

MS (EI^+): 196 $(MH)^+$, 178 $(M\text{-}H_2O)^+$, 160, $(M\text{-}2H_2O)^+$, 135, 122, 107.

Preparation of polystyrene-bound (*S*),(*S*)-1-(4-hydroxy-phenyl)-pyrrolidine-3,4-diol (217)



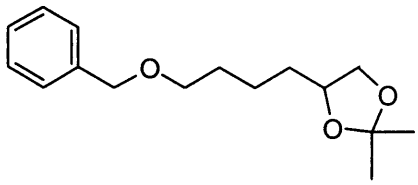
A 100mL, 3-neck round bottom flask, fitted with a reflux condenser and an overhead stirrer, was charged with (*S*),(*S*)-1-(4-hydroxy-phenyl)-pyrrolidine-3,4-diol (**216**) (0.80 g, 4.1 mmol) and acetone (15 mL) and THF (15 mL) were added. To the stirred mixture was added K_2CO_3 (0.63 g, 4.92 mmol) and 18-crown-6 (0.11 g, 0.41 mmol) and the mixture was stirred for 1 hour at room temperature, during which time it turned red. Merrifield resin (0.50 g, 1 mmol g^{-1} Cl) was added and the reaction heated to 60°C for 5 days. After cooling, the polymer beads were collected by filtration then washed with THF, THF/H_2O (1:1), EtOH, H_2O (100 mL of each, 3 cycles) and finally washed with acetone (2 x 100 mL) before being dried *in vacuo* at 70°C for 18 hours. The product was obtained as red beads (0.54 g).

^{13}C CP MAS (75.43 MHz, $CDCl_3$) δ: 155.21 (*i*-C_6H_4OC), 135.70 (*p*-C_6H_4OC), 115.83, 112.44, 76.08 (*C*HOH), 53.89 (NCH_2).

IR (ATR): 3366 (br), 3025, 2921, 1601, 1510, 1492, 1451, 1103 cm^{-1}

Elemental analysis: Expected Cl 0 %, N 1.19 %; Found Cl 2.08 % N 0.56 %

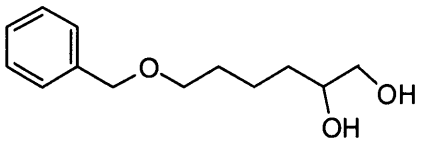
Preparation of 4-(4-benzyloxy-butyl)-2,2-dimethyl-[1,3]dioxolane (218)



A 100mL, 3-neck round bottom flask, fitted with a reflux condenser and an overhead stirrer was charged with sodium hydride (60% dispersion in mineral oil, 0.50 g, 12.5 mmol). The solid was washed with hexane (2 x 10 mL) and then THF (30 mL) was added. To the stirred suspension was added 4-(2,2-dimethyl-[1,3]dioxolan-4-yl)-butan-1-ol (**120**) (1.00 g, 5.75 mmol) and the mixture was stirred at room temperature for 30 minutes then refluxed at 75°C for 3 hours. The resulting brown solution was allowed to cool to room temperature then benzyl bromide (1.18 g, 6.90 mmol) was added by syringe. The mixture was stirred at room temperature overnight before being quenched by the addition of MeOH (5 mL). The mixture was diluted with H_2O (100 mL) then extracted with DCM (3 x 50 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure to give the product as a yellow oil (1.49 g, 98%) that was used directly in the next step. Characterisation was consistent with previously reported data.[175]

^{1}H (301.24 MHz, $CDCl_3$) δ: 7.40-7.25 (5H, overlapping m, *o,m,p*-C_6H_5), 4.51 (2H, s, $C_6H_5CH_2O$), 4.10-3.96 (2H, m, $CHCH_2OC$), 3.73 (2H, t, $^3J_{HH}$ = 7.1, CH_2CH_2OC), 3.51-3.38 (1H, m, $CHOC$), 1.70-1.53 (2H, m, CH_2CH_2CHOC), 1.52-1.41 (2H, m, CH_2CH_2OC), 1.40 (3H, s, CCH_3), 1.35 (3H, s, CCH_3), 1.32-1.22 (2H, m, $CH_2CH_2CH_2$).

Preparation of 6-benzyloxy-hexane-1,2-diol (220)



4-(4-Benzyloxy-butyl)-2,2-dimethyl-[1,3]dioxolane (**218**) (1.30 g, 4.92 mmol) was dissolved in 1,4-dioxane (40 mL) and HCl (1M, 10 mL) was added. The solution was stirred at 50°C for 4 hours then saturated aqueous $NaHCO_3$ solution (30 mL) was added and the mixture extracted with DCM (3 x 50 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure to leave a pale yellow oil. The residue was purified by chromatography on silica gel {EtOAc/hexane, 1:3, TLC: R_f = 0.10 (EtOH/toluene, 1:2)} to give the product as a colourless oil (0.74 g, 67%). Characterisation was consistent with previously reported data.[175]

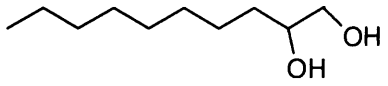
^{1}H (250.13 MHz, $CDCl_3$) δ: 7.44-7.32 (5H, overlapping m, *o,m,p*-C_6H_5), 4.50 (2H, s, $C_6H_5CH_2O$), 3.72-3.39 (5H, overlapping m, CH_2OH, $CHOH$ and CH_2CH_2O), 1.79-1.63 (2H, m, CH_2CHOC), 1.58-1.40 (4H, m, CH_2CH_2OH and $CH_2CH_2CH_2$).

^{13}C (62.90 MHz, $CDCl_3$) δ: 138.3 (*i*-C_6H_5), 128.3 (*m*-C_6H_5), 127.6 (*o*-C_6H_5), 127.5 (*p*-C_6H_5), 72.8 ($C_6H_5CH_2O$), 72.0 ($CHOH$), 70.1 (CH_2CH_2OC), 66.5 (CH_2OH), 32.7 (CH_2CHOH), 29.49 (OCH_2CH_2), 22.14 ($CH_2CH_2CH_2$).

MS (EI^+): 247 $(MNa)^+$, 190 $(M-2H_2O)^+$, 178, 132, 91.

HRMS (EI^+): calcd for $C_{13}H_{20}O_3$: 224.1413; found: 224.1412.

Preparation of decane-1,2-diol (221)[176]



Following an identical procedure to that described for the synthesis of compound **122**, 1-decene (1.00 g, 7.1 mmol) was dihydroxylated with AD-mix-β (5.10 g) to give the product as a white solid (1.19 g, 95.6 %).

^{1}H (300.13 MHz, $CDCl_3$) δ: 3.75-3.59 (2H, m, CH_2OH), 3.47-3.38 (1H, m, $CHOH$), 2.89 (2H, br s, $\nu_{1/2}$ = 36 Hz, OH), 1.49-1.30 (2H, m, CH_2CH_2CHOH), 1.30-1.18 (12H, overlapping m, $CH_2CH_2CH_2$ and $CH_3CH_2CH_2$), 0.85 (3H, t, $^3J_{HH}$ = 7.0, CH_3).

^{13}C (75.48 MHz, $CDCl_3$) δ: 72.4 ($CHOH$), 66.8 (CH_2OH), 33.2 (CH_2CHOH), 31.8, 29.63, 29.5, 29.2, 25.5, 22.6 (all CH_2; specific assignment not possible), 14.1 (CH_3).

M.p.: 54-56°C (Lit. Value 47-48).[176]

5.1 Catalysis procedures

General procedure for Diels-Alder reaction of methyl acrylate and cyclopentadiene using heterogenous catalysts prepared from polymer-bound diols 136-140

A Schlenk flask was charged with diol-functionalised resin (0.200 g, 0.18 mmol) and dried *in vacuo*. After backfilling with N_2, toluene (5 mL) was added and the flask cooled to 0°C. After 10 minutes, $TiCl_4$ (1M solution in toluene, 0.160 mL, 0.16 mmol, 2 mol %) was added by microsyringe. The mixture was allowed to warm to room temperature then shaken overnight. The solvent was removed from the polymer by cannula filtration and the beads were washed with toluene (1 x 5 mL) and DCM (2 x 5 mL) before remaining traces of volatile components were removed *in vacuo*. The polymer washings were combined and saved for ICP-AE (for analysis procedure see below). After backfilling with N_2, DCM (5 mL) was added and the beads allowed to swell (10 minutes), before methyl acrylate (0.720 mL, 8.00 mmol) was added by syringe. After shaking for 30 minutes, freshly prepared cyclopentadiene (1.5 equivalents, 0.880 mL, 12.00 mmol) was added and the mixture shaken at room temperature. At suitable intervals, the reaction solution was analysed for cycloaddition products **222** and **223** as follows: An aliquot (25 μL) was removed by microsyringe, transferred to a pipette plugged with cotton wool and washed into a vial with ethyl acetate (1.50 mL in two portions). The resulting ethyl acetate solutions were immediately analysed by GC-MS.

General procedure for Diels-Alder reaction of methyl acrylate and cyclopentadiene using homogenous catalysts prepared from diols 214-216

A Schlenk flask was charged with the diol (0.18 mmol) and dried *in vacuo*. After N_2, toluene (5 mL) was added and the flask cooled to 0°C. After 10 minutes, $TiCl_4$ (1M solution in toluene, 0.160 mL, 0.16 mmol, 2 mol %) was added by microsyringe. The mixture was allowed to warm to room temperature then shaken overnight. The solvent was removed *in vacuo*, and the resulting residue washed with Et_2O (2 x 10 mL) then dired *in vacuo*. After backfilling with N_2, DCM (5 mL) was added, resulting in a yellow solution, to which methyl acrylate (0.720 mL, 8.00 mmol) was added by syringe. After shaking for 30 minutes, freshly prepared cyclopentadiene (1.5 equivalents, 0.880 mL, 12.00 mmol) was added and the mixture shaken at room temperature. At suitable intervals,

the reaction solution was analysed for cycloaddition products **222** and **223** as follows: An aliquot (25 μL) was removed and transferred to a pipette plugged with cotton wool and a layer of silica (0.5 cm). The aliquot was washed into a vial with ethyl acetate (1.50 mL in two portions). The resulting ethyl acetate solutions were immediately analysed by GC-MS.

Preparation of solutions for ICP-AE analysis

The combined polymer-washings obtained from the preparation of catalysts for Diels-Alder reactions were shaken with nitric acid (1M, 2 mL), before volatile components were were removed under reduced pressure. The resulting residue was washed into a 25 mL volumetric flask with conc. nitric acid (30 %, 2 x 5 mL) and then H_2O was added to make a 25 mL solution. The solutions were submitted for ICP-AE analysis by E. Mansley (Department of Geology, University of Leicester).

General procedure for Diels-Alder reaction of methacrolein and cyclopentadiene using heterogenised catalysts prepared from polymer-bound diols 173, 191 and 217

Titanium dialkoxide-based catalysts (5 mol %) were prepared from diols **173**, **191**, and **217** (1.2 equivalents) and $TiCl_4$ (1M solution in toluene, 0.15 mL, 0.15 mmol) by the same method as described in the Diels-Alder reaction of methyl acrylate and cyclopentadiene using polymer-bound diols, the only exception being the addition of a stirrer bead to the reaction vessel. The prepared catalysts were dried *in vacuo* and, after backfilling with N_2, swollen with DCM (10 mL). The mixture was cooled to -78°C and methacrolein (0.248 mL, 3.00 mmol) was added. After stirring for 30 minutes, freshly prepared cyclopentadiene (1.5 equivalents, 0.37 mL, 4.50 mmol) was added. The mixture was stirred at -78°C for 6 hours, then allowed to warm to room temperature. The solution was filtered off from the polymer, and concentrated *in vacuo* to give the cycloaddition products **224** and **226** as a pale yellow oil. The crude product was analysed by ^1H NMR spectroscopy to determine the *exo*/*endo* selectivity. The ee was determined by addition of 0.3 equivalents of $Eu(hfc)_3$ and integration of the resulting signals arising from the diastereotopic formyl protons.

General procedure for Diels-Alder reaction of methacrolein and cyclopentadiene using homogenous catalyst prepared from diol 164

The titanium dialkoxide-based catalyst (5 mol %) was prepared from diol **164** (0.058 g, 0.18 mmol) and $TiCl_4$ (1M solution in toluene, 0.15 mL, 0.15 mmol) by the same method as described for the Diels-Alder reaction of methyl acrylate and cyclopentadiene using homogenous diols, the only exception being the addition of a stirrer bead to the reaction vessel. The prepared catalyst was dried *in vacuo* and, after backfilling with N_2, dissolved in DCM (10 mL). The mixture was cooled to -78°C and methacrolein (0.248 mL, 3.00 mmol) was added. After stirring for 30 minutes, freshly prepared cyclopentadiene (1.5 equivalents, 0.37 mL, 4.50 mmol) was added. The mixture was stirred at -78°C for 6 hours, then allowed to warm to room temperature and quenched by addition of 1M aqueous HCl (5 mL). The organic phase was separated and the aqueous layer extracted with Et_2O (2 x 20 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure to leave the cycloaddition products **224** and **225** as a pale yellow oil. The crude product was analysed by ^1H NMR spectroscopy to determine the *exo*/*endo* selectivity. The ee was determined by addition of 0.3 equivalents of $Eu(hfc)_3$ and integration of the resulting signals arising from the diastereotopic formyl protons.

Preparation of polymer-bound zinc dialkoxide 226

A Schlenk flask was charged with a stirrer bead and resin **173** (0.200 g, 0.18 mmol) and dried *in vacuo*. After backfilling with N_2, toluene (5 mL) was added followed by diethylzinc (1M solution in toluene, 0.15 mL, 0.165 mmol). The mixture was heated to 70°C, with gentle stirring, for 24 hours. After cooling, the solvent was removed from the polymer by cannula filtration and the beads were washed with toluene (3 x 5 mL) before remaining traces of volatile components were were removed *in vacuo*. The resulting polymer was immediately used to catalyse the addition of diethylzinc to benzaldehyde (see below/section).

General procedure for diethylzinc additions to benzaldehyde

Polymer-bound zinc dialkoxide **226,** or titanium dialkoxide-based catalysts (10 mol %) prepared from diols **164**, **168**, **173** (by the same method as described in the general procedure for homogenous or heterogenous catalysed Diels-Alder reactions of methyl acrylate and cyclopentadiene, accordingly), were dried *in vacuo* in the Schlenk flask in

which they were prepared. After backfilling with N_2, toluene (10 mL) was added and the mixture cooled to 0°C. Benzaldehyde (0.168 mL, 1.65 mmol) was added followed by diethylzinc (1.1 M solution in toluene, 3.00 mL, 3.3 mmol). The stirred solution was allowed to warm to room temperature then stirred for 24 hours before being quenched by addition of MeOH (5 mL), followed by 1M aqueous HCl (10 mL). The organic phase was separated, the aqueous layer extracted with Et_2O (2 x 10 mL) and the combined organic extracts were dried ($MgSO_4$). Subsequent removal of volatile components under reduced pressure gave a colourless oil, the composition of which was determined by ^1H NMR spectroscopy.

Chapter 6

References

6 References

1 R. R. Merrifield, *J. Am. Chem. Soc.*, 1965, **85**, 2149.

2 G. Jung and A. G. Beck-Sickinger, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 367.

3 M. H. Carruthers, *Science*, 1985, **230**, 281.

4 P. H. Seeberger, X. Beebe, G. D. Sukenik, S. Pochapsky and S. J. Danishevsky, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 491.

5 J. S. Früchtel and G. Jung, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 17.

6 F. Balkenhohl, C. von dem Bussche-Hünnefeld, A. Lansky and C. Zechel, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2288.

7 F. Z. Dörwald, "Organic Synthesis on Solid Phase", Wiley-VCH, Weinheim, 2002.

8 P. Hodge and D. C. Sherrington (editors), "Polymer-supported Reactions in Organic Synthesis", John Wiley and Sons, Chichester, 1980.

9 P. Hodge and D.C. Sherrington (editors), "Syntheses and Separations Using Functional Polymers", John Wiley and Sons, Chichester, 1988.

10 S.J. Shuttleworth, S.M. Allin and P.K Sharma, *Synthesis*, 1997, 1217.

11 G. Bhalay, A. Dunstan and A. Glen, *Synlett.*, 2000, **12**, 1846.

12 Y.R. de Miguel, *J. Chem. Soc., Perkin Trans. 1*, 2000, 4213.

13 C. A. McNamara, M. J. Dixon and M. Bradley, *Chem. Rev.*, 2002, **102**, 3275.

14 M. Benaglia, A. Puglisi and F. Cozzi, *Chem. Rev.*, 2003, **103**, 3401.

15 A. Kirshning, H. Monenschein and R. Wittenberg, *Angew. Chem., Int. Ed. Engl.*, 2001, **40**, 650.

16 Y. Iwasawa (Ed.), "Tailored Metal Catalysts", Riedel, Dordrecht, 1986.

17 K. G. Allum, R. D. Hancock, I.V. Howell, S. McKenzie, R. C. Pitkethly and P. J. Robinson, *J. Organomet. Chem.*, 1975, **87**, 203.

18 E. Lindner, T. Schneller, F. Auer and H. A. Mayer, *Angew. Chem., Int. Ed. Engl.*, 1999, **38**, 2154.

19 A. Choplin and F. Quignard, *Coord. Chem. Rev.*, 1998, 1679.

20 K. D. Behringer and J. Blümel, *Inorg. Chem.*, 1996, **35**, 1814.

21 U. Nagel and E. Kinzel, *J. Chem Soc., Chem. Commun.*, 1986, 1098.

22 D. C. Sherrington, *J. Chem Soc., Chem. Commun.*, 1998, 2275.

23 R. Santini, M.C. Griffith and M. Qi, *Tetrahedron Lett.*, 1998, **39**, 8951.

24 P. H. Toy, T. S. Reger and K. D. Janda, *Aldrich. Acta*, 2000, **33**, 87.

25 M. E. Wilson, S. R. Hammond, K. Paech, W-J. Zhou and M. J. Kurth, *J. Org. Chem.*, 1998, **63**, 5094.

26 B. Yan, J. B. Fell and G. J. Kumaravel, *J. Org. Chem.*, 1996, **61**, 7467.

27 B. Yan, Q. Sun, J. R. Wareing, C. F. Jewell, *J. Org. Chem.*, 1996, **61**, 8765.

28 I. Crowley and H. Rapoport, *J. Org. Chem.*, 1980, **45**, 3215.

29 F. Lorgé, A. Wagner and C. Mioskowski, *J. Comb. Chem.*, 1999, **1**, 25.

30 P.A. Keifer, *J. Org. Chem.*, 1996, **61**, 1558.

31 R. Riedl, R. Tappe and A. Berkessel, *J. Am. Chem. Soc.*, 1998, **120**, 8994.

32 R. Haag, *Chem. Eur. J.*, 2001, **7**, 327.

33 K. Heinze, U. Winterhalter and T. Jannack, *Chem. Eur. J.*, 2000, **6**, 4203.

34 W. K. Hall, *Acc. Chem. Res.*, 1975, **8**, 257.

35 P. Hodge, *Chem. Soc. Rev.*, 1997, **26**, 417.

36 R. H. Grubbs, C. Gibbons, L.C. Kroll, W.D. Bonds and C.H. Brubaker, *J. Am. Chem. Soc.*, 1973, **95**, 2374.

37 R. H. Grubbs, C. Gibbons, L.C. Kroll, E. S. Chandrasekaren, W. D. Bonds and C. H. Brubaker, *J. Am. Chem. Soc.*, 1975, **97**, 2128.

38 C. U. Pittman, S. E. Jacobsen and H. Hiramoto, *J. Am. Chem. Soc.*, 1975, **97** 4774.

39 W. Carruthers, "Cycloaddition Reactions in Organic Synthesis", Pergamon Press, Oxford, 1990.

40 L. A. Paquette in "Asymmetric Synthesis", Academic Press, New York, 1984.

41 E. J. Corey, *Angew. Chem., Int. Ed. Engl.*, 2002, **41**, 1650.

42 W. Oppolzer, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 876.

43 U. Pindur, G. Lutz and C. Otto, *Chem. Rev.*, 1993, **93**, 741.

44 C. Chapuis and J. Jurczak, *Helv. Chim. Acta*, 1987, **70**, 436.

45 K. Narasaka, N. Iwasawa, M. Inoue, T. Yamada, M. Nakashima and J. Sugimori, *J. Am. Chem. Soc.*, 1989, **111**, 5340.

46 E. J. Corey and Y. Matsumura, *Tetrahedron. Lett.*, 1991, **32**, 6289.

47 F. Rebiere, O. Riant and B. Kagan, *Tetrahedron Asymm.*, 1990, **1**, 199.

48 P. Devine and T. Oh, *J. Org. Chem.*, 1992, **57**, 396.

49 S.-H. Hashimoto, N. Komeshima and K. Koga, *J. Chem. Soc., Chem. Commun.*, 1979, 437.

50 S. Itsuno, K. Kamahori, K. Watanabe, T. Koizumi and K. Ito, *Tetrahedron Asymm.*, 1994, **5**, 523.

51 S. Itsuno, K. Watanabe, T. Koizumi and K. Ito, *React. Polym.*, 1995, **24**, 219.

52 K. Kamahori, K. Ito and S. J. Itsuno, *J. Org. Chem.*, 1996, **61**, 8321.

53 J. Irrure, A. Fernandez-Serrat and F. Rosanas, *Chirality*, 1997, **9**, 191.

54 J. Irrure, A. Fernandez-Serrat, M. Altayo and M. Riera, *Enantiomer*, 1998, **3**, 103.

55 J. M. Fraile, J. A. Mayoral, B. Altava, S. V. Luis, M. J. Vicent, J. I. Garcia and M. I. Burguete, *Angew. Chem., Int. Ed. Engl.*, 2000, **39**, 1503.

56 J. A. Mayoral, B. Altava, S. V. Luis, M. J. Vicent, J. I. Garcia and M. I. Burguete, *React. Func. Polym.*, 2001, **48**, 25.

57 J. M. Fraile, J. A. Mayoral, A. J. Royo, R. V. Salvador, B. Altava, S. V. Luis and M. I. Burguete, *Tetraherdron*, 1996, **52**, 9853.

58 R. Noyori and M. Kitamura, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 49.

59 L. Pu and H. B. Yu, *Chem. Rev.*, 2001, **101**, 757.

60 J.-P. Mazaleylat and D. J. Cram, *J. Am. Chem. Soc.*, 1981, **103**, 4585.

61 N. Ogumi and T. Omi, *Tetrahedron Lett.*, 1984, **25**, 2823.

62 M. Kitamura, S. Suga, K. Kawai and R. Noyori, *J. Am. Chem. Soc.*, 1986, **108**, 6071.

63 B. Schmidt and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1321;

64 D. Seebach, D. A. Plattner, A. K. Beck, Y. M. Wang and D. Hunziker, *Helv. Chim. Acta*, 1992, **75**, 2171.

65 K. R. K. Prasad and N. N. Joshi, *Tetrahedron Asymm.*, 1996, **7**, 1957.

66 S. Itsuno and J. M. Fréchet, *J. Org. Chem.*, 1987, **52**, 4142.

67 K. Soai, S. Niwa and M. Watanabe, *J. Org. Chem.*, 1988, **53**, 927.

68 K. Soai, S. Niwa and M. Watanabe, *J. Chem. Soc., Perkin Trans. 1,* 1989, 109.

79 M. Watanabe and K. Soai, *J. Chem. Soc., Perkin Trans. 1*, 1994, 837.

70 H. Sellner and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, 1999, **38**, 1918.

71 H. Sellner, P. B. Rheiner and D. Seebach, *Helv. Chim. Acta.*, 2002, **85**, 352.

72 D. W. L. Sung, P. Hodge and P.W. Stratford, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1463.

73 P. Hodge, D. W. L. Sung and P. W. Stratford, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2335.

74 J. T. Sparrow, *J. Org. Chem.*, 1976, **41**, 1350.

75 M. Tomoi, N. Kori and H. Kahiuchi, *Makromol. Chem.*, 1986, **87**, 2753.

76 H. Molinari and F. Montanari, *J. Chem Soc., Chem. Commun.*, 1977, 639.

77 F. Montanari and P. Tundo, *J. Org. Chem.*, 1981, **46**, 2125.

78 R. Alvarez, M. Houdin, C. Cavé, J. d'Angelo and P. Chaminade, *Tetrahedron Lett.*, 1999, **40**, 7091.

79 H. O. House, "Modern Synthetic Reactions", 2nd edn., Benjamin, Menlo Park, CA, 1972.

80 J. H. Clark and J. M. Miller, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1743.

81 D. P. Shrout and D. A. Lightner, *Synth. Commun.*, 1990, **20**, 2075.

82 J. Chiefari, R. V. Person and D. A. Lightner, *Tetrahedron*, 1992, **29**, 5969.

83 A. Gypser, C. Bülow and H. Scharf, *Tetrahedron,* 1995, **51**, 1921.

84 D. A. Oare and C. H. Heathcock, in "Topics in Stereochemistry", Wiley-Interscience, New York, 1989, vol. 19, 227.

85 M. Shibasaki, H. Sasai and T. Arai, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1236.

86 A. Soriente, A. Spinella, M. De Roase, M. Giordano and A. Scetrri, *Tetrahedron Lett.*, 1997, **38**, 289.

87 C. P. Frei and T. H. Chan, *Synthesis*, 1982, 467; H. Brunner and B. Hammer, *Angew. Chem., Int. Ed. Engl.*, 1984, **32**, 312; P. Kocovsky and D. Dvorak, *Tetrahedron Lett.*, 1986, **27**, 5015.

88 J. Christoffers, *J. Chem. Soc., Perkin Trans. 1*, 1997, 3141.

89 G. Bartoli, M. Bosco, M. C. Belluci, E. Marcantoni, L. Sambri and E. Torregiani, *J. Org. Chem.*, 1999, 618.

90 J. Dale, *J. Chem. Soc.*, 1961, 910.

91 G. Maier, C. Roth and K. R. Schmitt, *Chem. Ber.*, 1985, **118**, 704.

92 J. Barluenga, J. G. Resa, B. Olano and S. Fustero, *J. Org. Chem.*, 1987, **52**, 1425.

93 M. Moreno-Manas, N. Galvez, M. E. Lloris, J. Marquet and A. C. Siani, *Tetrahedron*, 1992, **48**, 3603.

94 L. Cazaux, G. Chassaing and P. Maroni, *C. R. Acad. Sc. Paris*, 1974, **278C**, 1305.

95 M. A. Tius and A. H. Faug, *J. Am. Chem. Soc.*, 1986, **108**, 1038.

96 G. Bartoli, M. Bosco, C. Cimarelli, R. Dalpozzo, M. Guerra and G. Palmieri, *J. Chem. Soc., Perkin. Trans. 2*, 1992, 649.

97 G. W. Stacy, R. A. Mikulec, S. L. Razniak and L. D. Starr, *J. Am. Chem. Soc.*, 1957, 3587

98 C. C. Leznoff and J. Y. Wong, *Can. J. Chem.*, 1973, **51**, 3756.

99 M. Tomoi, S. Shiiki and H. Kakiuchi, *Makromol. Chem.*, 1986, **187**, 357.

100 A. S. Hernández and J. C. Hodges, *J. Org. Chem.*, 1997, **62**, 3153.

101 J.-W. Huang, W.-J. Mei, J. Liu and L.-N. Ji, *J. Mol. Cat. A*, 2001, 261.

102 J. M. Frechet and C. Schuerch, *J. Am. Chem. Soc.*, 1971, **93**, 492.

103 P. Hodge and J. Waterhouse, *Polymer*, 1981, **22**, 1153.

104 I. Kilpeläinen and G. Brunow, *Holzforschung*, 1994, **48**, 222.

105 R. E. Hamon, J. L. Parson, D. W. Cooke, S. K. Gupta and J. Schoolenberg, *J. Org. Chem.*, 1969, **34**, 3685.

106 R. T. Morrison and R. N. Boyd, "Organic Chemistry", 6th addition, Prentice Hall, Englewood Cliffs, NJ, U.S.A, 1992.

107 K. B. Wiberg and K. A. Saebarth, *J. Am. Chem. Soc.*, 1957, **79**, 2822.

108 D. G. Lee and J. R Brownridge, *J. Am. Chem. Soc.*, 1973, **95**, 3033.

109 K. B. Wiberg and C. J. Deutsch, *J. Am. Chem. Soc.*, 1973, **95**, 3034.

110 A. J. Fatiadi, *Synthesis*, 1987, 85.

111 T. A. Foglia, P. A. Barr and A. J. Malloy, *J. Am. Oil. Chem. Soc.*, 1977, **54**, 858A.

112 W. P. Weber and J. P. Shepherd, *Tetrahedron Lett.*, 1972, 4907.

113 M. Schröder, *Chem. Rev.*, 1980, **80**, 187.

114 K. B. Sharpless and K. Akashi, *J. Am. Chem. Soc.*, 1976, **98**, 1986.

115 V. Van Rheenan, R. C. Kelly and D. Y. Cha, *Tetrahedron Lett.*, 1976, **17**, 1973.

116 R. Ray and D. S. Matteson, *Tetrahedron Lett.*, 1980, **21**, 449.

117 M. P. Singh, H. S. Singh, A. K. Arya, A. K. Singh and A. K. Sisodia, *Indian J. Chem.*, 1975, **13**, 112.

118 M. Minamoto, K. Yamamoto and J. Tsuji, *J. Org. Chem.*, 1990, **55**, 766.

119 C. Döbler, G. M. Mehltretter, U. Sundermaier and M. Beller, *J. Am. Chem. Soc.*, 2000, **112**, 10289.

120 K. B. Sharpless, A. Y. Teranishi and J.-E. Bäckvall, *J. Am. Chem. Soc.*, 1977, **99**, 3120.

121 S. G. Hentges and K. B. Sharpless, *J. Am. Chem. Soc.*, 1980, **102**, 4263.

122 K. A. Jørgensen and R. Hoffmann, *J. Am. Chem.Soc.*, 1986, **106**, 1867.

123 H. C. Kolb, M. S. Van Nieuwenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483.

124 H. C. Kolb and K. B. Sharpless in "Transition Metals for Organic Synthesis", M. Beller and C. Bolm (Eds), VCH-Wiley, Weinheim, 1998, Vol. 2, 219.

125 D. J. Berrisford, C. Bolm and K. B. Sharpless, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1059.

126 S. Hanessian, P. Meffre, M. Girard, S. Beaudoin, J.-Y. Sancéau and Y. L. Bennani, *J. Org. Chem.*, 1993, **58**, 1991.

127 B. B. Lohray, *Tetrahedron Asymm.*, 1992, **3**, 1317.

128 E. N. Jacobsen, L. Markó, W. S. Mungall, G. Scröder and K. B. Sharpless, *J. Am. Chem. Soc.*, 1988, **110**, 1968.

129 J. S. M. Wai, L. Markó, J. S. Svendsen, M. G. Finn, E. N. Jacobsen and K. B. Sharpless, *J. Am. Chem. Soc.*, 1989, **111**, 1123.

130 H.-L. Kwong, C. Sorato, Y, Ogino, H, Chen and K. B, Sharpless, *Tetrahedron Lett.*, 1990, **31**, 2999.

131 K. B. Sharpless, W. Amberg, Y. L. Bennanni, G. A. Crispino, J. Hartnung, K.-S. Jeong, H.L Kwong, K. Morikawa, Z.-M. Wang, D. Xu and X.-L. Zhang, *J. Org. Chem.*, 1992, **57**, 2768.

132 T. Göbel and K. B. Sharpless, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1329.

133 G. A. Crispino, K.-S. Jeong, H. C. Holb, Z.-M. Wang, D. Xu and K. B. Sharpless, *J. Org. Chem.*, 1993, **58**, 3785.

134 L. Wang and K. B. Sharpless, *J. Am. Chem. Soc.*, 1992, **114**, 7568.

135 H. C. Kolb, P. G. Andersen, Y. L. Bennanni, G. A. Crispino, K.-S. Jeong, H.-L. Kwong and K. B. Sharpless, *J. Am. Chem. Soc.*, 1993, **115**, 12226.

136 M. I. Donnoli, S. Superchi and C. Rosini, *J. Org. Chem.*, 1998, **63**, 9392.

137 J. A. Dale, D. L. Dull and H. S. Mosher, *J. Org. Chem.*, 1969, **34**

138 G. A. Olah, "Friedel-Crafts and Related Reactions", Wiley, London, 1963, vol. 1, p.39.

139 G. A. Olah, "Friedel-Crafts and Related Reactions", Wiley, London, 1963, vol. 1, p.68.

140 A. Jaxa-Chamiec, V. P. Shah and L. I. Kruse, *J. Chem. Soc., Perkin Trans. 1*, 1989, 1705.

141 C. Bolm and A. Gerlach, *Eur. J. Org. Chem.*, 1998, 21.

142 B. B. Lohray, A. Thomas, P. Chittari, J. R. Ahuja and P. K. Dahl, *Tetrahedron Lett.*, 1992, **33**, 5453.

143 B. M. Kim and K. B. Sharpless, *Tetrahedron Lett.*, 1990, **31**, 3003.

144 D. Pini, A. Petri, A. Nardi, C. Rossini and P. Salvadori, *Tetrahedron Lett.*, 1991, **32**, 5175.

145 D. Pini, A. Petri and P. Salvadori, *Tetrahedron Asymm.*, 1993, **4**, 2351.

146 M. Cernerud, J. A. Reina, J. Tegenfeldt and C. Moberg, *Tetrahedron Asymm.*, 1996, **7**, 2863.

147 H. Han and K. D. Janda, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1731.

148 Y. Xia, Z.-Y. Yang, A. Brossi and K.-H. Lee, *Org. Lett.*, 1999, 2113.

149 J. Skarzewski and A. Gupta, *Tetrahedron Asymm.*, 1997, **8**, 1861.

150 A. K. Ghosh, P. Mathivanan, and J. Cappiello, *Tetrahedron-Asymmetry*, 1998, **9**, 1.

151 K. Narasaka, *Synthesis*, 1991, 1.

152 H. B. Kagan and O. Riant, *Chem. Rev.*, 1992, **92**, 1007.

153 T. Naota, H. Takaya, and S.-I. Murahashi, *Chem. Rev.*, 1998, **98**, 2599.

154 S. Kobayashi, M. Murakami, T. Harada and T. Mukaiyama, *Chem. Lett.*, 1991, 1341.

155 L. Pu, *Chem. Rev.*, 1998, **98**, 2405.

156 M. M. Miller and D. C. Sherrington, *J. Catal.*, 1995, **152**, 368.

157 P. Wentworth Jr. and K. D. Janda, *J. Chem Soc., Chem. Commun.*, 1999, 1917.

158 D. E. Bergbreiter, *Chem. Rev.*, 2002, **102**, 3345.

159 J. W. Guiles, S. G. Johnson and W. V. Murray, *J. Org. Chem.*, 1996, **61**, 5169.

160 F. X. Woolard, J. Paetsch and J. A. Ellman, *J. Org. Chem.*, 1997, **62**, 6102.

161 S. Wendeborn, S. Berteina, W. K. D. Brill and A. De MesMaeker, *Synlett.*, 1998, 671.

162 W. L. F. Armarego and D. D. Perrin, *'Purification of Laboratory Chemicals'*, 3rd ed., Pergamon Press, New York, 1988.

163 ChemNMR Pro © 2002, CambridgeSoft Corp., 100 Cambridgepark Drive, Cambridge, MA 02140, USA.

164 H.-J. Deussen, S. Danielsen, J. Breinholt and T. V. Borchert, *Bioorg. Med. Chem.*, 2000, **8**, 507.

165 G. C. M. Lee, E. T. Syage, D. A. Harcourt, J. M. Holmes and M. E. Garst, *J. Org. Chem.*, 1991, **56**, 7007.

166 D. S. Clyne and L. Weiler, *Tetrahedron*, 1999, **55**, 13659.

167 J. Rhinesmith, *J. Am. Chem. Soc.*, 1936, **59**, 596.

168 D. Y. Jackson, *Synth. Commun.*, 1988, **18**, 337.

169 K. Takao, Y. Nigawara, E. Nishino, I. Takagi and K. Maeda, *Tetrahedron*, 1994, **50**, 5681.

170 P. Coutrot, C. Grison and C. Bomont, *J. Organomet. Chem.*, 1999, **586**, 208.

171 P. Kende, *J. Am. Chem. Soc.*, 1963, **85**, 1882.

172 C. Li and D. G. Peters, *Tetrahedron Lett.*, 2001, **42**, 6065.

173 N. Perlman, M. Livneh and A. Albeck, *Tetrahedron*, 2000, **56**, 1505.

174 D. H. R. Barton, J. Wozniak and S. Z. Zard, *Tetrahedron*, 1989, **45**, 3741.

175 J. Lehmann and P. U. Weitzel, *Carbohydrate Res.*, 1996, **296**, 65.

176 Q. Hawkins, *J. Appl. Chem.*, 1956, **6**, 1.

Chapter 7

Appendices

7 Appendices

7.1 CH501: Postgraduate Research Techniques

This is a compulsory module for all first year postgraduates.

Semester	Lecture Title	Lecturer	Attendance
1	Safety/Security	Mr. Acton	✓
1	Introduction to key techniques and equipment	Mr. Lee, Dr. Fawcett Dr. Eaton, Dr. Griffith	✓
1	NMR techniques I: 1D NMR	Dr. Griffith	✓
1	NMR techniques II: 2D NMR	Dr. Griffith	✓
2	NMR techniques III: the nOe effect	Dr. Griffith	✓
2	Advanced interpretation of spectra and presentation of spectra	Dr. Griffith	✓
2	ChemDraw/molecular modelling	Prof. Cullis	✓
2	Use of the library and computer based searches	Dr. Lloyd Dr. Solan	✓
2	Applications of 'Endnote'	Dr. Davies	✓
2	Advanced scientific writing	Dr. Malpass	✓
2	A course for demonstrators	Dr. Beasley	✓

7.2 Additional Modules Studied

Taken in the first year, as part of Postgraduate Training.

Code	*Module title*	*Grade*
Credits	*Convenor*	
CH231	Polymer Chemistry	52 %
(10 credits)	Dr. A. Abbott	
CH403	Advanced Structure Determination	74 %
(5 credits)	D. J. Malpass	
CH404	Chemical Crystallography	60 %
(5 credits)	Dr. P. Dyer	

7.3 External Conferences Attended

Avecia student symposium	Oral Presentation
29/11/01 Avecia, Blackley, Manchester	
RSC Catalysis symposium	Attended
30/04/01 Leicester University	
RSC Dalton division –	Attended
New vistas in organometallic and materials chemistry	
30/11/01 Imperial College	
RSC Catalysis symposium	Attended
04/11/02 Leicester University	
Avecia student symposium	Oral Presentation
29/11/01 Avecia, Blackley, Manchester	
226th ACS national meeting	Presented poster
07-10/11/03 New York City, U.S.A	

7.4 Inorganic Colloquia Attended

All the speakers were resident at Leicester University unless otherwise stated.

09/10/00	Dr. A. Sarkar (NCL Pune, India)	Conformation and reactivity of Fischer carbene complexes.
16/10/00	Dr. G. A. Solan Dr. P. W. Dyer	Literature session.
23/10/00	Mr. M. Hanton Ms. N. Patel	Literature session.
30/10/00	Workshop	Techniques, strategies and challenges in chemistry.
11/12/00	Dr. R. Villar-Compte (Imperial College)	Anions as templating agents in co-ordination chemistry.
29/01/01	Dr. J. Iggo (University of Liverpool)	If you can see it, it's not the catalyst – or is it? NMR for monitoring catalytic reactions.
05/01/01	Prof. R. Mulvey (University of Strathclyde)	Inverse crown ether complexes and related mixed metal macrocycles of the *s*-block. (RSC lecture).
07/01/01	Dr. S. Bennett (Open University)	Widening the appeal: the role of independent learning in chemistry. (RSC annual education lecture).
12/01/01	Mr. A. West Ms. R. Chagger Mr. R Chester.	Literature session.

26/01/01	Mr. C Davies Ms. S. Kandola **Mr. T Reeve** Mr. S. Suhard	1st year outlines.
21/03/01	Prof. L. D. Hall (University of Cambridge)	1st Tim Norwood memorial lecture.
14/05/01	Prof. S. Doherty (Queen's University Belfast)	Zirconacylces in phosphine synthesis: coordination chemistry and applications in platinum group-catalysed carboxylation of olefins and ethylene polymerisation.
04/06/01	**Mr. T. Reeve** Ms. S. Kandola	Literature session.
11/06/01	Mr. M. Hanton Mr. B. Croxtall	2nd year progress.
18/06/01	Mr. J. Sherrington Ms. N. Patel	2nd year progress.
25/06/01	Mr. D. Wood	3rd year progress.
04/10/01	Dr. P. O'Brien (University of York)	Basic instinct: new synthetic adventures with chiral bases.
10/10/01	Dr. D. Bourrisou (Université Paul Sabatier)	Stable carbenes and diradicals: new stabilization and bonding modes.
22/10/01	Dr. A. Hooper (Institute of Arable Crops Research, Rothamstead)	Sex and bugs and rock and roll.

29/10/01	Mr. M. Hanton Ms. N. Patel	Literature session.
05/11/01	Mr. P. Griffith Mr. D. Harding	Literature session.
26/11/01	Mr. G. Barth Mr. M. Dix Mr. M. Giardiello	Literature session.
03/12/01	Dr. P. Dyer Dr. G. Solan	Organometallic synthesis at Leicester.
04/02/02	Ms. A. Hickman Ms. K. Sharpe Mr. J. Pelletier	1st year outlines.
11/02/02	Dr. R. Bedford (University of Exeter)	High activity catalysts for C-C bond formation.
18/02/02	Mr. A. West Ms. R. Chaggar Mr. O. Duaij	1st year outlines.
04/03/02	Dr. H. Braunschweig (Imperial College)	Compounds with novel boron-containing ligands: transition metal complexes of boron and [1]borametallocenophanes.
06/03/02	Dr. R. Schutt (ExxonMobile)	Supercritical phase behaviour in ethene polymerisation and polymer separation.
11/03/02	Mr. B. Croxtall Ms. S. Kandola **Mr. T. Reeve**	Literature session.

25/03/02	Mr. C. Davies Mr. J. Sherrington Mr. S. Suhard	Literature session.
29/04/02	Ms. A. Hickman Mr. J. Pelletier Mr. A. West	Literature session.
08/05/02	Dr. N. Long (Imperial College)	Ferrocene ligand design.
20/05/02	Dr. M. Coles (University of Sussex)	Anionic and neutral guanidine ligands.
27/05/02	Mr. M. Hanton	3rd year talk.
27/05/02	Mr. B. Croxtall Mr. J. Sherrington	3rd year talks.
07/10/02	Ms. K. Sharp Ms. R. Chaggar Mr. A. West	Literature session.
14/10/02	Mr. J. Pelletier Mr. O. Duaij Ms. A. Hickman	Literature session.
21/10/02	Prof. P. R. Raithby (University of Bath)	Adventures in organometallic polymer chemistry.
28/10/02	Dr. C. Metcalf	Transition metal complexes and their interaction with DNA.

11/11/02	Ms. E. Carrington-Smith Mr. J. Bennett Mr. R. Buckby Mr. N. Abboyi *Chair*: **Mr T. Reeve**	Literature session.
18/11/02	Dr. M. Turner (University of Sheffield)	Synthesis of conjugated polymers for EL/electronics.
02/12/02	Ms. N. Dinsdale Ms. E. Filali Mr. R. Forster Ms. R. Muir	Literature session.
09/12/03	Prof. T. Marder (University of Durham)	The role of transition metal boryl complexes in catalysed borylations including rhodium catalysed C-H bond functionalisation.
20/01/03	Prof. V. McKee (University of Loughborough)	Manipulating metal arrays within macrocycles.
10/03/03	Prof. D. Bruce (University of Exeter)	Metallomesogens by design.
17/03/03	Dr. C. Carmalt (UCL)	Molecular design of precursors for the CVD of electronic materials.
12/05/03	Dr. A. Danopoulos (University of Southampton)	Functionalised N-heterocyclic carbene ligands in organometallic chemistry and catalysis.
02/06/03	Dr. Sarah Heath (University of Manchester)	Shedding light on biological systems: the development of dinuclear lanthanide probes.