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Abstract

This thesis describes the different synthetic routes carried out towards a dendritic catalyst. Various dendrimers were investigated as possible starting points for the exterior portion of the catalyst. These dendrimers were synthesised as well as their modified versions.

The attachment of a phosphine-containing moiety was thought to be crucial for high activity of these catalysts, in the hydroformylation of olefins. Different methods were investigated to affect the incorporation of a bis-phosphine. The tetra-phosphine, 4,5-bis(bis[{diphenyl-phosphanyl}methyl]aminomethyl)-2,2-dimethyl-[1,3]dioxolane, and the bis-phosphine, *N,N'*-Bis-(2-benzyloxyethyl)-*N,N'*-bis-[(diphenylphosphanyl)methyl]-ethane-1,2-diamine, were both synthesised and their rhodium(I) complexes were used successfully in the hydroformylation of many different olefins. Suggested pathways to bring together these exterior and interior pieces were then investigated.

During the synthesis of one of the core units a phosphine oxide compound, (diphenylphosphinoyl)phenyl-methanol was prepared. This compound is an excellent ligand in rhodium-catalysed hydroformylation reactions. As the phosphine oxide contained a chiral centre, it was resolved and employed in the enantioselective hyrdoformylation reactions of olefinic substrates.

Abbreviations

AIBN	2,2'-Azobisisobutyronitrile
anal	analytical
atm	atmosphere
BINAPHOS	(R)-2-(diphenylphosphino)-1,1`-binapthalen-2'-yl (S)-1,1'-binaphthalene-2,2'-diylphosphite
BOC	*tert*-butoxycarbonyl
br	broad
calcd	calculated
CI	chemical ionization
cod	1,5-cyclooctadiene
d	doublet
DCC	dicyclohexylcarbodiimide
dd	doublet of doublets
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
ee	enantiomeric excess
FMOC	9-fluorenylmethyl carbamate
FAB-MS	fast atom bombardment mass spectrometry
FT-IR	Fourier-transform infra red
g	grams
GC	gas chromatography

h	hours
HATU	[0-(7-azabenzotriaol-1-yl)-1,1,3,3-teramethyluronium hexafluorophosphate
HOBT	1-hydroxybenzotriazole
Hz	Hertz
J	coupling constant in Hz
M	molar concentration, in mol/litre
MeOH	methanol
mg	milligrams
min	minute
mL	milliliters
mmol	millimoles
mp	melting point
MS	mass spectrometry
NMR	nuclear magnetic resonance
ORTEP	Oak Ridge thermal ellipsoid plot
Ph	phenyl
ppm	parts per million
PTC	phase transfer catalysis
psi	pounds per square inch
q	quartet
r.t.	room temperature
t	triplet
TBAB	tetrabutylammonium bromide
THF	tetrahydrofuran

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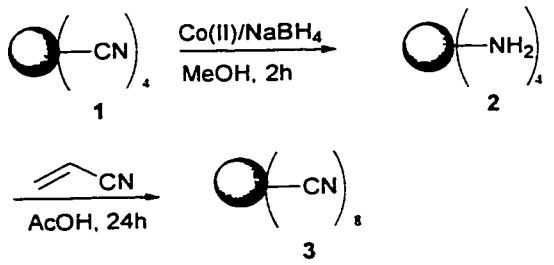
1

Introduction

1.1 General Introduction

Initially, research into branched macromolecules or dendrimers was driven by the desire to study synthetically perfect molecules with branching in defined places. Between 1941-42, Flory propagated many theoretical ideas and experimental results concerning branched chain polymers,[1-3] but the synthesis of exact branched macromolecules remained elusive. From the 1940's to the 1970's attempts towards the propagation of branched macromolecules, *via* a traditional one-pot polymerisation technique, were fruitless. However, as branched macromolecules began to be studied from a theoretical perspective, it was realised that the traditional polymerisation techniques were not a satisfactory approach to introduce branching into a polymer chain. The resulting polymers were completely random in size and shape. These results, and results from many other groups, which followed Flory's work, including Stockmayer,[4] paved the way for modern ideas for the preparation of cascade molecules. In 1978 Vögtle *et al.*[5] published a groundbreaking paper that was the beginning of extensive research into this new type of macromolecule, called a dendrimer. These molecules were constructed by repetitive reaction sequences and named either cascade molecules or dendrimers. The proposition was that such large molecules could be efficiently synthesised by frequent repetition of similar steps. In addition, due to the branching, these cascade molecules would contain cavities capable of binding small molecules internally, in a host-guest fashion. The synthetic

route, which Vögtle employed, involved the reduction of a nitrile followed by a Michael type addition to a terminal primary amine (Scheme 1.1).



Scheme 1.1 Vögtle's original synthesis

The introduction of branching into a dendrimer comes from a monomer AB_n, where n= 2,3, whereas a linear polymer would start from a monomer AB. Each additional repetitive cycle leads to a new "generation" of dendrimer and approximately doubles (AB_2) or triples, (AB_3) the size of the molecule. The structure and synthesis of the dendrimers, could be readily adjusted to change the exact physical, electronic and optical properties, as required.

This iterative synthetic approach was not new, as five years earlier Lehn[6] had indicated, in discussing the synthesis of macrocyclic organic complexing reagents, a stepwise repetitive synthesis was needed in order to achieve the desired large molecule. Early examples of dendrimers were published shortly after Vögtle's initial paper. First Denkewalter *et al.*[7-9] patented a polylysine based dendrimer, followed by two major publications from two pioneering groups in this area, Newkome[10] and

Tomalia.[11] Newkome constructed a carbon based branched polyol **4** (Figure 1.1). and used the term arborols for these molecules from the Latin word *arbor*, meaning

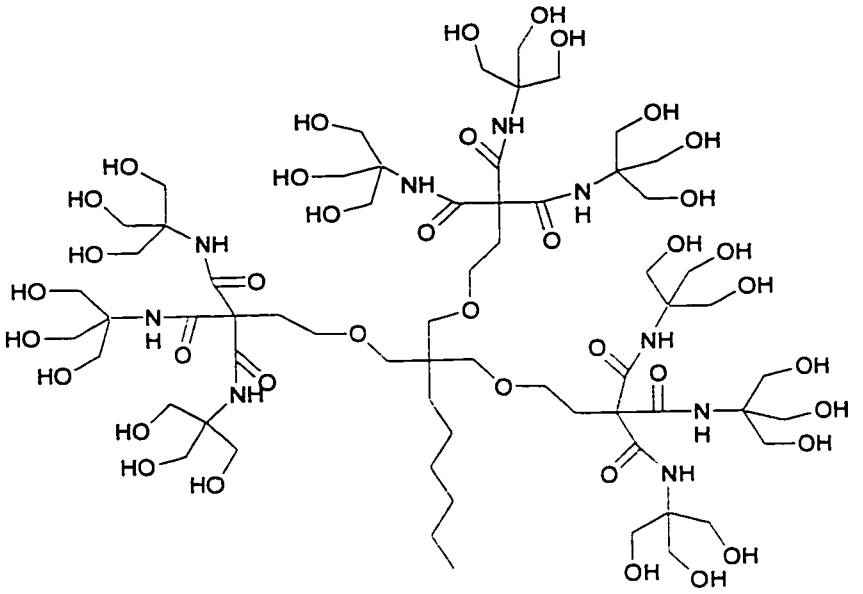


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Figure 1.1 Newkome's polyol

tree. Tomalia constructed what is still the most widely studied, researched and modified dendrimer, a poly(amidoamine) dendrimer, (PAMAM) **5** (Figure 1.2). Tomalia used the word dendrimer to describe his molecules from the Greek word *dendro*, meaning tree-like. Tomalia and coworkers[12] also reported another series of macromolecules named Starburst poly(ethyleneimine) dendrimers. Shortly after, two groups published modifications to Vögtle's original cascade synthesis.[13, 14] Wörner and Mülhaupt[14] used Raney Nickel to reduce the nitrile, this enabled them to continue the synthesis up to the fifth generation. de Brabander-van den Berg and Meijer[13] also managed to reach the fifth generation, using Raney cobalt, but on a

kilogram scale. Now the research involving these dendrimers, arborols or cascade molecules is widely carried out across a variety of fields. There are many applications in biomedical research,[15;16] catalysis,[17;18] electrochemistry[19-21] and photochemistry.[22]

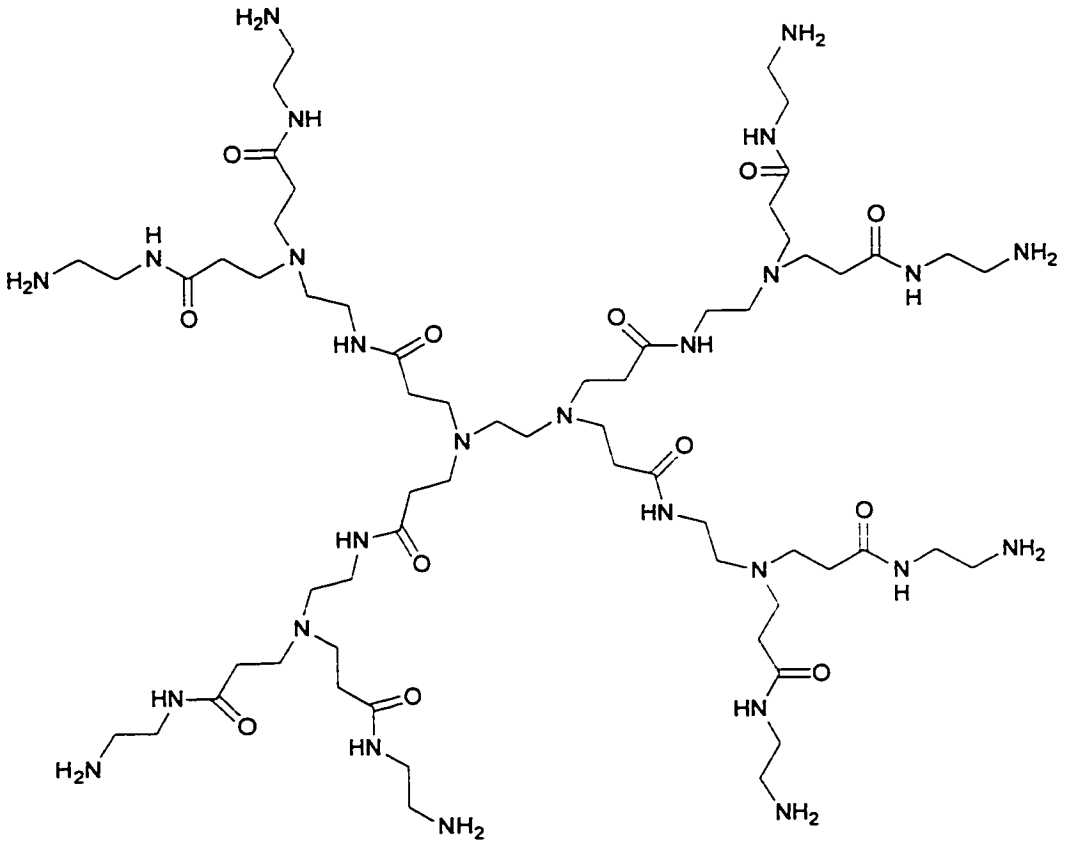

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Figure 1.2 Poly(amidoamine) dendrimer

1.2 Dendrimer Synthesis

1.2.1 Divergent synthetic methods

The first dendrimers were all synthesised using a divergent approach. This is the sequential addition of a monomer to a central core building out to the periphery (Figure 1.3). A problem arising from such an approach is defective growth resulting from incomplete or side reactions. According to de Gennes and Hervet[23] there is a theoretical limit to the size of generation of dendrimer that can be reached. If the number of peripheral groups becomes too high, so problems in the synthesis begin as the end groups become too congested. de Gennes and Hervet specifically investigated this aspect for the PAMAM dendrimer series and they related the steric hindrance limitation for generation growth to the length of spacer employed and created a mathematical model to reflect this relationship. Therefore, depending on the spacer a final defective-free generation number is predicted. They also concluded that the density of the dendrimer is lowest at the core. As mentioned, side reactions during the growth of many dendrimers can also be a problem. During the growth of the poly(propyleneimine) DAB dendrimer series there is a possibility of missed Michael reactions and/or cyclizations occurring at low generations. The estimate of dendritic purity, i.e. the amount of pure defect free dendrimer, for a fifth generation DAB dendrimer, was calculated to be only 23 %.[24] This estimate was calculated by means of data from an electrospray ionization mass spectrometry experiment. Similar data for the PAMAM series reports a dendritic purity of 8 % for a fourth generation

dendrimer.[25] Incomplete reactions can be forced to completion with excess reagents but this may introduce purification problems at each step.

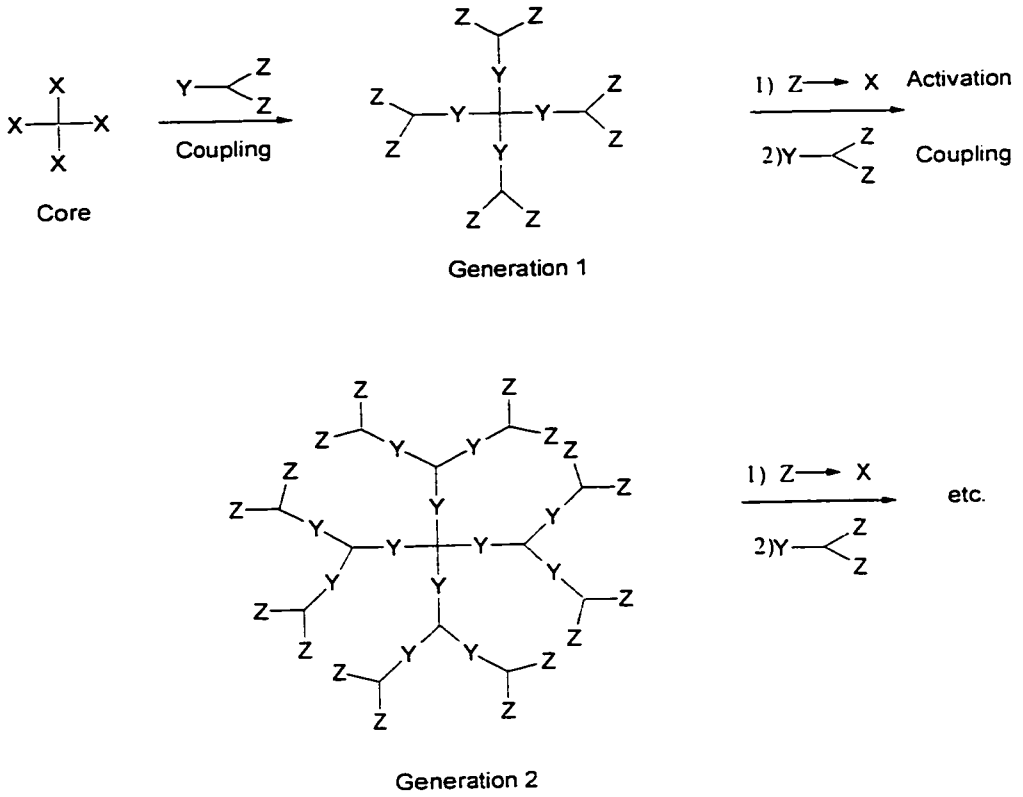

Figure 1.3 Divergent Synthesis

1.2.2 Convergent synthetic methods

The first convergent synthesis was reported by Fréchet *et al.*[26,27] for the preparation of a macromolecule based on a poly(arylether). Using this method dendrimers are built from the outside towards the central core (Figure 1.4). Miller and Neenan[28] used the same approach to build an entirely aromatic-based

hydrocarbon dendrimer. The resultant dendrimers are thought to be more homogeneous than the divergently grown macromolecules as defective products are easier to remove, due to the more "organic synthesis" nature of the method. Statistically, more defects appear at higher generation number and simple convergent dendrimers, due to steric congestion at the focal point, are not grown to such high generations as divergent dendrimers. Mass spectrometry experiments, as those on divergently synthesised dendrimers, have been carried out on convergently grown dendrimers indicating, for example, that Fréchet-type dendrimers[29] contain very small amounts of impurities. Likewise, Moore's convergent phenylacetylene dendrimers[30] (Figure 1.5) were found to have a very high degree of purity.[31]

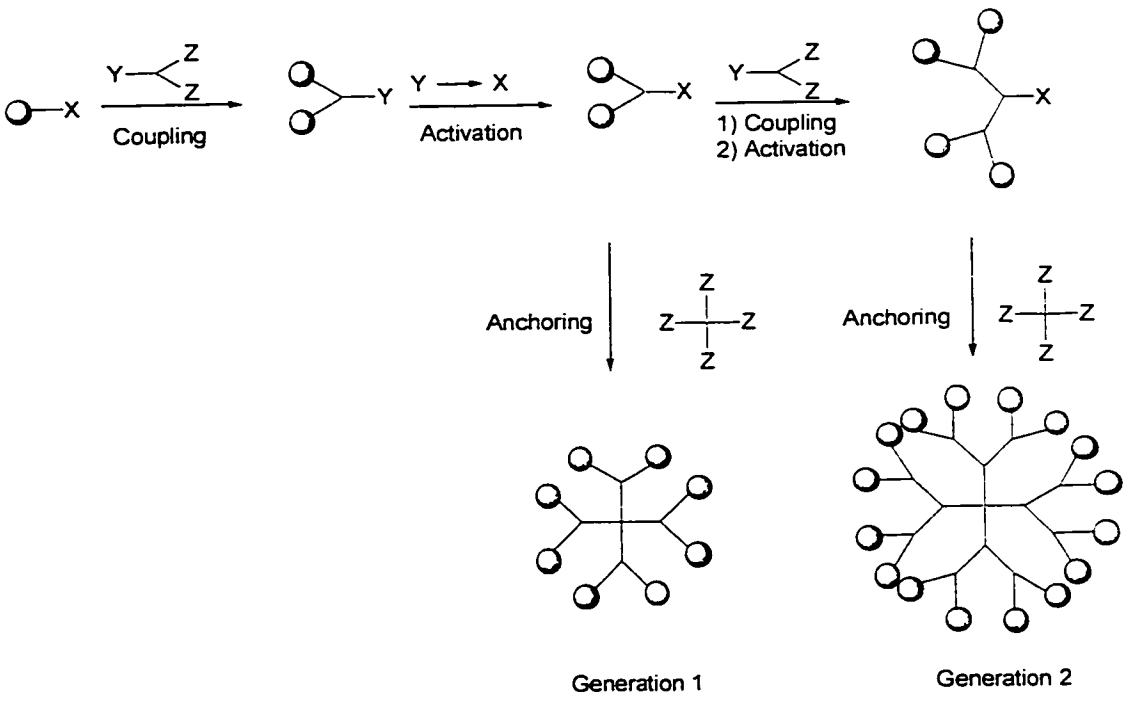

Figure 1.4 Convergent synthesis

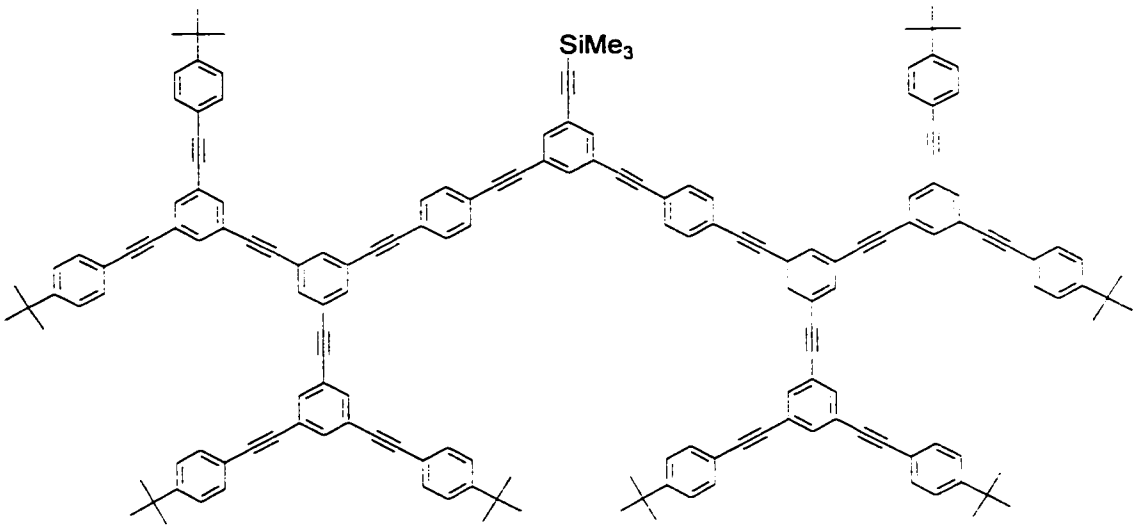

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Figure 1.5 Poly(acetylene) dendrimer

1.2.3 Recent developments

To accelerate both of these processes several more approaches to dendrimer construction have been developed, notably by Fréchet *et al.*.[32-34] These methods include making the core multivalent or using a branched monomer, called the double-stage hypercore convergent growth method, the branched monomer approach and the two-monomer approach. Another more recent synthesis involves growing dendrimers on solid supports.[35;36] The advantage of this method is that reagents can be used in large excess to force reactions to completion and minimise defective growth.[37,38] Purification can then be carried out simply by washing away the unreacted reagents from the solid bound dendrimer. Until recently this was a low yielding method which

produced defective dendrimer fragments. However, more recently some groups are having a higher degree of success with this approach.[39]

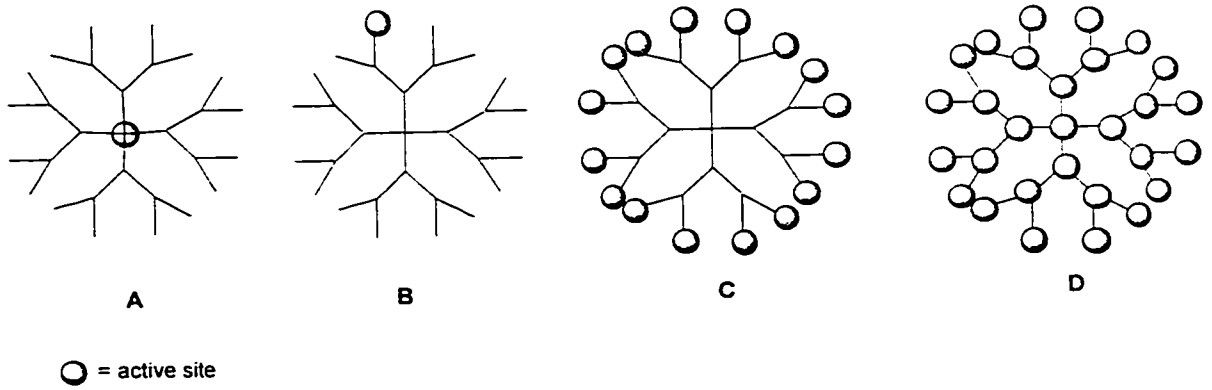
1.2.4 Dendrimer characterisation

Dendrimers are characterised by standard polymer techniques: size exclusion chromatography, viscosity and light scattering measurements and also by standard organic synthesis techniques; ^{1}H NMR, ^{13}C NMR, ^{31}P NMR and mass spectrometry. The polymer techniques are beneficial for obtaining the molecular weight of the dendrimer and also the dendritic purity by looking at the polydispersity of the macromolecule. However, ^{13}C NMR is invaluable at discovering defects in a symmetrical dendrimer.

1.3 Metallodendrimers

The initial incentive for research into dendrimers was the new capability to build molecules with as high molecular weight as possible, under controlled conditions. However, by the early 1990's the emphasis switched to research directed towards the synthesis of dendrimers with an application. Research first began into complexation of metals to dendrimers in 1991 when bipyridyl groups were investigated with hexametal ruthenium branching units.[40] Exploration further into metallodendrimers revealed many interesting physical, optical, electrochemical and

photochemical properties.[41;42] Since the first investigations into metal complexation, dendrimers have been designed with the direct placement of the metal site or sites at an exact location, this maybe at the centre of the dendrimer, in the arms or at the periphery (Figure 1.6).[43] An enormous range of metals have been incorporated into dendrimers, including, ruthenium,[37;38;40;44] platinum,[45] copper,[46] cobalt,[37;47] gold,[48;49] iron,[37] palladium,[18;50;51] nickel,[52] rhodium,[17;48;53] iridium,[54] zinc,[55] manganese[56] and titanium.[57]



A- active site at core, **B-** one peripheral active site, **C-** many peripheral active sites, **D-** actives sites both internal and external to dendrimer matrix.

Figure 1.6 Active sites in dendrimers

An early example of a metal being placed at the core was published by Inoue and co-workers.[55] A zinc porphyrin molecule was surrounded by poly(arylether) moieties called Fréchet wedges. This dendrimer exhibited novel biological and

photochemical properties. At the core of metallodendrimers, bipyridyl and terpyridyl[37;58] in addition to the porphyrin moieties, appear to be the most common ligand moieties.

With regards to metals at the periphery, van Koten *et al.*[52] developed carbosilane dendrimers with nickel containing groups. The same group later produced a similar carbosilane dendrimer having several palladium groups σ-bonded at the surface.[18] Liao and Moss[59-61] employed a convergent approach to prepare a benzyl ether based dendrimer containing 48 peripheral ruthenium groups. Further, ferrocenyl containing moieties have become the most consistently applied [21;62;63] metallo groups found at the periphery of, what is now, a diverse range of dendrimers (Figure 1.7) and appear to be extremely useful in the formation of redox catalysts.[64]

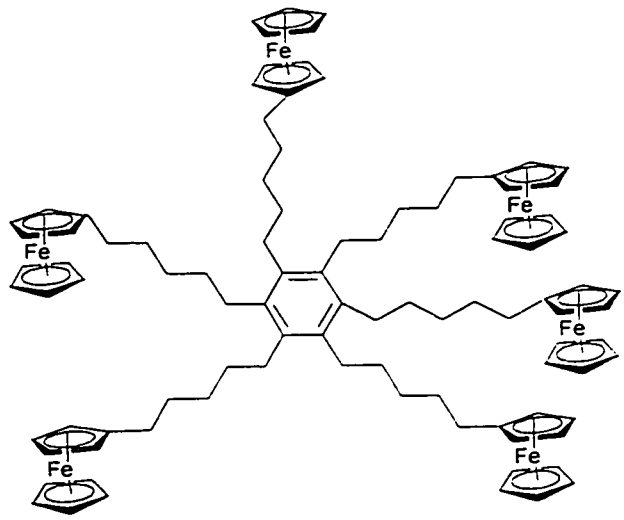


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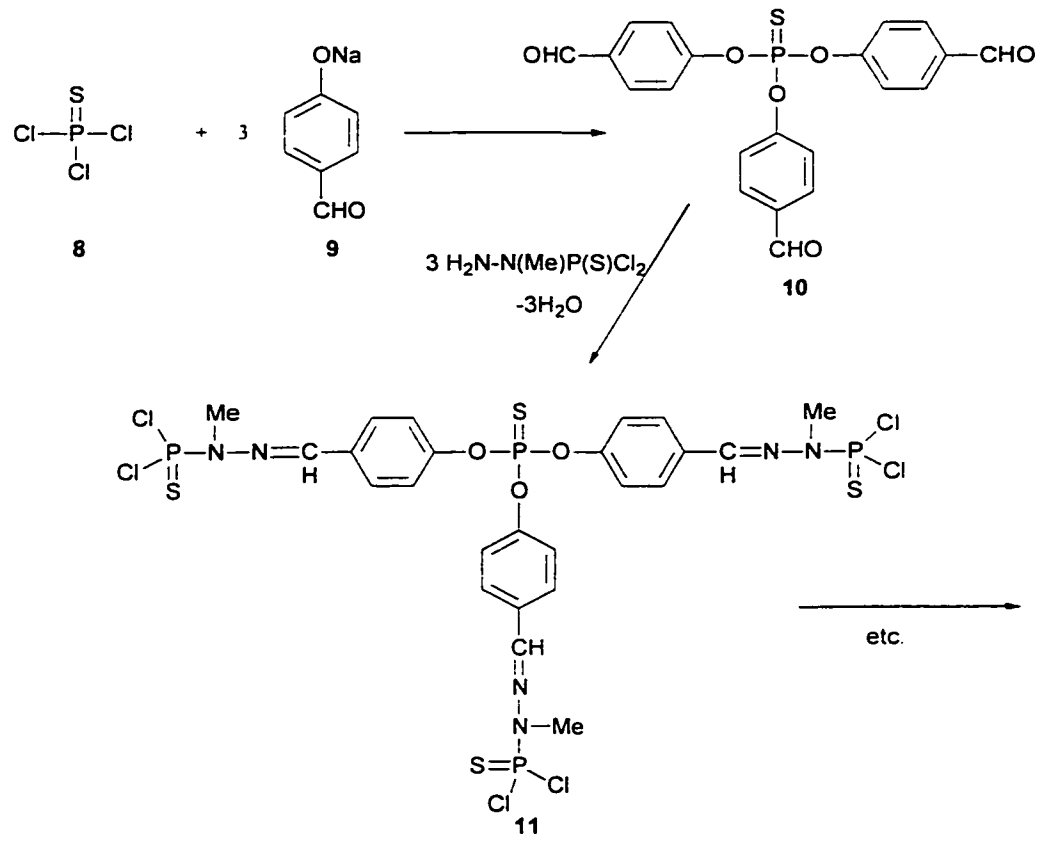
Figure 1.7 Iron redox catalyst

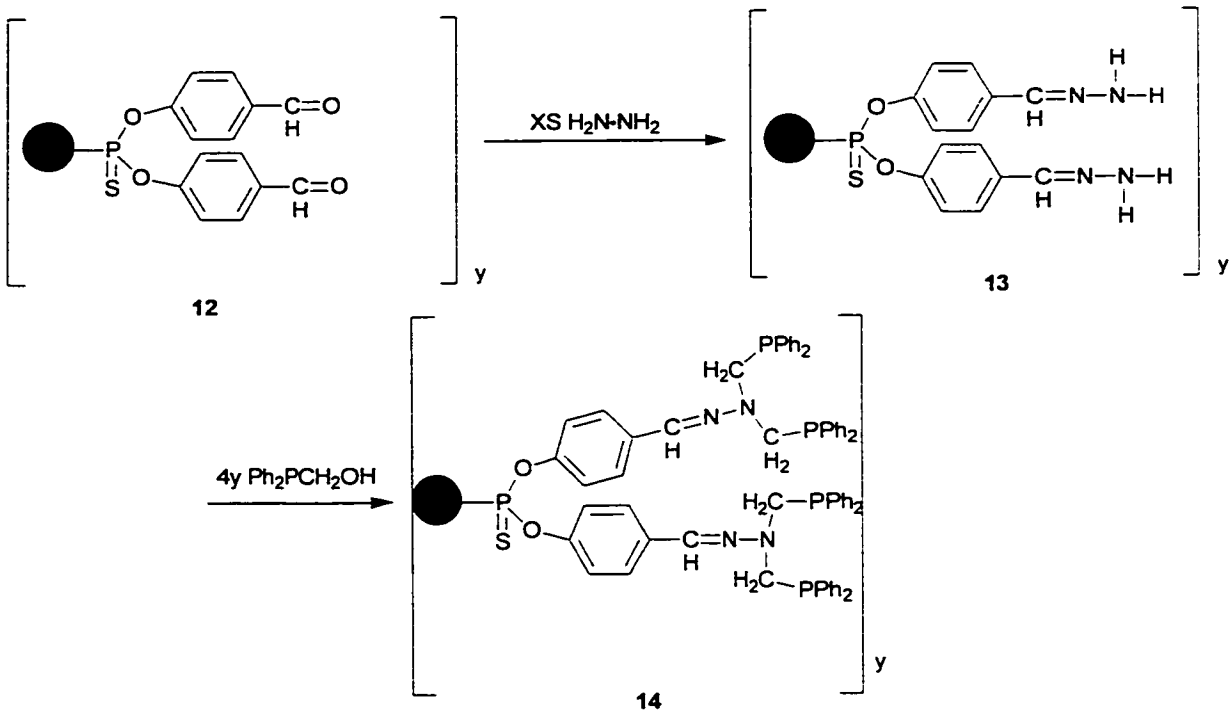
1.4 Phosphorus containing dendrimers

Phosphorus was first used in dendrimers in 1990 by Engel and Rengan.[65] They synthesised a cascade molecule containing phosphonium ion sites. The first paper involving phosphines and metals in a dendrimer was by Dubois *et al.*.[66] Diphenylphosphino groups were used to complex palladium species onto a dendrimer which also contained phosphorus atoms as branching units. Majoral *et al.*[49; 67-72] have investigated the use of phosphorus extensively in dendrimers. They have introduced phosphorus at many stages in the growth of dendrimers. One of their first syntheses involved a three step repetitive process to grow phosphorus dendrimers up to the third generation containing up to 48 periphery groups. This strategy involved a Schiff reaction between an aldehyde and excess hydrazine, followed by a substitution reaction and then a Staudinger reaction. These dendrimers had phosphorus atoms at the core, in the arms and after functionalisation, at the periphery. A faster, simpler route was investigated shortly after, and consisted of repeating substitution reactions followed by a Schiff reaction (Scheme 1.2). After the first set of reactions there are 6 chlorine atoms set up for the next round of reactions. This macromolecule was constructed up to the twelfth generation with phosphines grafted onto the periphery to form terminal groups. In fact, Majoral has studied many methods of functionalising the end groups of dendrimers, including a Mannich type reaction.



Scheme 1.2 Synthesis of a phosphorus containing dendrimer

In this case, a terminal benzaldehyde is treated with excess hydrazine then diphenylphosphanyl-methanol, which is formed *in situ* from paraformaldehyde and diphenylphosphine (Scheme 1.3). This reaction was first used with dendrimers by Reetz *et al.*.[17] Using this method they have prepared dendrimers with up to 3072 phosphine groups on the surface. Complexation of many different transition metals to these macromolecules was the next aim in an attempt to form easy separable, highly active catalysts for a wide range of organic reactions.



Scheme 1.3 Phosphination using diphenylphosphanyl-methanol

1.5 Catalytically active dendrimers

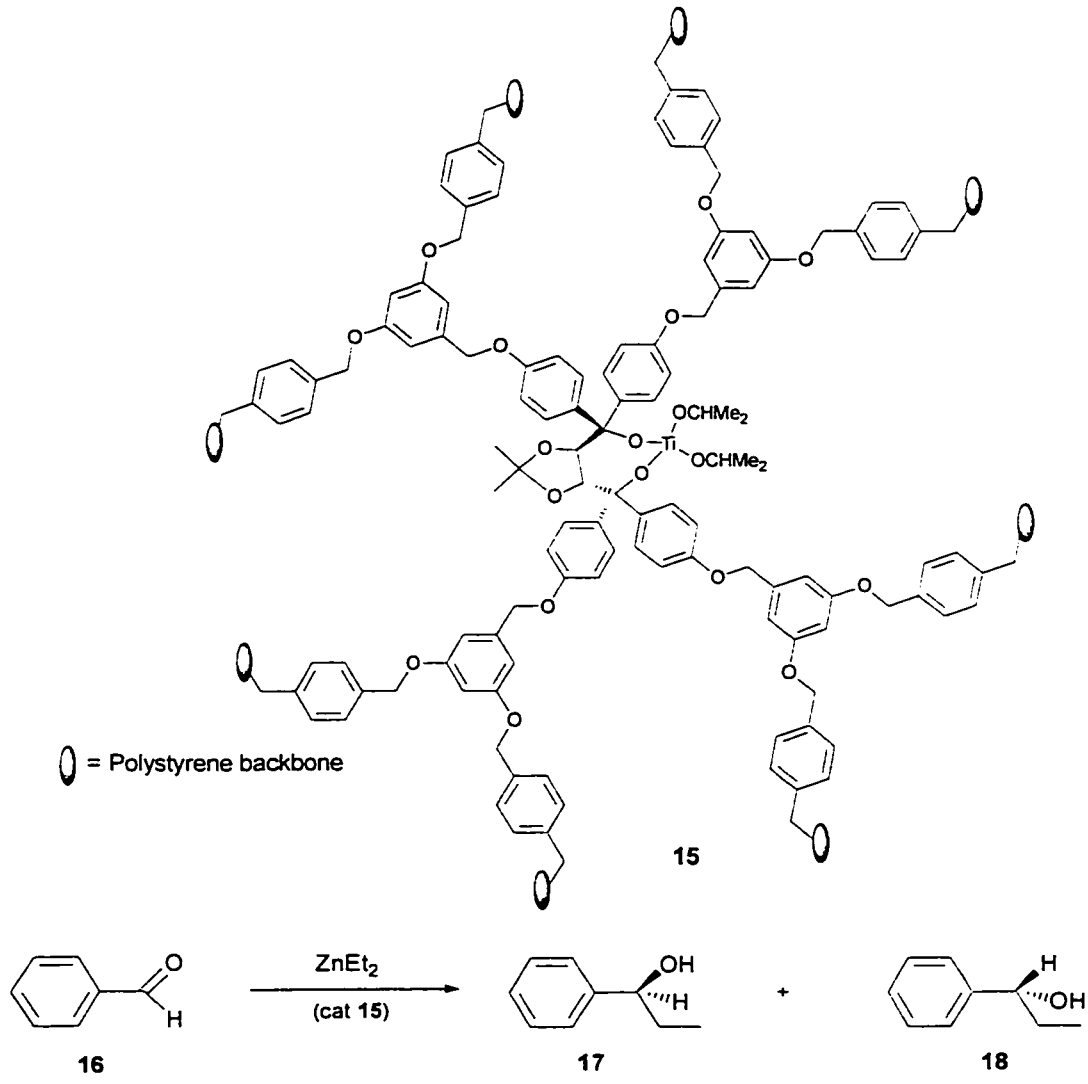
As many metallodendrimers began to appear in the literature, it was hoped that dendrimers could breach the gap between homogeneous and heterogeneous catalysis. In general, homogeneous catalysts exhibit higher activity than heterogeneous catalysts, however, most industrial processes are catalysed by heterogeneous catalysts because the expensive metal catalysts can be recovered easily, making the overall process cheaper. Therefore, if the benefits of both heterogeneous and homogeneous catalysts could be combined, then an extremely

efficient catalyst would result. Many dendrimers, unlike polymers of a similar size, are soluble in a variety of organic solvents, which should boost the activity of the catalyst and the nanoscopic size of many large dendrimers enables precipitation or ultrafiltration techniques for recovery.[18:73]

1.5.1 Metals at the centre of the dendrimer

Brunner[74] described a new set of ligands with a diphosphinoethane centre bound to a transition metal, surrounded by a space filling dendrimer. These molecules were named "dendrizymes" as they contain a distinct metal centre like an active site, set up to catalyse a certain reaction, surrounded by a dendrimer likened to the supporting protein of an enzyme. The encapsulation of a metal at the core of a dendrimer allows the potential to modifiy the steric environment of the active site. This can affect the regioselectivity and the rate of the catalysed organic transformation. Dendritic wedges surrounding a metal can confine the space at a catalytic centre. For example, Suslick *et al.*[56] used a manganese(III) chloride porphyrinato central core surrounded by a polyester dendrimer, as a catalyst for an epoxidation reaction. The regioselectivity was high but not as high as the reaction with the parent compound. Another example of a confined metal core was a TADDOL ($\alpha,\alpha,\alpha',\alpha'$ – tetraaryl-1,3-dioxolane-4,5-dimethanol) type titanium(IV) catalyst synthesised by Seebach *et al.*[57;75] (Scheme 1.4). The dendrimer acts as a crosslinking moiety in a polystyrene backbone. The catalyst was employed in the

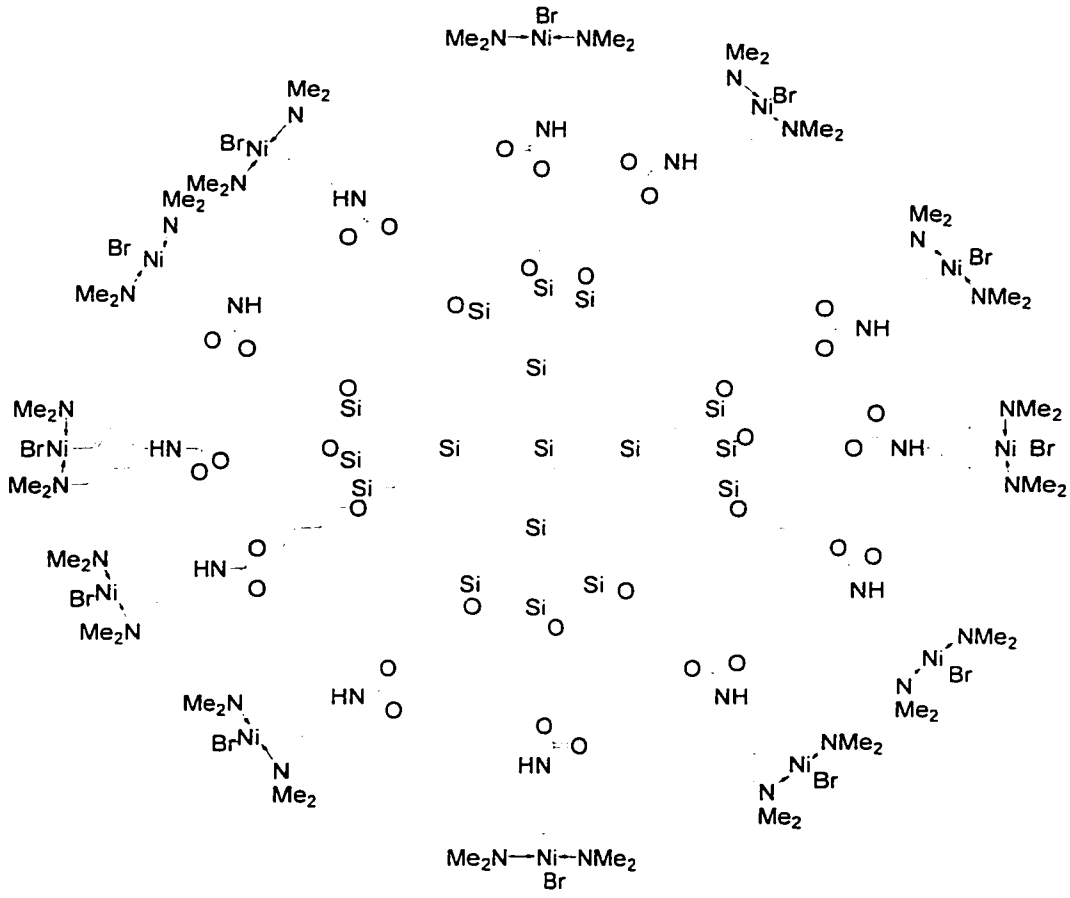
enantioselective nucleophilic addition to aldehydes. High enantioselectivities were found for the diethylzinc addition to benzaldehyde; the catalyst showed similar activity and selectivities to its monomer. After the reaction the catalyst was recycled by filtration and reused. Initially, the turnover numbers were slightly less than those of the monomeric analogues although they remain fairly steady for up to 20 cycles.



Scheme 1.4 Dendrimer and polymer bound TADDOL type catalyst

1.5.2 Metals at the periphery of the dendrimer

Prior to the examples of metal core containing dendrimers (section 1.5.1), van Koten investigated the catalytic activity of a carbosilane dendrimer (**19**).[18]



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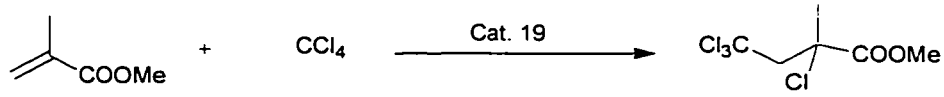
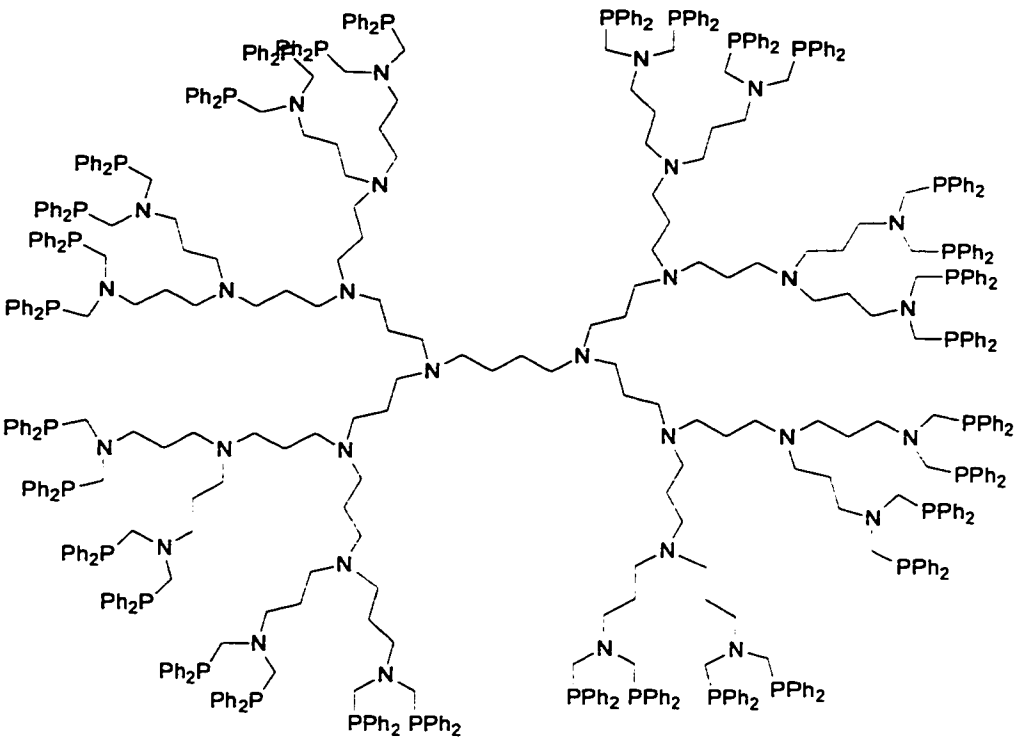


20 **21**

Scheme 1.5 Nickel containing carbosilane dendrimer

This metallodendrimer which contains nickel(II) moieties, was successfully used in the Kharash addition of poly(halogenoalkanes) to simple alkenes (Scheme 1.5). The activity of the dendrimeric catalyst was 20-30% lower than that of monomeric catalyst, however, with these catalysts the possibility of recycling is a compromise for a loss in activity. The loss or retention of activity upon precipitation and recycling was not mentioned. In a later paper van Leeuwen[76] reported a similar carbosilane palladium catalyst in a continuous process membrane reactor for an allylic alkylation with good results. Up to this point, all previous attempts at improving the performance of some catalytic reactions had failed in that the dendrimeric catalyst did not outperform the monomeric catalyst. Finally, Reetz *et al.*[17]achieved this goal with a modified DAB dendrimer (**22**) (Scheme 1.6). Following the phosphination of the dendrimer, it was reacted with $[Pd(CH_3)_2(tmeda)]$, presumably with the elimination of tmeda (tetramethylethylenediamine).



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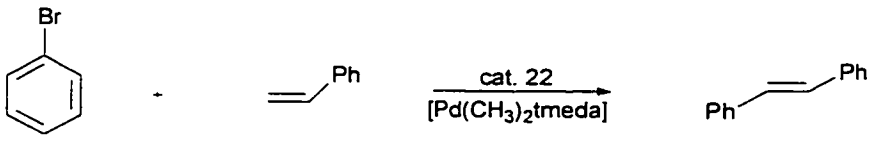

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Scheme 1.6 Phosphinated dendrimer for Heck reaction

The resulting complex was then employed as a catalyst in a Heck reaction of bromobenzene and styrene. The conversion was between 85-90% with 89% of the desired product, 1,2-diphenylethene. Even more encouraging was after the catalyst had been precipitated and reused, the conversion and yield of the desired product were comparable. The overall turnover number for this catalyst was higher than that

of the parent compound. The same group also used a rhodium containing DAB dendrimer for the hydroformylation of 1-octene with reasonable results. In 1999 Reetz *et al.*[77] performed an allylic substitution in a continuous homogeneous membrane nanofiltration reactor. They used the same phosphinated DAB dendrimer (**22**) with palladium. The larger fourth generation catalyst overall was more successful than the third generation. The initial conversion of starting material was 100% falling to 80% after the catalyst had been recycled approximately 25 times. There was some leaching of the palladium catalyst, as is the case for many polymer bound catalysts, but the catalyst appeared successful overall. At least one other group[78] has noticed that an increase in generation of the catalyst improves performance. This may be explained by examining where the active sites actually are. Where the periphery ends, and hence the exact place of the active metal sites, are a matter of conflicting debate. de Gennes and Hervet[23] originally predicted that dendrimers were inflexible and the end groups are firmly at the periphery of the macromolecule. Since then many researchers[41] have disagreed with this. Backfolding of wedges in certain dendrimers, and incomplete reactions, have been postulated to lead to poor catalytic performance. Higher generations of dendrimers, and organometallic dendrimers, appear to be less susceptible to backfolding problems. This may be why these dendrimers are the most successful catalysts as their catalytic sites are freely accessible. Many other reactions have been studied using a dendrimeric catalyst with varying degrees of success; including, asymmetric hydrogenation,[79] hydrogenation in an aqueous media[80] and allylation.[81] The focus

of this research will be on hydroformylation reactions that have been investigated in this laboratory previously, employing both homogeneous and heterogenous catalysts.[82;83]

1.6 Hydroformylation

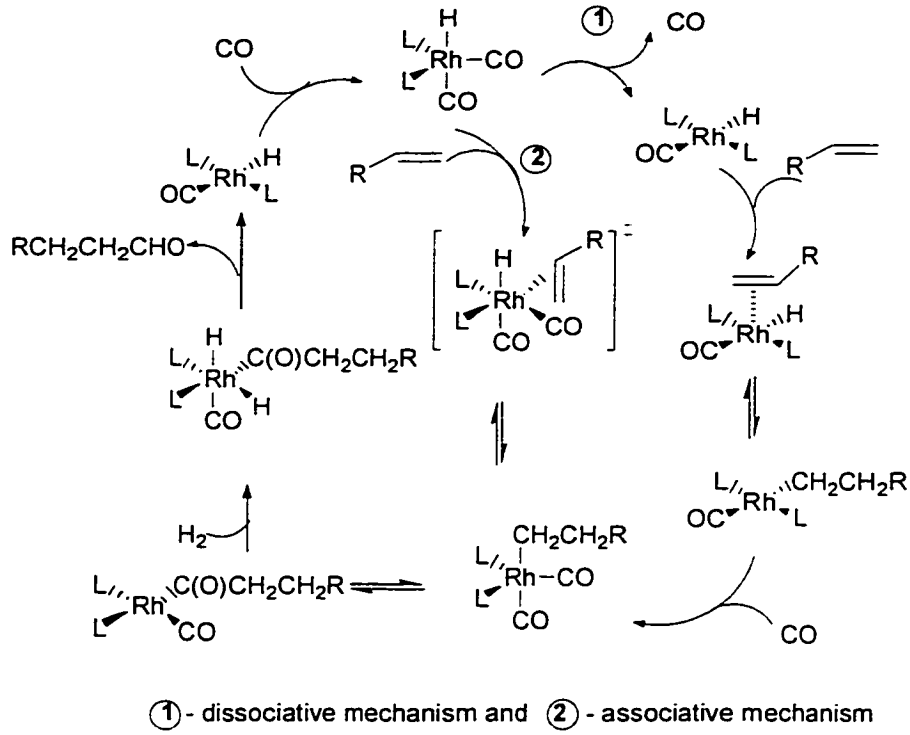
The reaction of an alkene in the presence of carbon monoxide and hydrogen gas resulting in the addition of a formyl group across the double bond is known as hydroformylation (eq. 1.1). First detected by Otto Roelen in 1938,[84] it is now one of the most industrially important reactions involving homogeneous catalysts. This reaction forms a mixture of branched and linear aldehydes, which can then be transformed chemically into many different functional groups

Eq.1.1

1.6.1 The catalysts

The first processes at BASF, Ruhrchemie and ICI, all used cobalt as the basis of their hydroformylation catalysts. In these cases the reaction required high pressures (ranging from 2900 psi to more than 5000 psi) and temperatures (between 130°C and 180°C). During the 1960's a transition was made from cobalt catalysts

towards rhodium-phosphine catalysts, such as Wilkinson's catalyst.[85;86] Hydroformylations using rhodium-phosphine catalysts were able to be carried out on a wide range of substrates at 25°C and 1 atm. The Celenase Corporation was first to use this type of metal-phosphine catalyst on an industrial scale for the production of butyraldehyde.[87] The metal catalysts for this catalytic process are based almost exclusively upon cobalt, rhodium, platinum and ruthenium, however, only cobalt and rhodium systems have found industrial application. The activity of platinum and ruthenium is too low to be of industrial significance but studies on these systems have given valuable mechanistic insights. These transition metals are all capable of forming the metal carbonyl hydride species, $H_xM_y(CO)_2L_n$, which is thought to be an important intermediate in the mechanism of hydroformylation (Scheme 1.7).



Scheme 1.7 Wilkinson's associative and dissociative mechanism

In the associative mechanism, initially it is thought that the alkene complexes to the metal. The dissociative mechanism is thought to begin by the dissociation of a carbon monoxide molecule followed by the co-ordination of the alkene to the metal complex, then addition of a carbon monoxide ligand. The two mechanisms are then the same; the metal acyl group is formed by the addition of carbon monoxide into the metal-carbon bond, followed by oxidative addition of hydrogen and reductive elimination of the aldehyde. The co-ordination of another carbon monoxide molecule regenerates the catalyst. For unhindered olefins, e.g. 1-octene, it is believed the reductive elimination of the aldehyde is the rate-determining step, whereas for hindered olefins, e.g. styrene, the rate-determining step is thought to be the

complexation to the metal. The dissociative mechanism is considered the most likely, unless there are very high concentrations of phosphine and catalyst.

The catalyst can be "unmodified" in which case the ligand, L, consist of both carbon monoxide and hydrogen, or the ligands can be "modified". The "modified" catalyst has other ligands such as phosphine. Only phosphines, triphenylphosphine oxide and some phosphites have been employed as ligands in industrial processes. However, there is a wider range of ligands in the literature including ligands containing heteroatoms. The bite size of the phosphine is thought to affect the branched to linear ratio of the products,[88] along with temperature, the partial pressures of the gases and the concentration of catalyst.

1.7 Research Objectives

Although the number of investigations into the use of dendrimers as homogeneous and heterogeneous catalysis is extensive many of these catalysts still do not outperform the monomeric analogues and this research area remains one of considerable current interest.

The initial objectives of this project were to synthesise a novel ligand based on dendrimeric syntheses and place the metal at the core of the molecule. An example of a targeted phosphine is shown in Figure 1.8. In order to evaluate the possible usefulness of the catalyst, studies on the hydroformylation of a range of substrates were envisaged. As with many of the other dendrimer catalysts we were

hopeful that due to the ligand's size, precipitation of the catalyst would be achieved followed by reuse with minimal loss of activity.

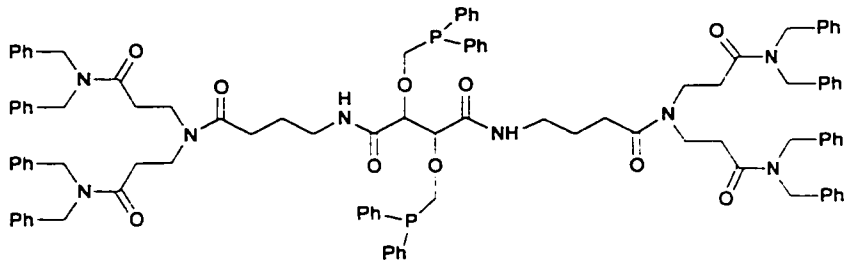


Figure 1.8 Target phosphine compound

Chapter 1 References

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2

Synthesis of Outer Dendron Fragments

2.1 Introduction

Amongst the many dendrimer catalysts in the literature there are several that have been designed with the metal at the core of the dendrimer.[1-4] In the case of Seebach and coworkers,[4] the placing of a metal, coordinated to a phosphine ligand, at the centre of a dendrimer increased the regioselectivity in the enantioselective nucleophilic addition of diethyl zinc to aldehydes, compared to the non-dendrimeric analogue (Scheme 1.4). Suslick and coworkers have reported another example where improved regioselectivities were found, when the metallodendrimer is used as the catalyst in place of the analogous molecular complex.[1] They employed a manganese-porphyrin containing dendrimer for the epoxidation of unconjugated dienes. The regioselectivity in the reaction we plan to investigate, hydroformylation, is extremely sensitive to both the steric and the electronic nature of the ligand. We intend to investigate how changes to the ligand affect the regioselectivity.

2.1.1 Initial aims

The desired potential catalyst was based on a metal core, surrounded by dendrimeric arms. The preparation of this catalyst was addressed by separating the synthesis into four distinct parts; an exterior dendron fragment, a symmetrical core, which contained a phosphorus moiety, the connection of these two fragments and the complexation of a metal species (Figure 2.1).

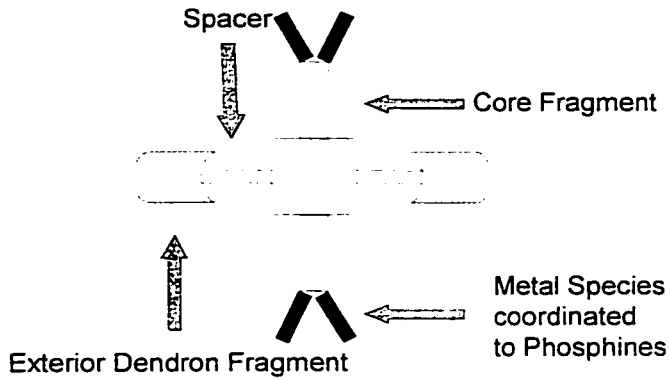
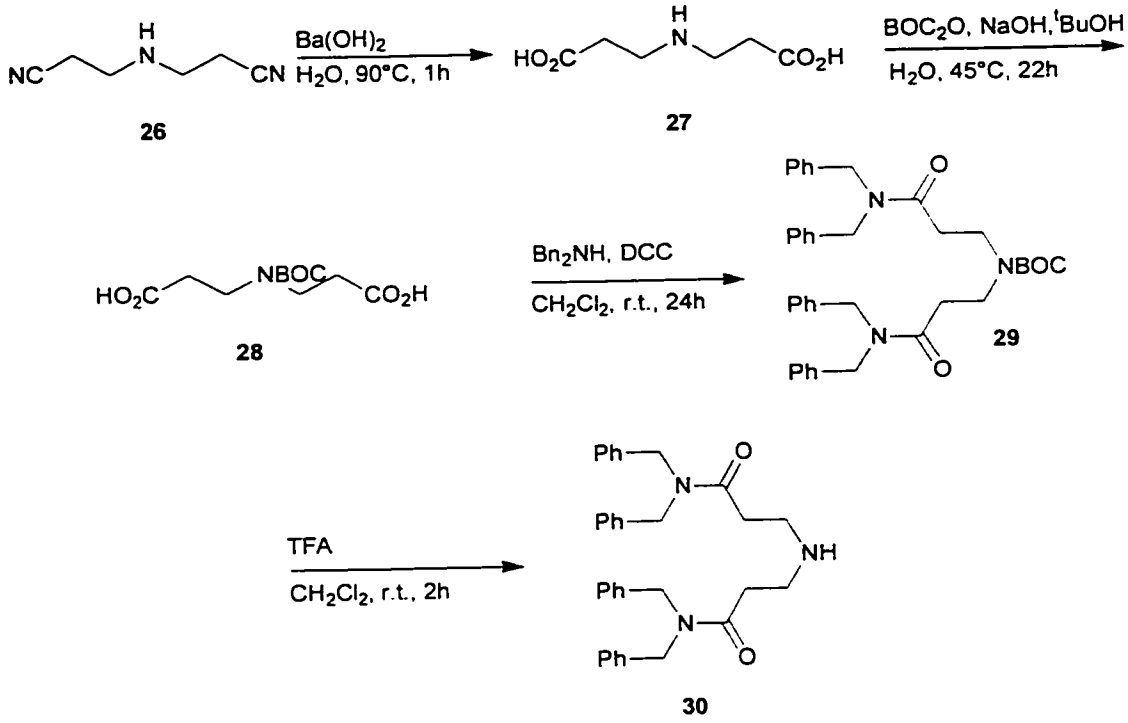


Figure 2.1 Proposed diagram of catalyst

For the exterior component, several convergent syntheses, previously employed by Fréchet and coworkers, were investigated.[5,6] This approach was considered reasonable due to the retrosynthetic disconnections that can be envisaged from a convergently synthesised dendrimer. When considering a convergent synthesis, the term dendron is adopted for a small fragment of a full dendrimer, of which several can be connected to form a complete dendrimer. The core fragment envisioned was a small molecule, with several functional groups, which could be selectively protected and deprotected. A protected core could be attached to the exterior and then subsequently deprotected to allow a phosphine moiety to be introduced. This would be followed by complexation of a transition metal species.

2.2 Preparation of amine (30)

The first dendron (**30**) to be considered for the exterior component had an amine at the focal point and could be attached to the central core *via* a carboxylic acid functionality. The outline of the synthesis, following literature procedures,[6;7] is shown below (Scheme 2.1).



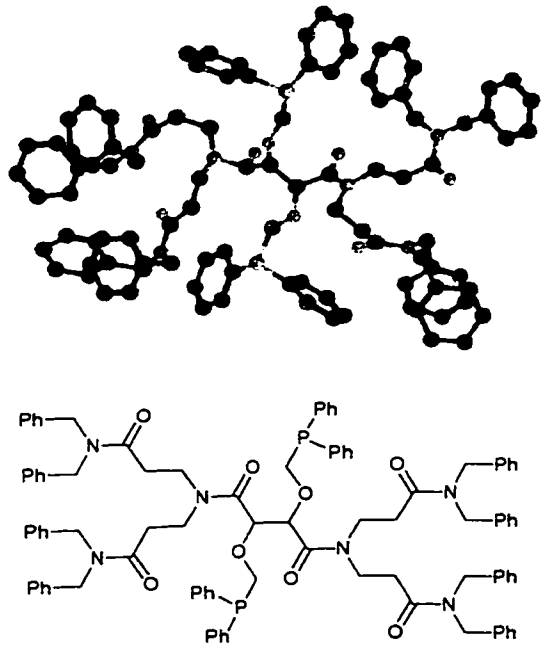
Scheme 2.1 Preparation of *N,N*-dibenzyl-3-(2-dibenzylcarbamoyl-ethylamino)-propionamide (30)

After the barium hydroxide hydrolysis[7] of the propionitrile (**26**) to its carboxylic acid (**27**), the resultant amine was protected using di-*t*-butyl dicarbonate under basic

conditions,[6] to give the dicarboxylic acid, **28**. The dicarboxylic acid (**28**) was reacted with dibenzylamine and dicyclohexyl carbodiimide (DCC) in dichloromethane affording the dendron **29**, which then undergoes swift deprotection of the BOC group using trifluoroacetic acid in methylene chloride. Subsequent to this deprotection the amine is available for further modification. Further generations can be constructed by the repetition of the DCC mediated and deprotection steps.

2.2.1 Spacer construction for amine 30

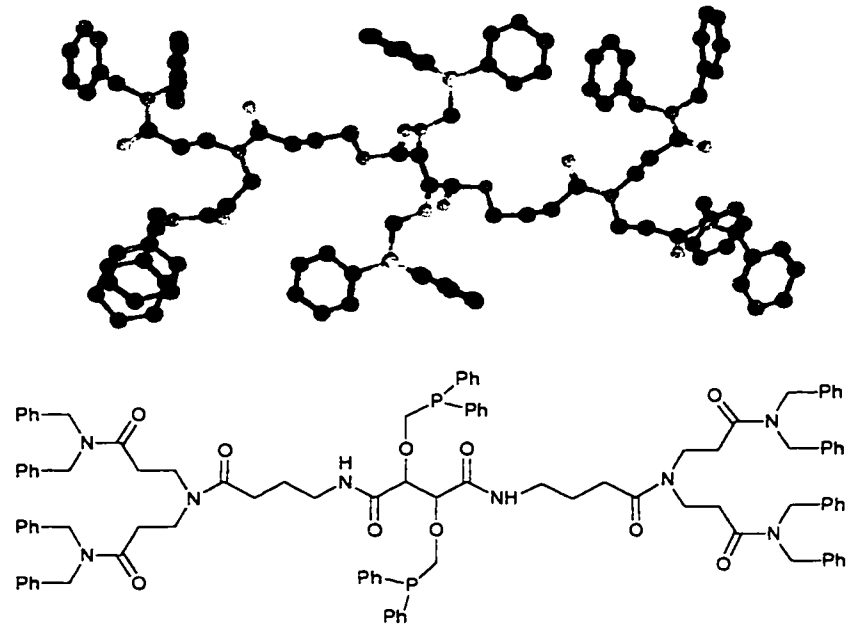
The molecular model in Figure 2.2 shows amine **30** coupled to a simple tartrate-type central core unit. If this was to be complexed to a rhodium(I) species *via* coordination to the phosphines, the central area could well be extremely hindered. This could even suppress catalysis at a later stage. The facilities to carry out the molecular modelling with the metal coordinated were not available.



31

Figure 2.2 Molecular model of proposed ligand without spacer

The addition of a small three-carbon chain linker between the dendritic amine and the central phosphorus containing core (**32**) appeared to alleviate this steric problem, based on molecular modelling (Figure 2.3).

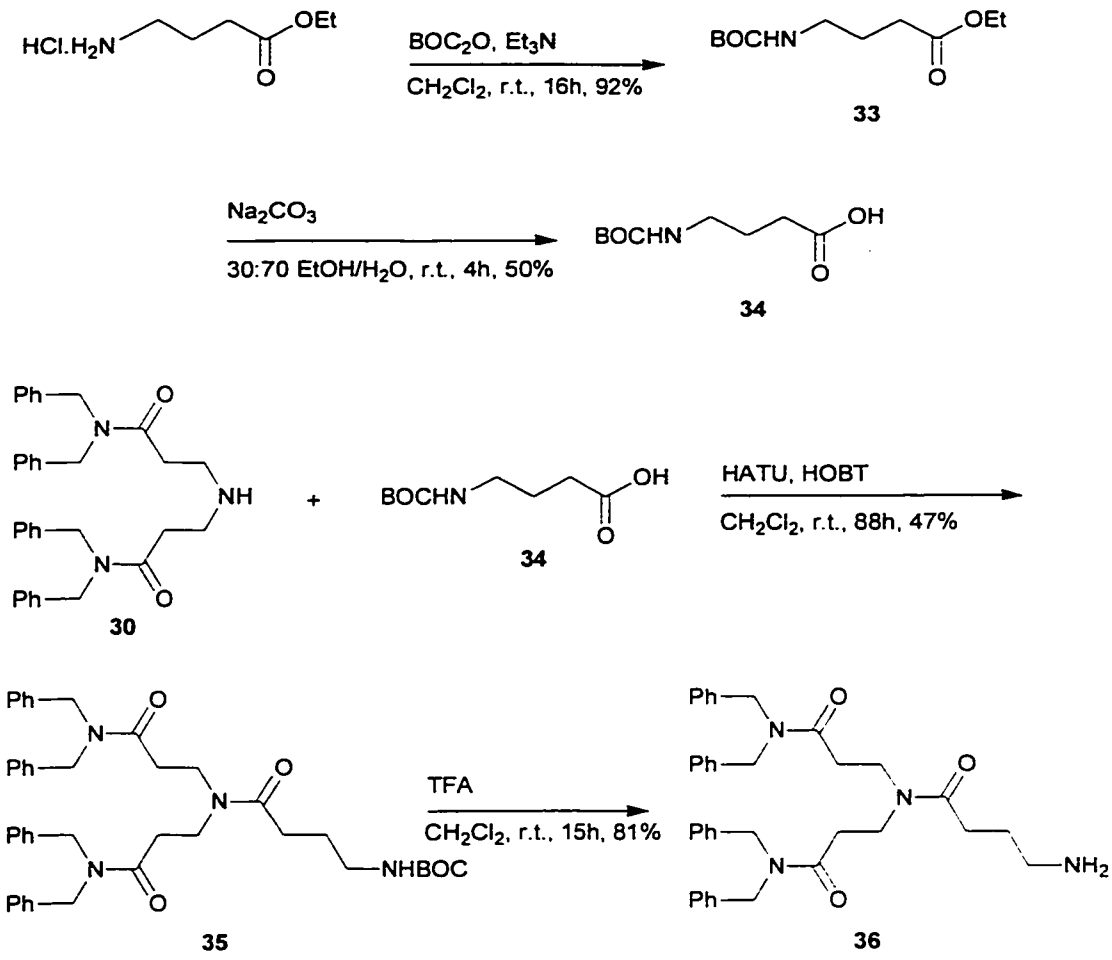


32

Figure 2.3 Molecular model of proposed ligand with spacer

This small creation of space around the catalytic centre was important as it was the intention to also study the size effect of the dendron on the reactivity of the catalyst. In addition, upon increasing the generation size of the dendrimer, the ease of separating the catalyst from the substrate at the end of the reaction may increase. However, this must be weighed against the risk of decreasing the rate of the catalysis due to the bulkiness at the exterior. This could also lead to the risk of impeding coordination of the substrate to the active species. Chow and Mak[8;9] used a modified poly(benzylether) with a copper core as a Diels-Alder catalyst and noticed indeed a significant drop off in rate from generation three onwards, presumably due to the shielding of the active catalytic site from the substrates.

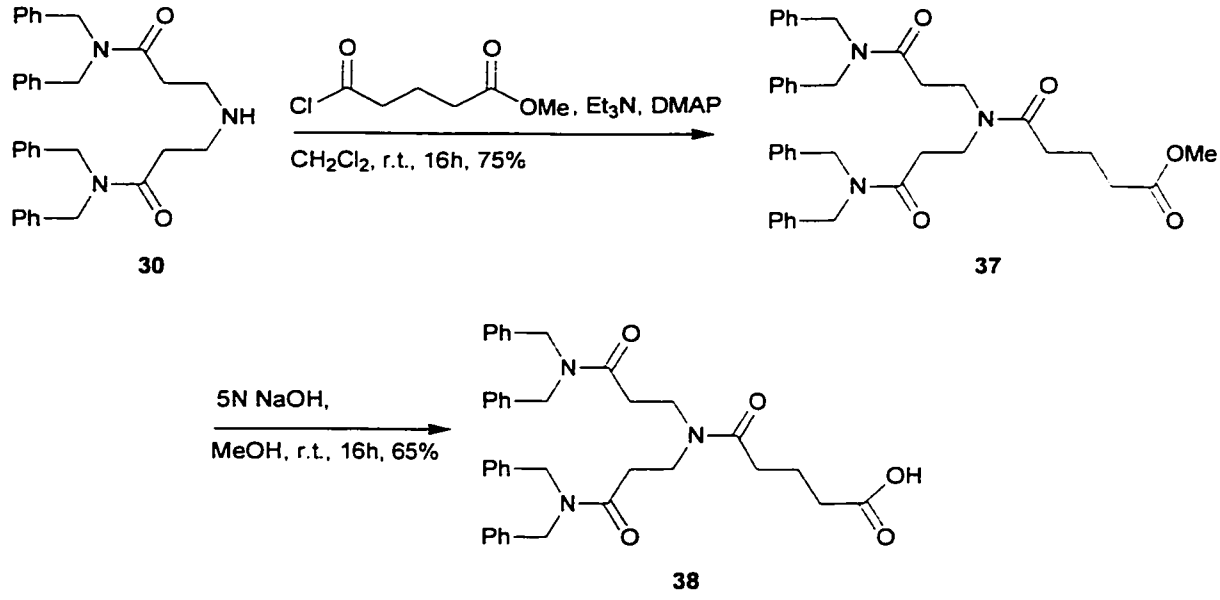
In order to have two different functionalities as focal points for our dendrons, two different small molecules were synthesised to act as spacers between the dendron and core. These small molecules were coupled to the dendritic amine **30**. The construction of the first amine spacer is shown in Scheme 2.2. Commercially available ethyl-4-aminobutyrate-hydrochloride salt was treated with di-*t*-butyl-dicarbonate and then the ester functionality of the resulting product (**33**) was hydrolysed under basic conditions to give **34** in an overall yield of 46%. The coupling of the amine (**30**) to the carboxylic acid (**34**) proved to be problematic. When standard DCC coupling methods were employed the yield was low and purification problems ensued. The coupling with HATU and HOBT resulted in a 47% yield of BOC-protected amine (**35**).[10]



Scheme 2.2 Synthesis of amine terminated dendron 36

BOC-protected amine (**35**) was subsequently deprotected to give amine **36**, so that it could be connected to a carboxylic acid terminated central unit. Alternatively, it was envisioned that a terminal carboxylic unit for the dendron would also prove useful for connection to either an alcohol or amine (Scheme 2.3). This was carried out by the reaction of amine **30** with methyl-4-(chloroformyl) butyrate in methylene chloride,

affording the methyl ester (**37**) in 75% yield. Hydrolysis of **37** in methanolic sodium hydroxide gave the carboxylic acid, **38**.



Scheme 2.3 Synthesis of carboxylic acid terminated dendron (38)

2.3 Synthesis of Poly(benzylether) dendrons

Due to the incomplete reactions that occurred between the previous dendrons **36** and **38** and the central cores, to be discussed later, attention was turned to the synthesis of a poly(benzylether) dendron. The first poly(benzylether) dendrimer was synthesised by Fréchet to demonstrate the first convergent synthesis (Figure 2.4).[5]

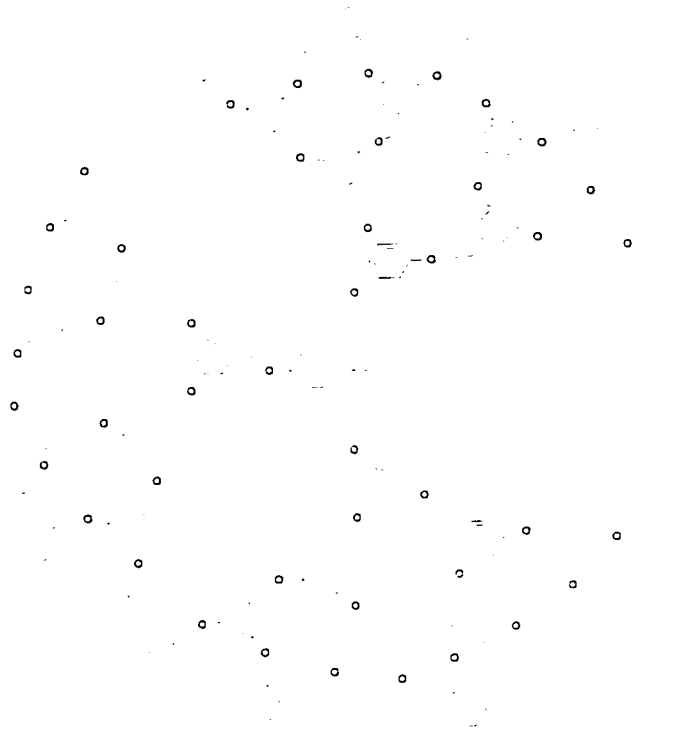


Figure 2.4 Poly(benzylether) dendrimer

This particular poly(benzylether) dendrimer has been adapted and used both by Fréchet and many other groups.[11-13] In 1998 Fréchet and coworkers reported using an oligothiophene core with poly(benzylether) dendrons tethered on either end (Figure 2.5).[12] The method of parallel synthesis of core and dendrimer followed by connection used to synthesise the product in Figure 2.5 was the technique we intended to employ in our synthesis.

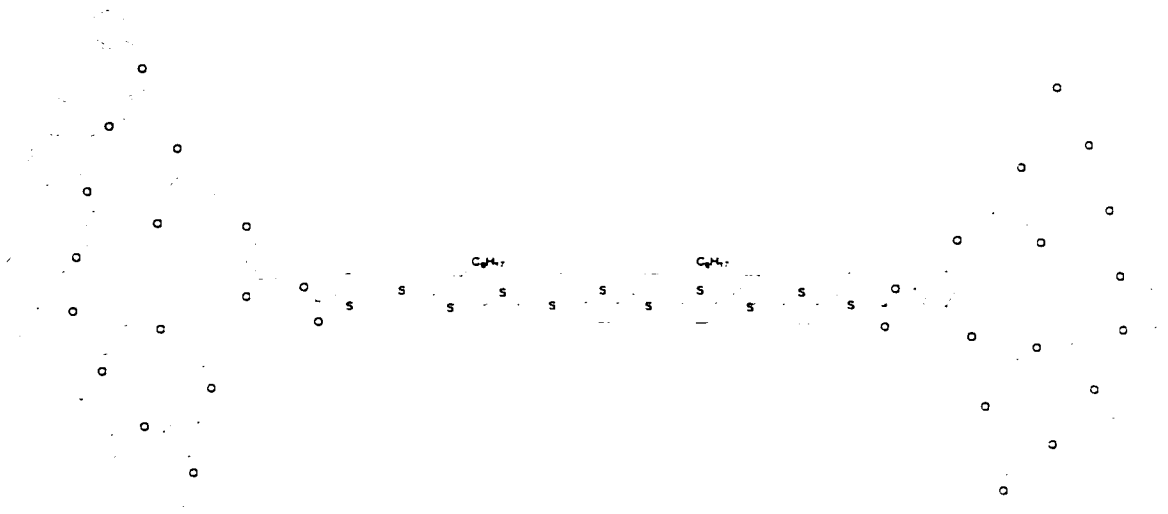
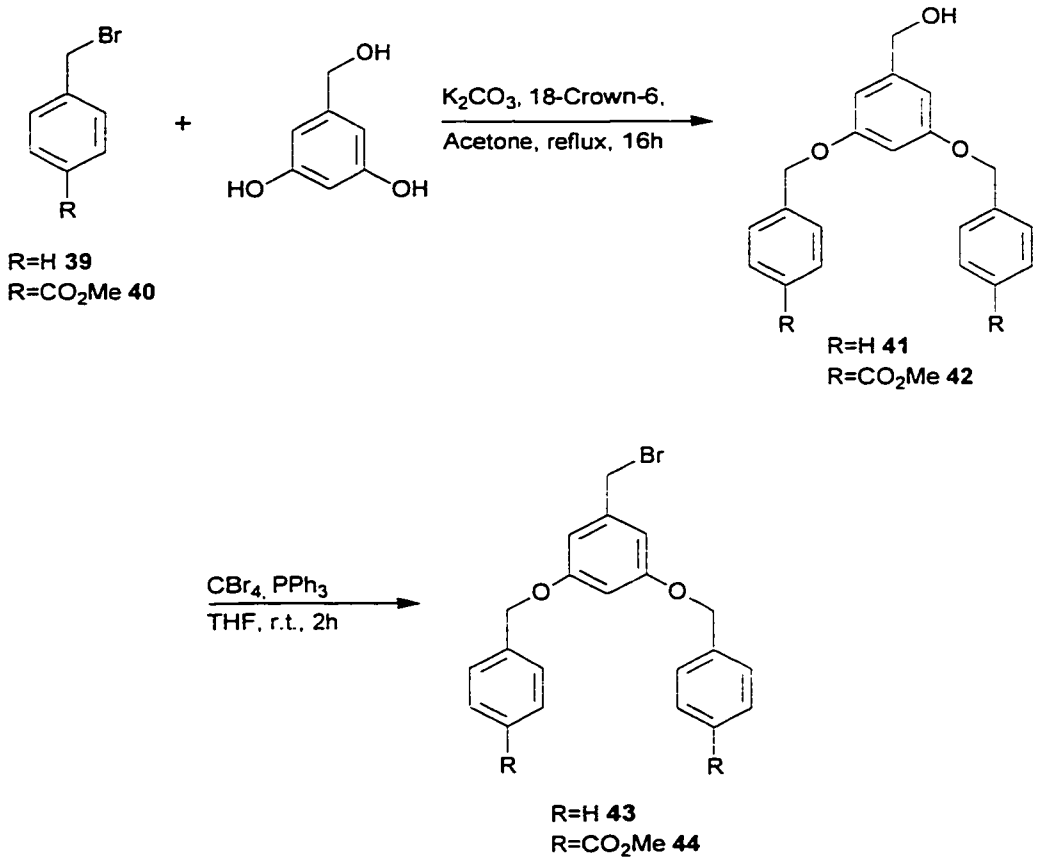


Figure 2.5 Poly(benzylether) dendrimer with thiophene oligimer core

2.3.1 Synthesis of (3,5-benzyloxy)-benzylbromide (43) and [3,5-bis-(4-methylester-benzyloxy)-benzylbromide] (44)

The main repetitive synthesis of this poly(benzyl ether) is shown in Scheme 2.4. Under mild basic conditions the 3,5-hydroxy-benzyl alcohol was converted to the alcohol **41** or **42** in dry, refluxing acetone. Alcohol **41** or **42** was then brominated in tetrahydrofuran with triphenylphosphine and carbon tetrabromide. Initially, this dendrimer was formed with a terminal ester functionality (**44**), which could be manipulated later to affect the hydrophobicity of the catalyst. This ester functionality however limited the reaction conditions for the connection of [3,5-bis-(4-methylester-

benzyloxy)-benzylbromide] (**44**) to a central core. Under basic conditions hydrolysis of this ester led to a mixture of products.

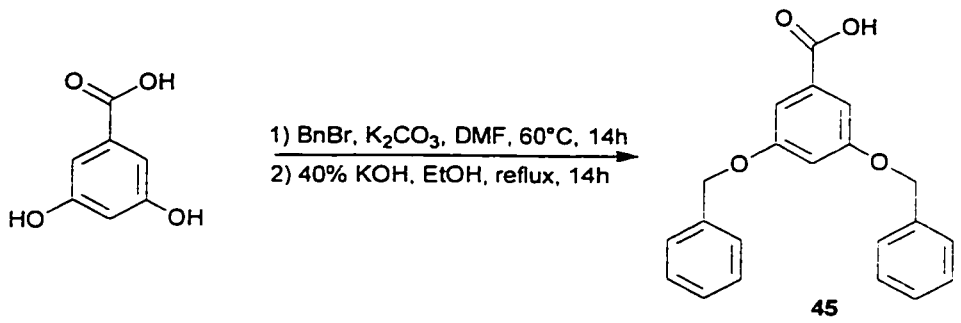


Scheme 2.4 Synthesis of bromides 43 and 44

2.3.2 Synthesis of (3,5-benzyloxy)-benzoic acid (45)

A third dendron was synthesised in a manner similar to that of dendrons **43** and **44**. Instead of the bromination of alcohol **41**, an oxidation was carried out. To improve the yield, carboxylic acid **45** was synthesised, however, *via* a more

economical procedure, starting from 3,5-dihydroxybenzoic acid. The alcohols and the carboxylic acid functionalities were protected with benzyl bromide, followed by hydrolysis of the benzyl ester with base to afford the carboxylic acid, **45** (Scheme 2.5).[14]



Scheme 2.5 The synthesis of 3,5-bis-benzyloxy-benzoic acid (45)

2.4 Conclusions

The synthesis of five exterior dendritic pieces to be used in the synthesis of a dendritic catalyst has been carried out. The terminal groups of these dendrons included two carboxylic acids, two bromides and an amine. This variability furnished us with several possibilities as to the terminal functionalities of the core units.

Chapter 2 References

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3

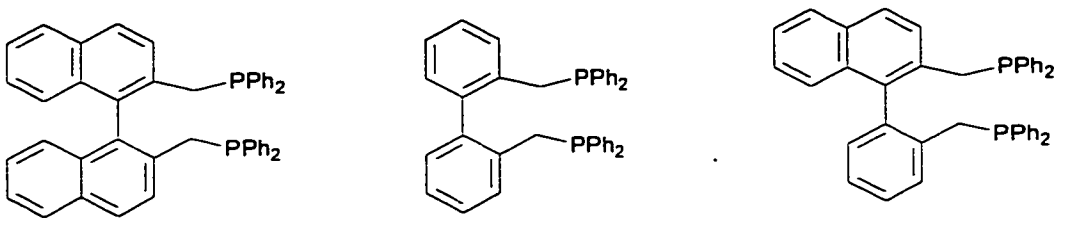
Synthesis of the Core

3.1 Introduction

Many dendrimers have been synthesised with metal containing moieties at the periphery, in the centre or in the arms of the dendrimer. The potential of these organometallic dendrimers as catalysts has been widely exploited. Dendrimer type catalysts have been investigated with metal containing terminal groups.[1-6] This may be advantageous in creating a very active catalyst by increasing the number of active sites present in the catalyst, however, the active sites must be accessible to the substrate for catalysis to occur. Recent studies indicate significant backfolding of dendritic wedges,[7] and presumably many metal containing sites are buried in the arms of the dendrimer and inaccessible to the substrate. So far organometallic terminated dendrimers, which have been used as catalysts, have exhibited lower activities than their monomeric analogues.[2] Leaching of metal from the dendrimer is also a problem encountered by terminal functionalised dendrimers.[8] This could be due to the exposed metal sites. If however, the catalytic site was encapsulated on the inside of the dendrimer, this may lead to a reduction of leaching and interesting stereochemical and/or regioselective results. With this in mind, the aim of this study was to prepare a dendrimer with a phosphine at its core. The reasons why a phosphine core was chosen will be discussed in the next section.

3.1.1 Bisphosphines as ligands

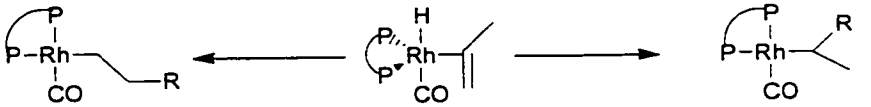
We were interested in preparing dendrimeric catalysts for use in hydroformylation reactions. This reaction is the biggest homogeneous catalytic reaction in industry to date. Every year hundreds of papers are published dealing with new types of ligands and modifications to old ones. In the late 1960's, Wilkinson introduced the phosphine-stabilised rhodium complex, $HRh(CO)_2(PPh_3)_2$, as a hydroformylation catalyst.[9;10] However, it was not until the mid 1970's that a phosphine was used in an industrial process.[11] The control of regioselectivity is extremely important in this reaction. For short, straight chain alkyl alkenes the economic interest lies with the linear aldehyde. One of the biggest uses of this reaction is the hydroformylation of propene to *n*-butanal, which is an important intermediate in the synthesis of plasticizers. For aryl alkenes, the desired product is the branched aldehyde, which are useful intermediates in drug and fertiliser synthesis. Bisphosphines were introduced in the 1980's, but at first did not exhibt the same high regioselectivity as triphenylphosphine. Eastman Kodak developed a series of bisphosphines based on NAPHOS (**46**); BISBI (**47**) and PHENAP (**48**) (Figure 3.1) which showed excellent regioselectivity for the hydroformylation of 1-hexene, affording *n*-heptanal as the major product.



NAPHOS **46** BISBI **47** PHENAP **48**

Figure 3.1 Eastman Kodak's bisphosphines

Exactly how the ligand affects the regioselectivity of the reaction is still very much under discussion, and there appears to be many factors which govern the regiocontrol. The step that is believed to control the regioselectivity is insertion of the alkene into the Rh-H bond of the five-coordinate species, H(alkene)Rh(CO)L_2 (**49**) to give either a primary or secondary alkyl complex, (alkyl)Rh(CO)L_2 (**50**) (Scheme 3.1). The intermediate **49** is generally thought to exist in a trigonal bipyramidal geometry.



50b **49** **50a**

Scheme 3.1 Insertion of an alkene into a rhodium intermediate

After carbon monoxide insertion and reductive elimination, intermediate **50a** leads to the branched aldehyde and **50b** to the linear aldehyde. This step is largely irreversible in the case of straight chain alkenes. In the case of styrene, the insertion of the alkene into the Rh-H bond appears to be reversible in some instances.

Therefore, the geometry of the 5-co-ordinate species, **49**, is vital in the determination of the regioselectivity. In turn, this geometry is governed by the arrangement of the five co-ordinate species formed before the insertion of the olefin. This species is thought to exist in two different forms, axial-equatorial and equatorial-equatorial (Figure 3.2).

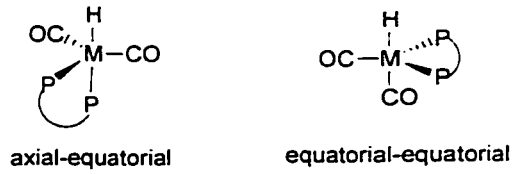


Figure 3.2 Proposed geometery of the bisphosphine trigonal bipyramidal intermediate

Casey introduced the bite angle model,[12] "The natural bite angle is the preferred chelation angle determined only by the ligand backbone constraints not metal valence angles." The bite angle of the bisphosphine aids in the determination of whether it occupies two equatorial sites in the trigonal bipyramidal intermediate or an equatorial and an axial site. Casey and coworkers investigated electronically comparable bisphosphines with varying bite angles; $Ph_2PCH_2CH_2PPh_2$ (DIPHOS) with a bite angle near 90°, and BISBI (Figure 3.1, **47**) with a bite angle near 120°. For the hydroformylation of 1-hexene, the percentage of linear aldehyde produced appears to increase with natural bite size. The reason postulated is that these larger bisphosphine ligands exist primarily in the equatorial-equatorial conformation, due to their large

bite size, and that this geometry favours formation of the linear aldehyde. van Leeuwen and coworkers[13] agree that the natural bite angle does affect regioselectivity but not due to the control over the chelation mode. In fact, they suggest that an increase in bite angle increases the steric bulk around the rhodium centre which results in the formation of the sterically less demanding straight chain intermediate. Despite these predictions, many other factors can affect the regioselectivity, including the ligand/metal ratio, electronic and steric effects of the ligand and the partial pressures of the gases. As bisphosphines are important in the regioselective control of hydroformylation, we attempted to prepare a dendrimer with a phosphine core, which we hoped would be a useful ligand.

3.2 Synthesis of a phosphine core

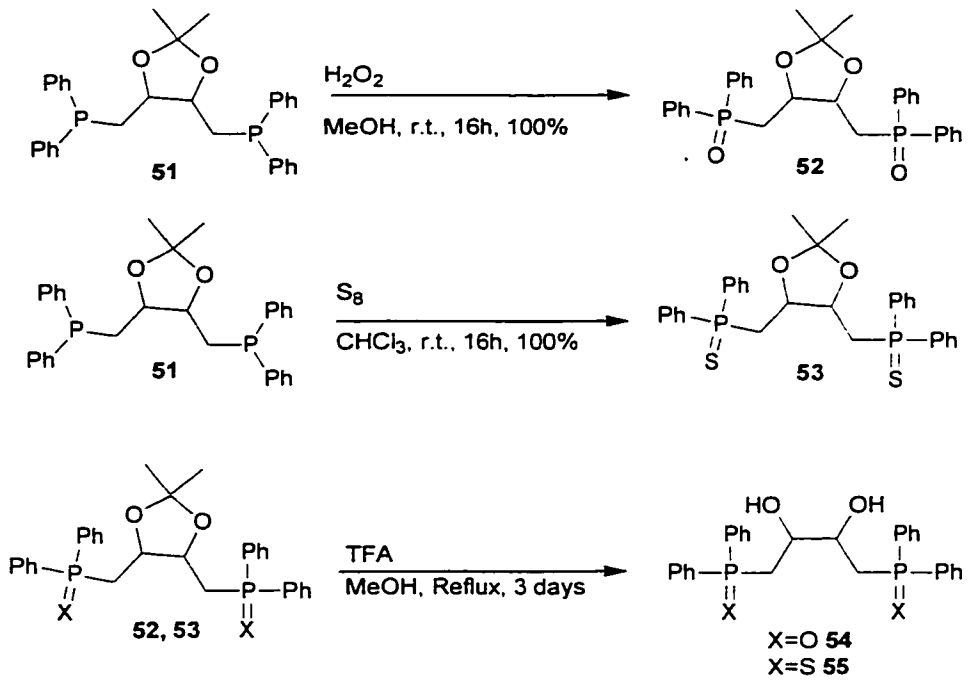
To introduce the phosphine moiety as part of a starting material might prove to be advantageous in the synthesis of the phosphine-containing core. The phosphine could be protected at the beginning and deprotected at an ensuing part of the preparation. In addition, using a known previously employed catalyst as a core compound would be a logical starting point, and is a method that Seebach followed.[14] With this idea in mind, an appropriate starting compound was chosen, 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP) (**51**)

(Scheme 3.2). This compound had been used many times as a ligand in metal catalyzed hydroformylation reactions since the early 1970's.[15]

3.2.1 Synthesis employing DIOP (2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane) (51)

The phosphine **51** was protected as both the phosphine oxide (**52**) and phosphine sulfide (**53**)[16;17]. The isopropylidene group was then subsequently removed under acidic conditions to give the alcohols, **54** or **55**. A sodium hydride mediated alkylation with methyl bromoacetate, ethyl bromoacetate or *t*-butyl bromoacetate was effected.[a] Extremely complicated mixtures were attained, which included monoaddition products. Since the reactions were not clean, the reaction mixtures were difficult to purify due to the polar nature of the starting material and the products.

[a] Appendix 3.1



Scheme 3.2 Modification of DIOP ligand

3.3 The introduction of a phosphine moiety

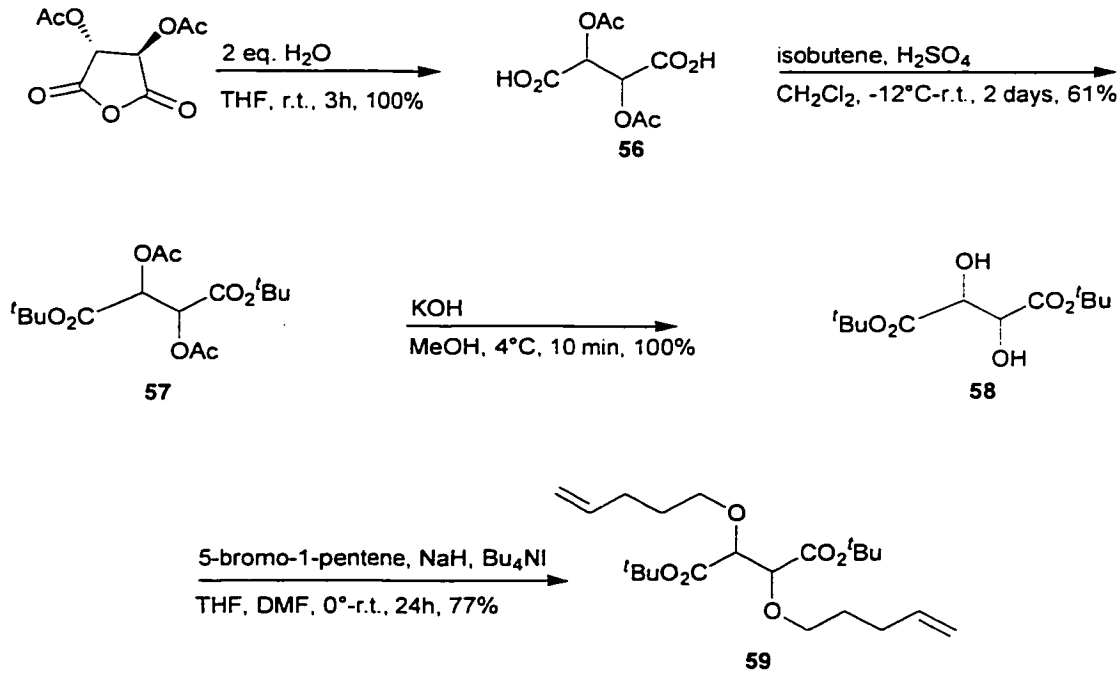
Due to the low yields and purification problems, the introduction of the phosphine early into the synthesis was reconsidered. Consequently, the preparation of the core containing a functional group that could be transformed to a phosphine was attempted.

There are many ways of introducing a dialkyl or diaryl phosphine species.[18] A few of the more common ways were investigated. Secondary or tertiary phosphines can be prepared from a halide, by the addition of a primary or secondary phosphine. Also, phosphines can be formed by the radical addition of

diphenylphosphine across an alkenyl or a double bond. Addition of the radical occurs at the least substituted carbon. If an amine is present in the starting compound a phosphinite can be added to form more complicated phosphine oxides.

3.3.1 Synthesis of alkene 59

Our initial strategy was to form an alkene which could be converted to a phosphine under radical conditions. Therefore, a short synthesis towards a compound containing an alkene was carried out. Scheme 3.2 illustrates how alkene **59** was formed starting from diacetyl tartaric anhydride (Scheme 3.3).

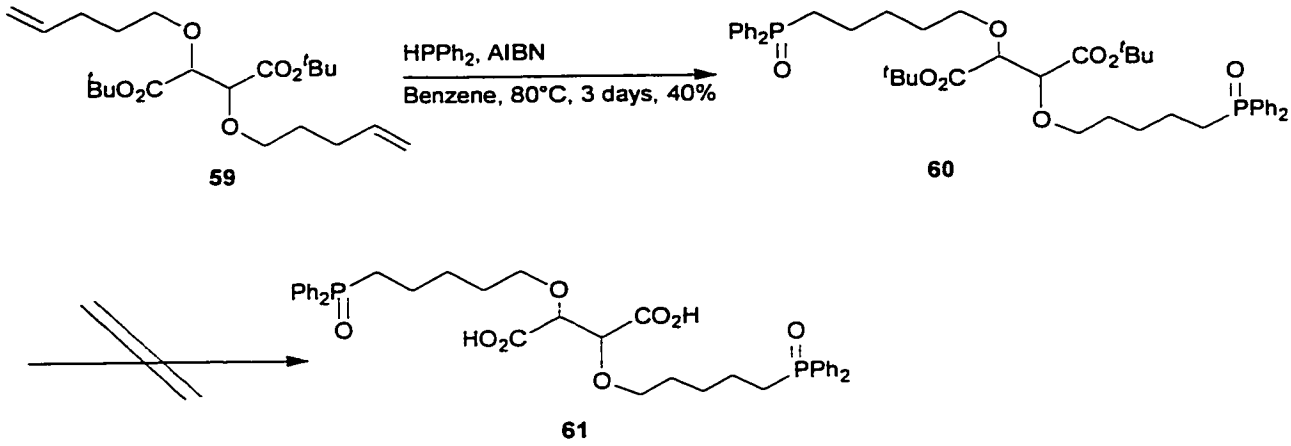


Scheme 3.3 Synthesis of alkene 59 from diacetyl tartaric anhydride

After aqueous hydrolysis of diacetyl tartaric anhydride, dicarboxylic acid **56** was treated with isobutene under acidic conditions for 2 days. 2,3-diacetoxy-succinic acid di-*tert*-butyl ester (**57**) underwent base hydrolysis to remove the acetyl groups in quantitative yield. Addition of 5-bromo-1-pentene to alcohol **58** was carried out, using sodium hydride to deprotonate the diol, and gave the desired product **59** in good yield (77%).

3.3.2 Radical addition of diphenylphosphine

Previously in the literature, both alkynes and activated alkenes had been subjected to diphenylphosphine addition using 2,2'-Azobisisobutyronitrile (AIBN) as a radical initiator.[19;20] We wanted to add diphenylphosphine across an unactivated alkene, as it turned out, the yield was not very high in this case (Scheme 3.4).



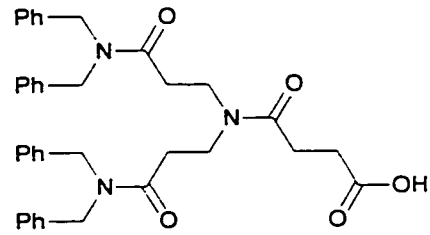
Scheme 3.4 Radical phospination of alkene

After three days in refluxing benzene, with a catalytic amount of AIBN present, the phosphine oxide was recovered in 40% yield, following purification. The oxidation of the phosphine may have taken place either during the reaction or the purification. Unfortunately, the *t*-butyl ester protecting group was extremely difficult to remove. The ester was treated with an excess of trifluoroacetic acid, and also subjected to phase transfer conditions using hydrogen bromide, neither of which removed the *t*-butyl group, or led to decomposition. A similar alkene to compound **59** was synthesised, except with an ethyl ester protecting group. However, even under comparable reaction conditions as in the *t*-butyl ester case, the yields were very low and it was considered unproductive to continue along to this route.

3.4 Formation of an amine terminated core

3.4.1 Synthesis of (4-*tert*-Butoxycarbonylamino-2,3-dihydroxy-butyl)-carbamic acid *tert*-butyl ester (65)

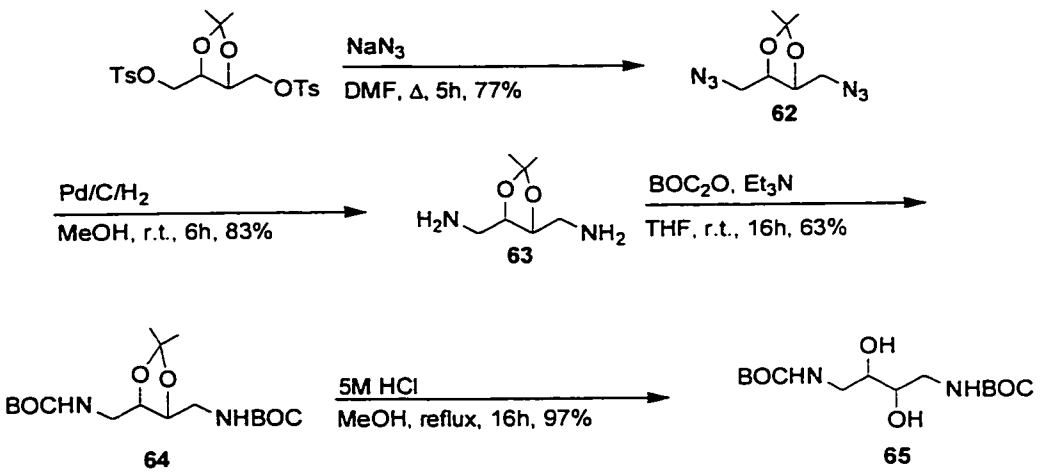
It was thought that the carboxylic acid terminated dendron **38** (Figure 3.3), described in chapter 2, would be suitable for coupling to an amine terminated core unit.



38

Figure 3.3 Dendron 38

In parallel to the previous scheme of reactions the synthesis began to build a core unit which contained an amine and also an alkene in the same molecule (Scheme 3.5). An alkene would be profitable in terms of addition of a phosphine.



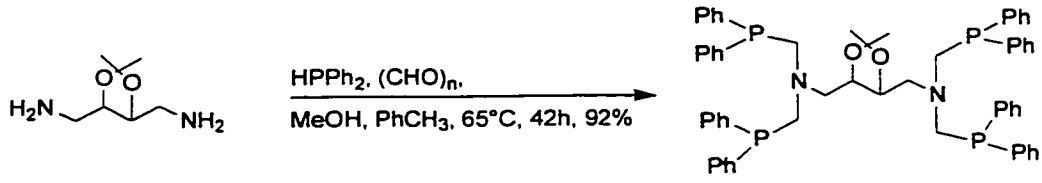
Scheme 3.5 Formation of amine terminated core

1,4-di-*O*-tosyl-2,3-*O*-isopropylidene-*D*-threitol was treated with sodium azide in refluxing dimethylformamide, to give the bis-azide, **62**, in 77% yield.[21] Hydrogenation of **62** using 10% palladium on carbon and hydrogen gas afforded the diamine **63** in 83% yield. The primary amine was protected under basic conditions with di-*t*-butyl dicarbonate, and subsequently the isopropylidene protecting group was removed under acidic conditions. The diol was then available for alkylation using the same method that been previously employed.

3.4.2 Alkylation of diol 65

Alkylations of diol **65** were carried out using phase transfer conditions, and also by employing sodium hydride to deprotonate the two alcohol groups. These reaction conditions were low-yielding and it was thought a more profitable approach would be to view amine **63** slightly differently. The nitrogens, instead of the

oxygens, could be the site for alkylation with a view to phosphination. This was carried out by the *in situ* formation of diphenylphosphanyl methanol from paraformaldehyde and diphenylphosphine. Reetz and coworkers[6] and then Majoral and coworkers[22] both used this reaction to add a diphenylphosphino group to an amine and introduce a methylene between the phosphorus and the nitrogen (Scheme 3.6). This compound would have a restricted bite angle and potentially favour the formation of the branched aldehyde during hydroformylation. Diphenylphosphine and paraformaldehyde were mixed together in toluene at reflux for an hour before the addition of amine **63**, to form the intermediate alcohol, diphenylphosphanyl-methanol. The resulting phosphine was allowed to oxidise to aid in the purification because the excess diphenylphosphine was removed by repeated washings with diethyl ether. The two main impurities in this reaction were diphenylphosphine and diphenylphosphanyl methanol. Both compounds proved difficult to remove using Kugelrohr distillation or column chromatography, both led to decomposition of the product. An alternative approach to maintain an oxygen free synthesis was carried out, followed by sublimation of the diphenylphosphine and diphenylphosphanyl methanol proved to be successful affording the phosphine in good yield.



63 66

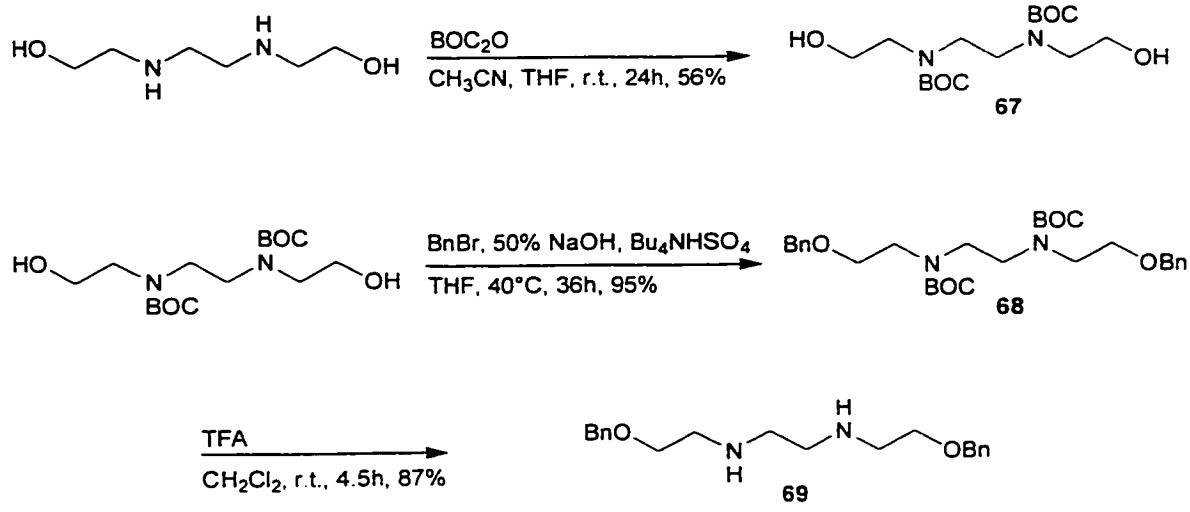
Scheme 3.6 The phosphination of 4,5-di(aminomethyl)-2,2-dimethyl-[1,3]dioxolane (63)

3.5 Manipulation of *N,N'*-bis(2-hydroxyethyl)-ethylene diamine as a potential core unit

Bisphosphines are certainly the main choice when considering a ligand for hydroformylation. Their natural bite angle may indeed affect the regioselectivity (see above) but the rigidity of the backbone of the ligand must also be considered. Casey[12] proposed that not only is a large bite angle necessary for the ligand to assume an equatorial-equatorial (e-e) geometry (Figure 3.2), but also flexibility about the backbone of the ligand could induce the ligand to assume the e-e conformation. Therefore, the synthesis of a symmetrical starting material where two phosphines can be introduced at close proximity to each other, and also to two amino groups, was undertaken. It was thought the amino groups in the molecule could be exploited in P-N complexation to the metal, which has been investigated by other groups.[23-27] Therefore *N,N'*-bis(2-hydroxyethyl)-ethylenediamine was chosen as a starting material for the synthesis of an alkene which could be subsequently phosphinated.

3.5.1 Synthesis of alkene 70 for radical phosphination

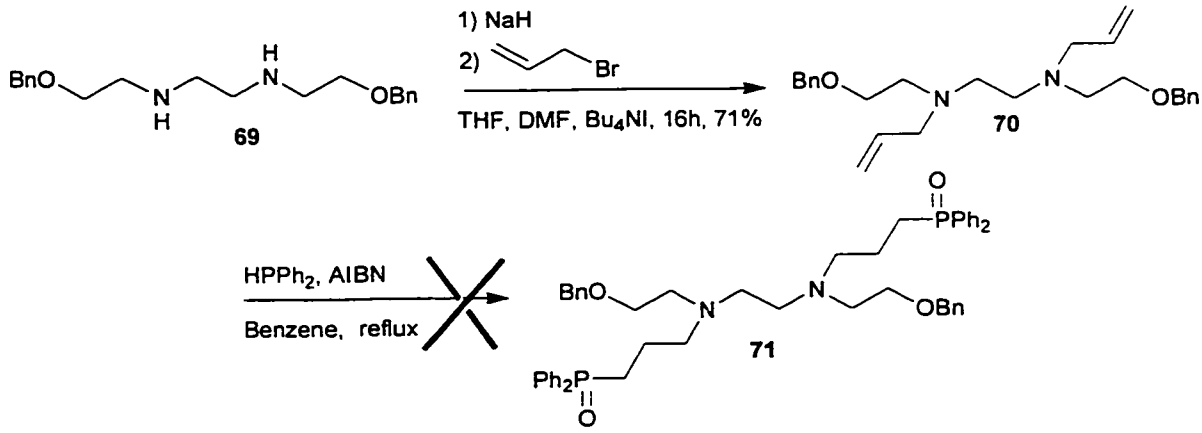
The amino groups of *N,N'*-bis(2-hydroxyethyl)-ethylenediamine were protected as their BOC derivatives in 56% yield (Scheme 3.7). The primary alcohols were protected using benzyl bromide, employing phase transfer conditions, and then the BOC groups were removed using trifluroacetic acid, both steps occurring in excellent yield.



Scheme 3.7 Synthesis of *N,N'*-Bis(2-benzyloxyethyl)-ethane-1,2-diamine (69)

Deprotonation using sodium hydride followed by alkylation employing allyl bromide introduced two alkene moieties to amine **69**, in 71% yield (Scheme 3.8). Radical phosphination was then carried out using AIBN as a radical initiator and diphenylphosphine. This phosphination however, was ineffectual, suggesting the

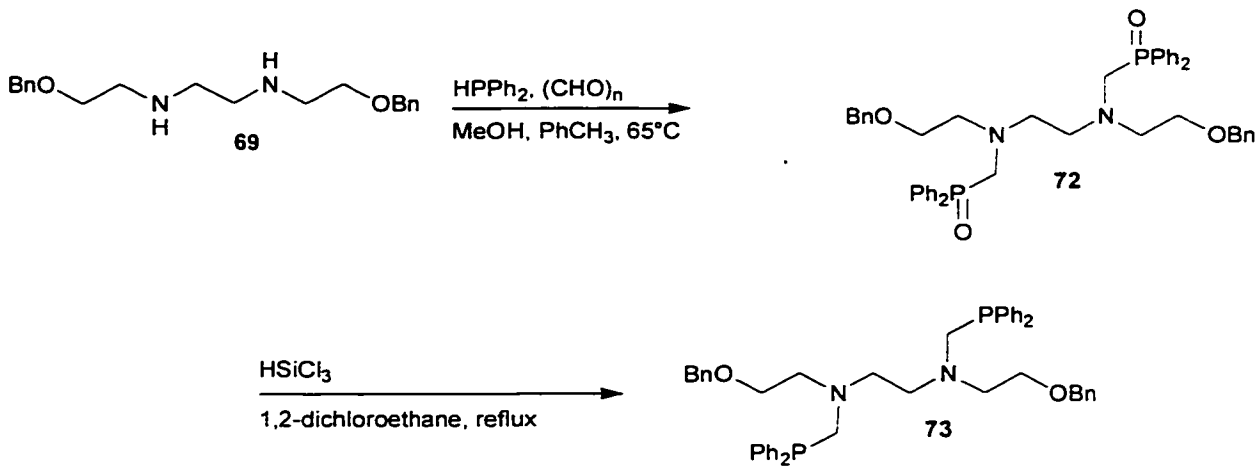
alkene was less reactive than the previous alkenes employed. Due to the nature of the radical and the reaction, slight changes in the electronics of the double bond could adversely affect the reaction. The diphenylphosphino radical is said to be stable and persistant in nature, which affects its reactivity. In addition, due to the size of the radical, an encumbered alkene could further retard the reaction. The radical addition reaction of diphenylphosphine is known to be reversible under some conditions, therefore any one or all of these reasons could adversely affect the outcome of the reaction. Another method of phosphination was carried out.



Scheme 3.8 Phosphination under radical conditions

3.5.2 Phosphination by *in situ* generation of diphenylphosphanyl-methanol

Instead of a three carbon spacer between the phosphine and amine on molecule **71**, a phosphine with just a methylene between them was synthesised. This allows for P-P co-ordination with a bite size of nine (Scheme 3.9).

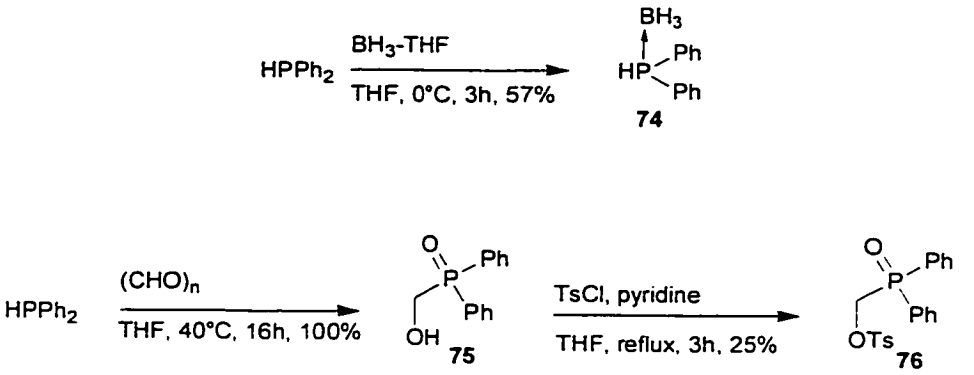


Scheme 3.9 Suggested addition of diphenylphosphanyl methanol

Primarily, the diamine **69** was phosphomethylated using a method similar to that employed in scheme 3.6. This method, at first involved the oxidation of the phosphine and then the purification of the compound as its phosphine oxide (**72**). An additional step was then required to reduce the phosphine oxide, which was possible with trichlorosilane. However, purification of the phosphine oxide was not as facile as anticipated. The first solution tried was to address the problem of the excess diphenylphosphine required to promote this reaction, which would possibly reduce the purification problems. Two derivatives of diphenylphosphine thought to be more reactive were synthesised.

3.5.3 Alternative phosphinating reagents

The two derivatives of diphenylphosphine synthesised were; diphenylphosphine borato complex (**74**) and toluene-4-sulfonic acid diphenyl-phosphinoylmethyl ester (**76**) (Scheme 3.10).



Scheme 3.10 Derivatisation of diphenylphosphine

The diphenylphosphine borato complex (**74**) was formed, in 57% yield, by the addition of borane-tetrahydrofuran to diphenylphosphine at 0°C. Toluene-4-sulfonic acid diphenyl-phosphinoylmethyl ester (**76**) was synthesised by the tosylation of the corresponding primary alcohol **75**. The yield of the tosylation was only 25%, due to side reactions, the formation of phosphorus sulfide compounds, and the reaction was not optimised due to the lack of activity in the subsequent reaction. The diphenylphosphine borato complex was used as a substitute for diphenylphosphine in the reaction of amine **69** to form phosphine oxide **72** (Scheme 3.9), and also to form phosphine oxide of phosphine **66** (Scheme 3.6). Tosylate **76** was used in the same

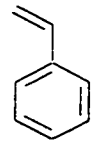
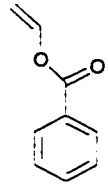
reactions as the borato complex **74** as a substitute for both diphenylphosphine and paraformaldehyde. With both of these sets of reactions, yields were low, and it appears that any modification to diphenylphosphine decreases its reactivity. Gilbertson *et al.*[28] reported similar findings when using diphenylphosphine oxide, diphenylphosphine sulfide and the diphenylphosphine borane in the phosphination of vinyl triflates. The alternative procedure employed with amine **66** was eventually used. This meant converting amine **69** to phosphine **73** under inert conditions, followed by sublimation of the impurities affording phosphine **73** in 75% yield.

3.6 Complexation of phosphines and catalytic activity

3.6.1 Complexation of phosphine 66

Attempts to complex a small amount of phosphine **66** to chlorodicarbonyl rhodium(I) dimer led to immediate decomposition. The same phosphine was then complexed to dicarbonyl acetylacetonato rhodium(I). The resulting complex appeared not to decompose as readily as the previous one. However, it was not isolated but used directly for the hydroformylation of several olefins. To compare this complex, hydroformylation experiments were also carried out using the parent metal complex e.g. chlorodicarbonyl rhodium(I) dimer and adding the phosphine separately to the mixture to allow the active species to form *in situ* (Table 3.1).

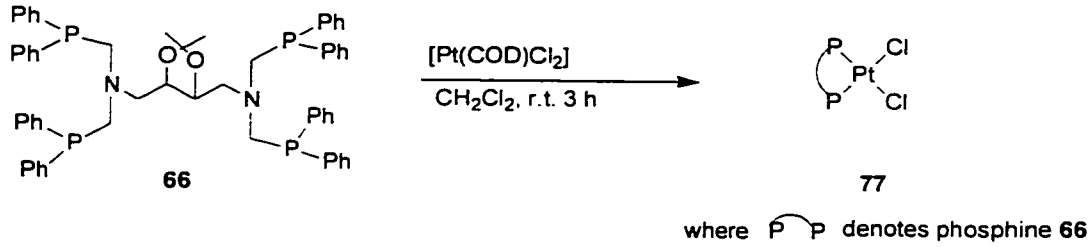
Table 3.1 Hydroformylation employing phosphine 66

Run No.	Substrate[a]	%Rh to substrate	Temp (°C)	Pressure[b] (psi)	Time (h)	Conversion[c] (%)	(% branched aldehyde)[d]
1[e]		2	60	600	20	80	93
2[f]		2	60	600	8	75	94
3[f]		2	60	600	20	95	95
4[g]		2	60	600	8	88	93
5[g]		2	60	600	20	100	93
6[f]		2	50	1000	20	66	100[h]
7[f]	1-octene	2	60	600	13	67	40

[a]2 mmol of substrate and 2 mL of chloroform were used in each reaction. [b]Total pressure of a 1:1 mixture of CO and H_2. [c]Determined by GC/^{1}H NMR. [d] Determined by GC/^{1}H NMR, the remainder of which was linear aldehyde. [e]Rh(acac)CO_2-phosphine **66** complex. [f]Rh(acac)CO_2, phosphine **66** added separately. [g]$[Rh(CO)_2Cl]_2$ and phosphine **66** added separately. [h]15% hydrogenated product.

The differences in the figures resulting from the various catalyst preparations are subtle. The catalyst formed when employing $[Rh(CO)_2Cl]_2$ (entry 4) appears to be more reactive than Rh(acac)CO_2 (entry 2), although the Rh(acac)CO_2 complex is slightly more selective in nature. When this complex was used for the hydroformylation of 1-octene, the linear aldehyde was the major product.

In order to aid with characterisation, dichloro(1,5-cyclooctadiene) platinum (II) was complexed to phosphine **66** (Scheme 3.11). In this way, it was hoped to promote crystallisation.



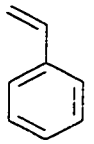
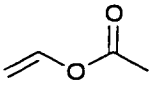
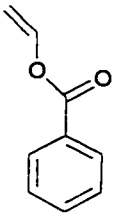
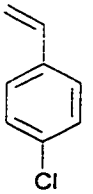
Scheme 3.11 Complexation of phosphine 66

After washing with pentane a white crystalline solid was recovered. Due to the large coupling constant present between the platinum and the phosphorus, (J=3396 Hz) a *cis*-configuration was suspected.[29] The mass spectrum suggested that indeed four diphenylphosphino groups had been added to the primary amine.

3.6.2 Complexation of phosphine 73

The same procedure of complexation for phosphine **66** was carried out with phosphine **73**. This phosphine underwent complexation with both dichloro(1,5-cyclooctadiene)platinum(II) and chlorodicarbonyl rhodium(I) dimer. Again, the rhodium species was not isolated; it was used, as generated, for the hydroformylation of various alkenes (Table 3.2).

Table 3.2 Hydroformylation employing phosphine 73

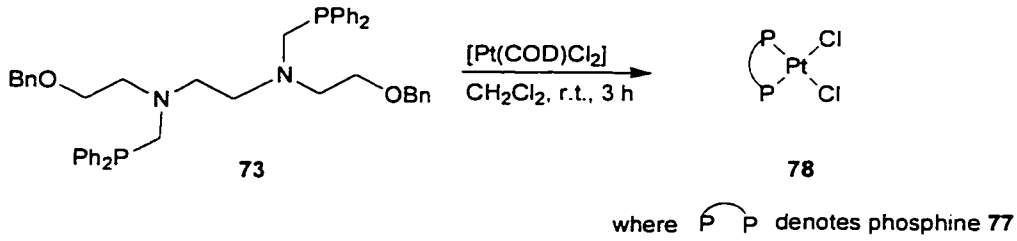
Run No.	Substrate[a]	%Rh to substrate	Temp (°C)	Pressure[b] (psi)	Time (h)	Conversion[c] (%)	(% branched aldehyde)[d]
1		2	65	600	21	100	95
2		1.5	45	600	20	99	96
3		2	40	500	20	88	95
4		1	40	600	20	60	96
5		2	50	800	20	10	e
6		2	70	1000	20	36	92
7	1-octene	1.5	70	600	20	92	40
8		2	50	1000	20	99	94
9		2	50	600	20	91	96

[a]2 mmol of substrate and 2 mL of chloroform were used in each reaction. [b]Total pressure, a 1:1 mixture of CO and H_2. [c] Determined by GC/^{1}H NMR. [d] Determined by GC/^{1}H NMR, the remainder of which was linear aldehyde. [e]Only branched product was detectable on GC, and by ^{1}H NMR due to low conversion.

This phosphine-rhodium complex appears to give reasonable results for the hydroformylation of several olefinic substrates. At low temperatures, pressures and concentration of rhodium the catalyst still gave good conversion and selectivities.

However, this complex appears to be unstable, since as the reaction mixture is removed from the autoclave it can be seen that the mixture varies between a dark red and black colour. This may suggest some decomposition during the hydroformylation reaction.

The phosphine **73** was complexed to a platinum species again, in the hope that this would aid in characterisation of the compound. The initial ^{31}P NMR of the complex indicated that there was one symmetrical compound present in over 70% purity. Due to the large Pt-P coupling constant it appears that the *cis* complex **78** is the major product (Scheme 3.12). While this complex was being recrystallised in order to attain a crystal structure, it decomposed.



Scheme 3.12 Complexation of phosphine 73 with dichloro(1,5-cyclooctadiene)platinum(II)

3.7 Conclusion

It appears that the *in situ* formation of diphenylphosphanyl methanol is an effective method for the phosphomethylation of primary or secondary amines. The

two phosphines **66** and **73** successfully acted as ligands when complexed to a rhodium(I) species, and both stabilised the rhodium metal during the hydroformylation reaction of several olefins. It can be proposed that the tetra-phosphine, **66**, appeared to stabilise the rhodium to a greater extent during these reactions than phosphine **73**. There was less evidence of decomposition seen after the completed reactions involving phosphine **73**. The tetra-phosphine **66** also contains an acetonide functionality which could be removed under acidic conditions, allowing access to a diol, which could be potentially useful to attach this ligand to a dendrimer.

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4

Connection of Dendrons to the Core

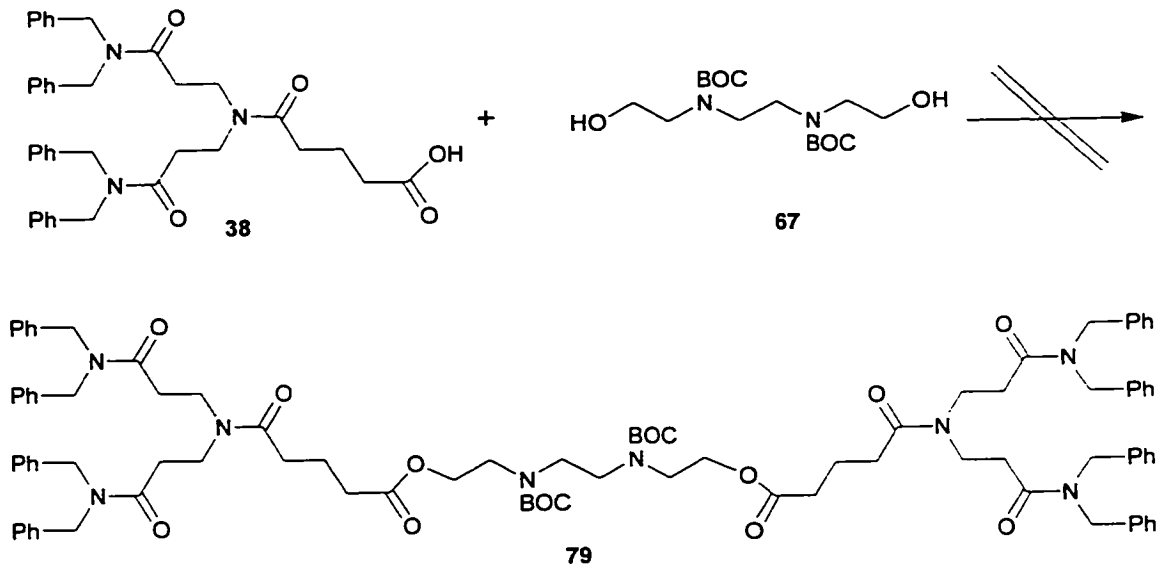
4.1 Introduction

The preliminary synthetic strategy was to couple the dendrons, prepared in chapter 2, with the alcohol, bis-1,2-{*tert*-butoxycarbonyl-(2-hydroxyethyl)-amino-ethane (**67**) as the core. Subsequent to the connection being formed, it was envisaged that the *t*-butoxycarbonyl (BOC) group could be removed under acidic conditions, thus allowing phosphination to be carried out to give the desired synthetic target.

4.2 Syntheses involving dendrons based on *N,N*-dibenzyl-3-(2-dibenzylcarbamoyl-ethylamino)-propionamide

4.2.1 Connection of carboxylic acid 38 with alcohol 67

Initially, we investigated the coupling of 4-[bis-(2-dibenzylcarbamoyl-ethyl)-carbamoyl]-butyric acid (**38**) with alcohol **67** to hopefully give the diester **79** (Scheme 4.1). Various sets of conditions and reagents were employed in this synthesis, all of which involved either activating the carboxylic acid or alcohol to provide a better leaving group to facilitate nucleophilic attack.



Scheme 4.1 The attempted formation of diester (79)

The carboxylic acid (**38**) was treated with trifluoroacetic anhydride in benzene,[a(1)] to form a mixed anhydride, this intermediate was then treated with alcohol **67**. The diester was not formed as expected, however, it was discovered that the major product, was formation of only one ester bond, compound **80** (Figure 4.1). The monoaddition product, **80**, was taken and re-reacted with carboxylic acid **38** under the same conditions, but no further reaction was observed.

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[a] Appendix 4.1

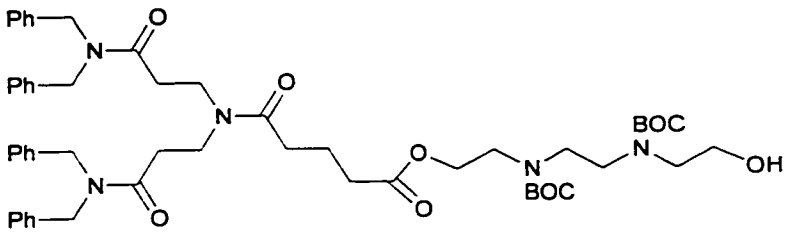
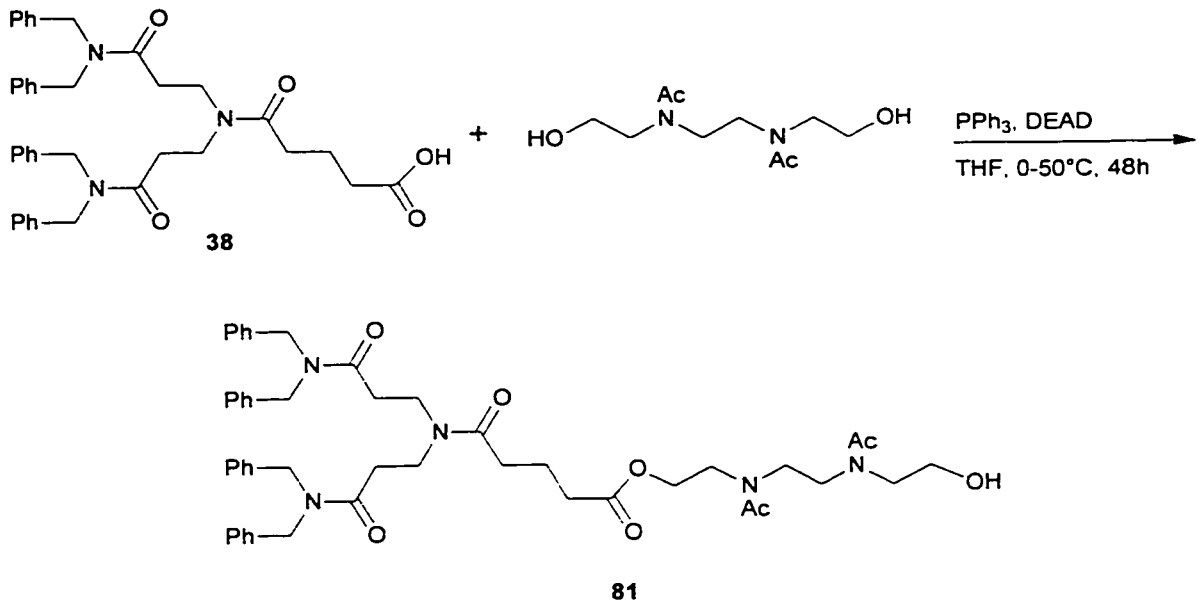


Figure 4.1 The mono-addition product (80)

Alternative reagents were also investigated for the reaction of alcohol **67** and carboxylic acid **38**. For example, dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) were employed several times.[2] Despite changing the conditions and the ratio of the reactants present, the main product again was **80**. The third set of reactants utilised was triphenylphosphine and diethylazodicarboxylate (DEAD).[3] Usually esters are readily formed under Mitsunobu conditions. The alcohol is activated by a complex generated *in situ* from DEAD and triphenylphosphine, and then upon addition of a carboxylic acid, the ester is usually formed. However, with our reactants, the formation of the second ester bond did not occur. This may be due to the appearance of compound (**80**) in solution, once the first ester bond is formed, the terminal alcohol functionality could be far more hindered than is initially expected. For example, the 3-dimensional structure may contain internal hydrogen bonding due to back-folding. The reaction was repeated when the bulky BOC amine-protecting group on compound (**67**) was exchanged for a less sterically demanding acetimide group. The reaction was carried out using

triphenylphosphine and DEAD, but again afforded the mono-addition product (Scheme 4.2).[b]

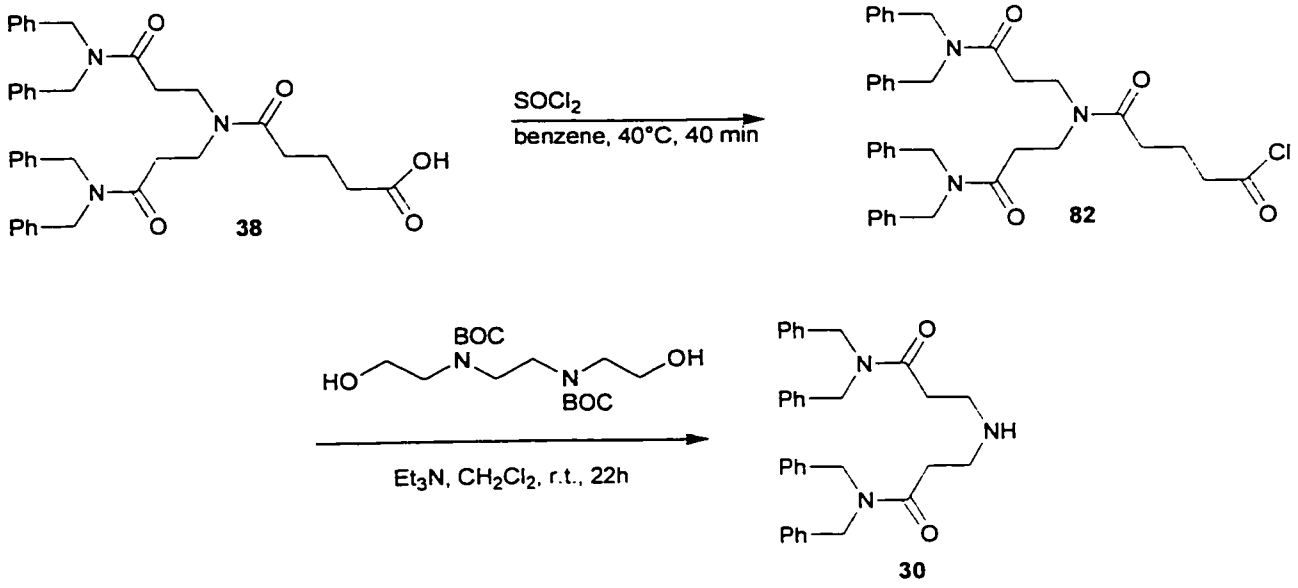


Scheme 4.2 Reaction of carboxylic acid 38 with an alternative alcohol

[b] Appendix 4.2

4.2.2 Formation of acid chloride 82

It was hoped that the acid chloride of carboxylic acid **38** might react more readily with alcohol **67** to give the di-addition product. Carboxylic acid **38** was modified by thionyl chloride and the acid chloride was formed *in-situ*. A small amount of the reaction mixture was removed and the presence of the acid chloride **82** was confirmed by IR spectroscopy. Alcohol **67** was then introduced into the reaction medium.[c] This synthetic route proved to be unsuccessful again and the main product from the reaction was amine **30**, a decomposition product of **38** (Scheme 4.3).



Scheme 4.3 Modification of carboxylic acid 38 to an acid chloride

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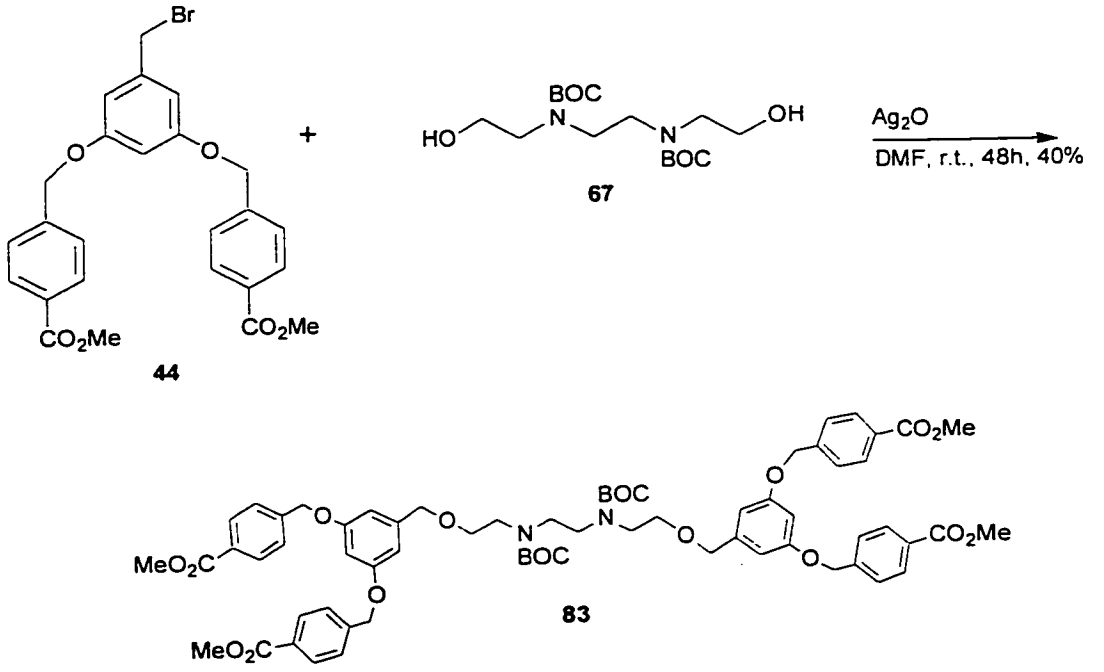
[c] Appendix 4.3

4.3 Reactions of Poly(benzylether) based dendrons

4.3.1 Ether synthesis

Since all the synthetic results using the poly-amide based dendrimer system were unsuccessful, we investigated a poly(benzylether) based system. [3,5-Bis-(4-methylester-benzyloxy)-benzylbromide] (**44**) (see chapter 2) was treated with silver oxide in dimethylformamide[4] along with alcohol **67** to afford compound **83**, but only in 40% yield (Scheme 4.4). Alternatively, when phase transfer conditions were used,[5] complicated mixtures of products were formed involving hydrolysis of the methyl esters groups present.



Scheme 4.4 Synthesis of amine 83

It was not obvious why these reactions were low yielding. The two reactants, bromide **44** and alcohol **67**, in the ether synthesis were separately subjected to different reaction conditions, with simpler substrates (Scheme 4.5). Bromide **44** was reacted with 1,6-hexanediol employing the silver (II) oxide conditions and again a mixture of products resulted,[d] but the expected ether was not detected. When alcohol **67** was subjected to benzyl bromide under phase transfer conditions the expected product was produced in high yield.

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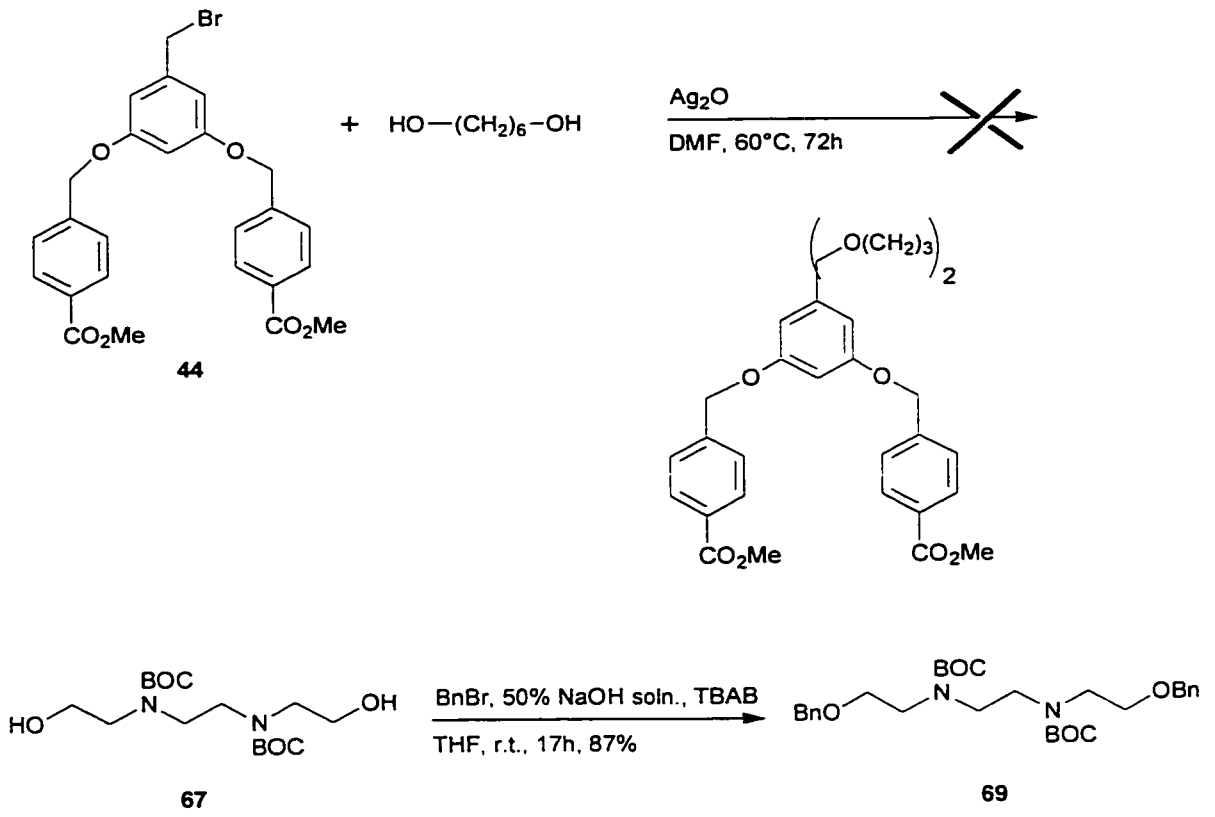
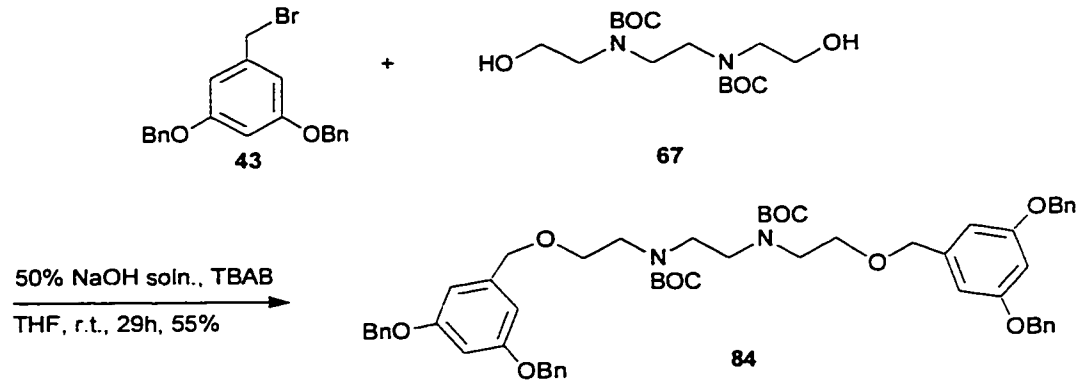
[d] Appendix 4.4



Scheme 4.5 Investigation of PTC method

It appeared that without the added complication of the methyl ester groups, in the *para* position on the benzene rings, that an alternative potentially higher yielding synthesis could be pursued. Therefore, the synthesis was modified to remove these groups (Scheme 2.4) and a substitute ether synthesis was investigated (Scheme 4.6).

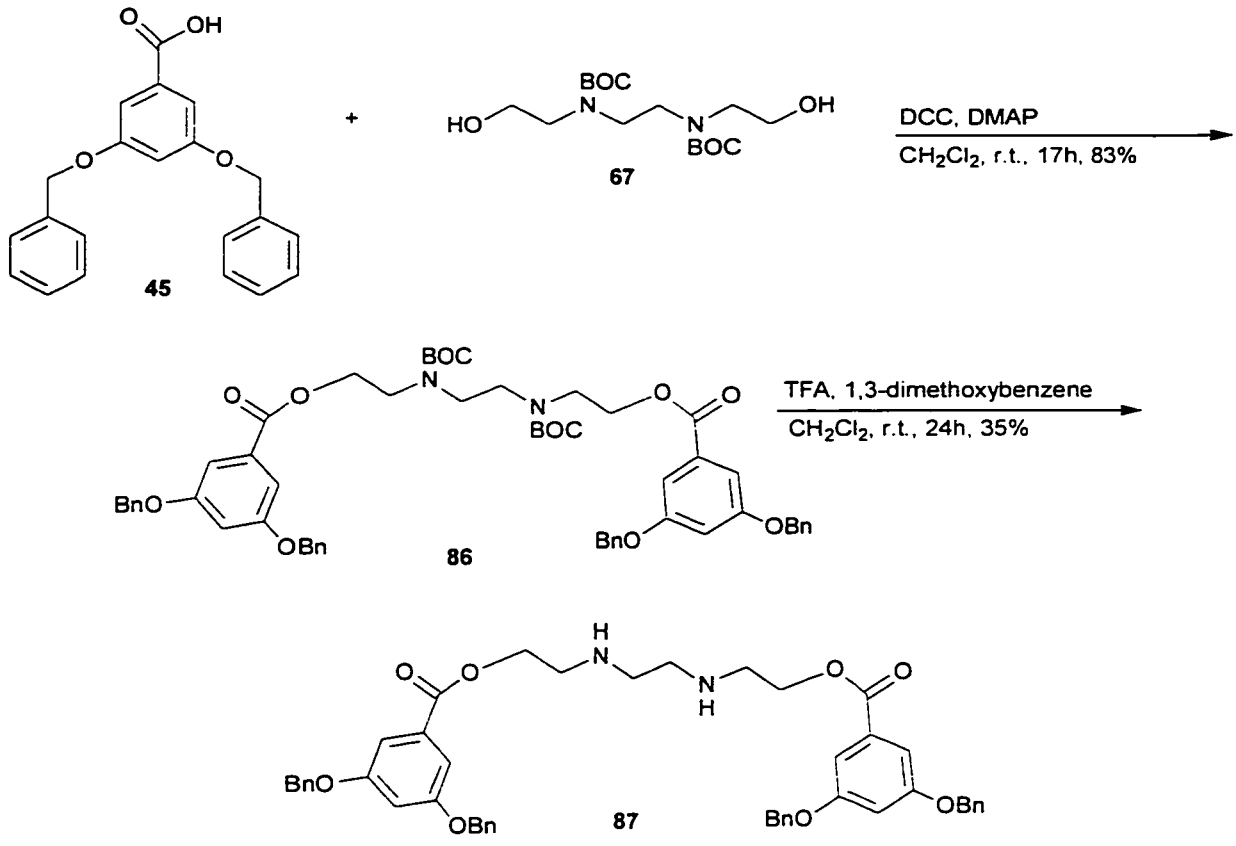


Scheme 4.6 Preparation of amine 84

The 55% yield of the reaction for the connection of alcohol **67** and bromide **43** was slightly better than the previous attempt with silver oxide. However, when trifluoroacetic acid was present, for the removal of the BOC group, compound **84** underwent decomposition. Due to the moderate yield encountered for the synthesis of **84**, a slight modification in the synthesis of the reactants was looked at.

4.3.2 Connection of 3,5-bis(benzyloxy)benzoic acid with alcohol 67

Instead of the formation of an ether bond to connect the core to the dendron, an ester bond was considered due to the wide range of reagents available for this type of reaction.[6] Ester **45** (prepared in Chapter 2) was reacted with the alcohol **67**, using the coupling reagent dicyclohexylcarbodiimide and DMAP, to give ester **86** in good yield (Scheme 4.7).



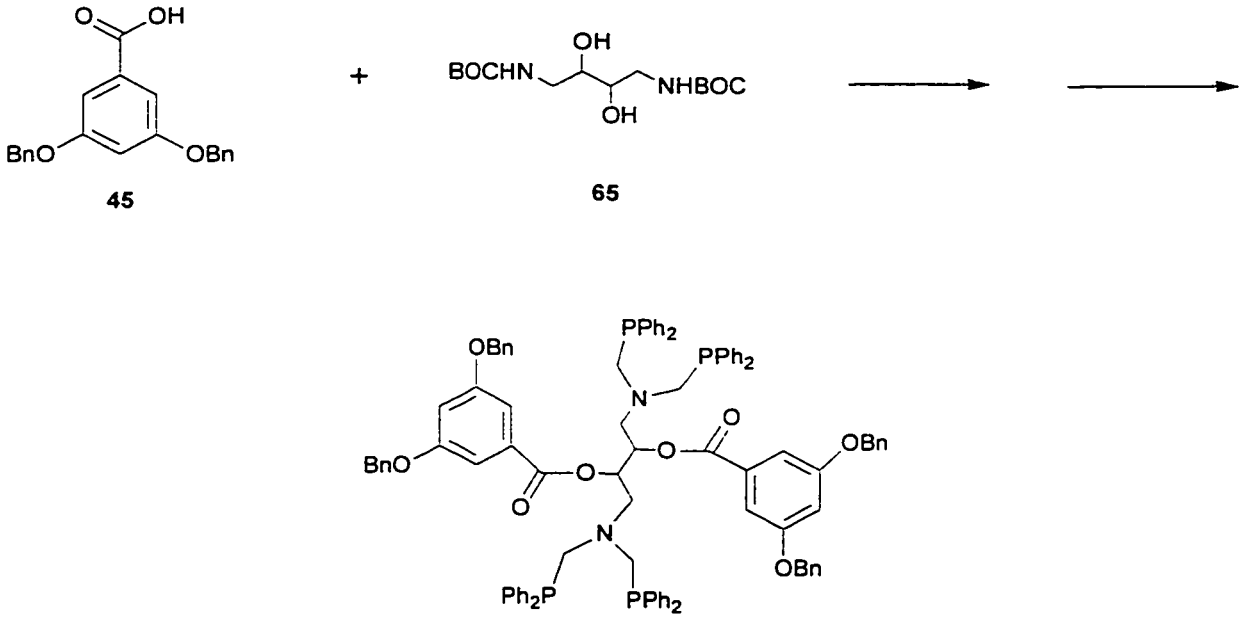
Scheme 4.7 Formation of ester 87

Under acidic conditions the BOC groups were then removed, providing free secondary amino groups in compound **87** for phosphination. The deprotection of the BOC moieties in amine **84** had led to decomposition of the product, therefore, when the same reaction was carried out to deprotect the BOC groups in amine **86**, 1,3-dimethoxybenzene was added to the reaction. The 1,3-dimethoxybenzene is thought to act as a scavenger for the *tert*-butyl carbocation.[7]

4.4 Conclusions

The synthetic pathway to form amino compound **87** appeared to be the most efficient, despite the low yield for the BOC deprotection step. Unfortunately, the scope of this project did not allow for the optimization of the next reaction step, which was the phosphination of the amino groups in compound **87**. A similar substrate, **69**, was phosphinated successfully using a method which could be applied in the future to compound **87**.

A future synthesis could include the addition of amine **65** to 3,5-(benzyloxy) benzoic acid (Scheme 4.8).



Scheme 4.8 Synthesis of potential phosphine ligand

Chapter 4 References

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5

(Diphenylphosphinoyl)phenylmethanol-A Phosphine Oxide Ligand for Hydroformylation Reactions

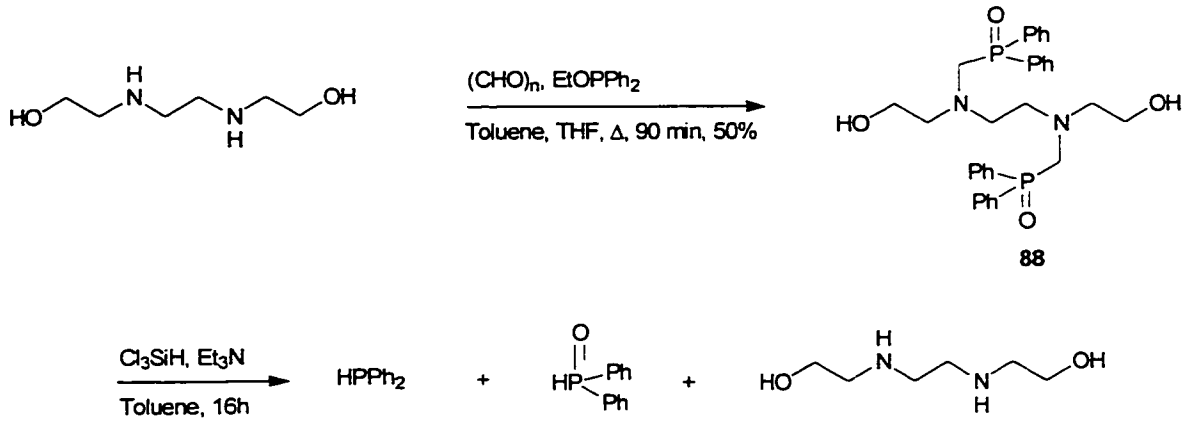
5.1 Introduction

As discussed in chapter 3, amine **69** was phosphomethylated by paraformaldehyde and diphenylphosphine (Scheme 3.9). In order to remove the excess diphenylphosphine after the reaction, the first method used was to wash the mixture repeatedly with diethylether and the phosphine was oxidised to phosphine oxide **72**. This aided with the separation. Then the reduction of phosphine oxide **72** (Scheme 3.9) was carried out using trichlorosilane and triethylamine. When an aliquot of the reaction mixture was removed, the ^{31}P NMR showed that only one product was present. After the work up procedure, the ^{31}P NMR of the product became more complicated, peaks indicating that some diphenylphosphine and its oxide were present, had appeared. The presence of diphenylphosphine was presumably due to decomposition of the product. In order to investigate whether this was a general decomposition pathway, an alternative synthesis of a modified phosphine oxide (**72**) was carried out.

5.1.1 Synthesis of analogues *N,N'*-bis-(2-benzyloxyethyl)-*N,N'*-bis-[(diphenylphosphanyl)methyl]ethane-1,2-diamine (73)

Komakibara *et al.* described the synthesis of phosphine oxides by reacting phosphinites with various carbonyl compounds.[1] Utilising a similar synthetic route,

N,N'-bis(2-hydroxyethyl)-ethylenediamine was heated to reflux with paraformaldehyde and ethyl diphenylphosphinite to afford compound **88**. The latter was then subjected to phosphine oxide reduction conditions of trichlorosilane and triethylamine (Scheme 5.1).

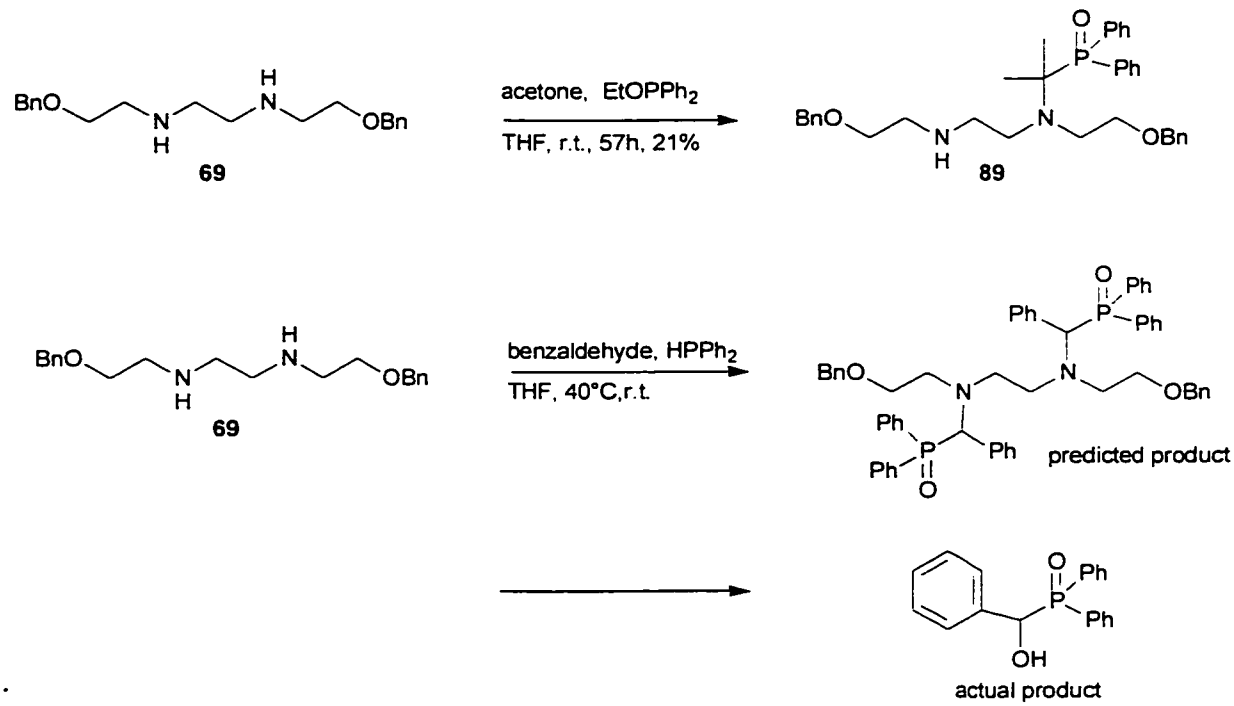


Scheme 5.1 An alternative introduction of a (diphenylphosphinoyl)methylene moiety

The phosphine oxide, **72**, appeared to be less stable than its benzyl ether protected analogue. Reduction of this compound gave complete decomposition to diphenylphosphine. The mechanism for this decomposition was investigated further.

5.1.2 Modification of the phosphination process

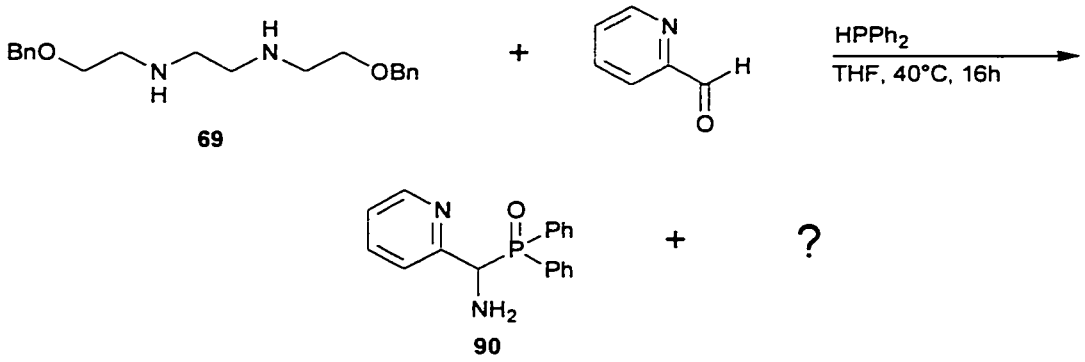
The methylene group, adjacent to the phosphino group of compound **72**, could potentially be modified in order to see whether decomposition could be avoided. Two separate reactions were carried out to modify this methylene unit. One approach involved substituting paraformaldehyde for acetone in one synthesis and benzaldehyde in a second synthesis (Scheme 5.2).



Scheme 5.2 Modification of phosphine oxide 72

Unfortunately, neither reaction afforded the predicted products. The reaction of diamine **69** with acetone and ethyl diphenylphosphinite gave only mono addition leaving a free secondary amine in compound **89**. Perhaps more interesting was the

reaction of benzaldehyde with diphenylphosphine and amine **69**, which resulted in the formation of a large amount of a white crystalline solid. Also, two repeat reactions were carried out replacing the benzaldehyde by 2-pyridine carboxaldehyde, and by *p*-anisaldehyde. A solid state structure of this white crystalline solid, **90**, was determined by a single crystal X-ray analysis (Figure 5.1) of the product from the reaction of **69** with 2-pyridinecarboxaldehyde (Scheme 5.3). The structure was proposed to be *C*-(diphenylphosphinoyl)-*C*-pyridin-2-yl-methylamine.



Scheme 5.3 Addition of 2-pyridine carboxaldehyde to amine 69

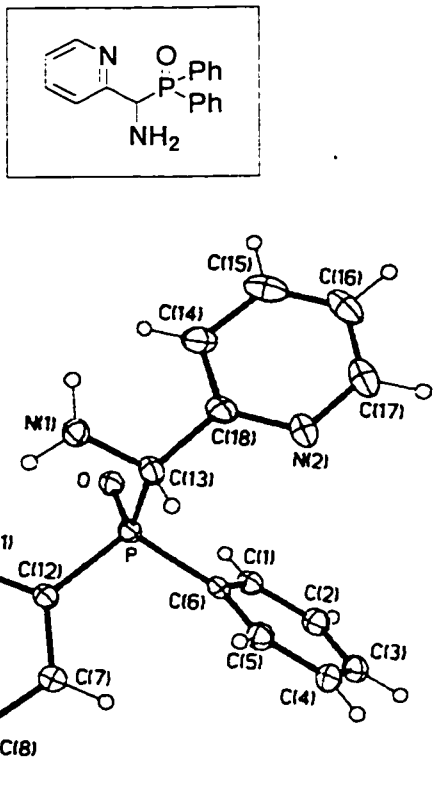
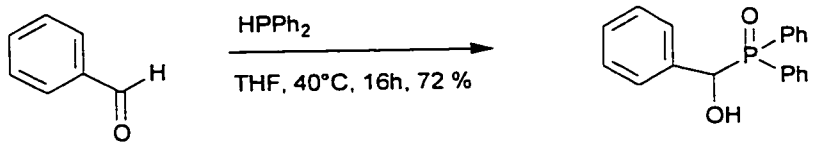


Figure 5.1 ORTEP of the proposed structure of compound 90

How could this class of compound have been formed? The mechanism for dealkyation at one of the nitrogen atoms in amine **69** appeared unfeasible. The ^{1}H NMR spectra of all of these compounds were extremely simple (appendix 5.1). They consist of multiple peaks in the aromatic region, a signal assigned to the CH adjacent to the phosphorus, and a broad singlet. Initially, the broad signal was assigned as a primary amine, however, it could also be due to a secondary alcohol. Electrospray ionization mass spectrometry was also used to decipher the structure of the product. This method often gives several parent ions clustered together; {(M), (M+1), (M+2)} and therefore, this did not give unequivocal evidence for either of the proposed

structures. The data collected for the crystal of **90** was re-examined and the crystal structure was recalculated. If the data was refined as a secondary alcohol rather than a primary amine, a similar R-factor was attained. The temperature factors for a nitrogen atom and an oxygen atom are similar depending on the quality of the crystal data, and, therefore, it was difficult to categorically determine the nature of the product by x-ray analysis. The reaction of benzaldehyde and diphenylphosphine, without the bis-amine present, confirmed the structure of the compound (Scheme 5.4). Without the amine, the product gave the same spectral data as the unknown compound. A crystal structure of the product from the reaction below revealed the same structure as the analogous product in figure 5.1 (Figure 5.2).



91

Scheme 5.4 Synthesis of (diphenylphosphinoyl)phenyl-methanol 91

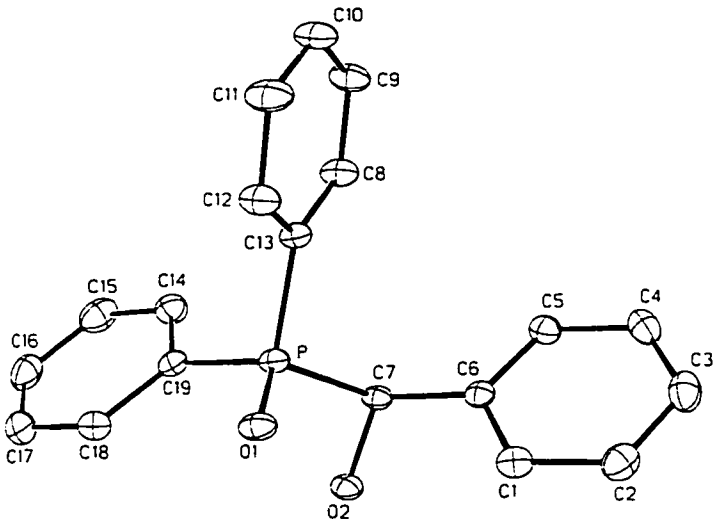


Figure 5.2 ORTEP of the proposed structure of 91

5.2 Hydroformylation using (diphenylphosphinoyl)phenyl-methanol (91)

The potential of (diphenylphosphinoyl)phenyl-methanol as a ligand for rhodium catalysed hydroformylation reactions was investigated. First a search of the previous literature in this area was conducted.

5.2.1 Previous examples of phosphine oxides as ligands

Mixed bidentate ligands have been examined in the past for both hydroformylation and carbonylation reactions, including, ligands containing P-S, P-

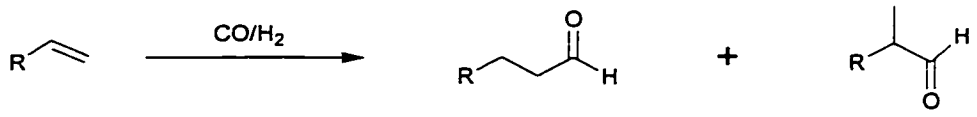
N, N-S, N-O and P-O moieties.[2-7] In fact mixed phosphine-phosphine oxide ligands have shown to be useful in catalytic systems for the carbonylation of methanol.[8] Also, more recently, mixed aminophosphine oxide complexes have outperformed their phosphine analogues in the hydroformylation of aryl alkenes.[9] However, the use of monodentate phosphine oxides has received little attention. Indeed it has been thought that phosphine oxides decrease the rate of hydroformylation and consequently have not been further investigated.[10]

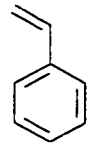
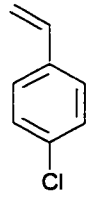
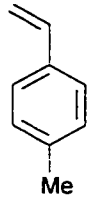
5.2.2 Hydroformylation of styrene

Hydroformylation reactions were investigated, using many substrates, employing (diphenylphosphinoyl)phenyl-methanol as the ligand and chloro dicarbonyl rhodium(I) dimer in chloroform. Styrene was used as the model compound for investigating the conditions (Table 5.1). At first, when fairly high temperatures were used, the conversion was high, and after only 2 hours the reaction was almost complete (entry 1). However, high temperatures led to lower regioselectivity. Upon lowering the temperature to 40°C, the conversion dropped to 77% after 20h but a higher branched to linear ratio was attained. For example in entry 6 the ratio is 24:1. When the reaction was conducted under the same conditions, except in the abscence of (diphenylphosphinoyl)phenyl-methanol as the ligand, the conversion was only 2.5%. Substitution of the benzene ring in styrene did not affect either the reactivity or the regioselectivity (entries 11-14). Both *p*-

methylstyrene and *p*-chlororstyrene exhibited excellent branched to linear ratios under the same conditions as were employed for styrene. *p*-Chlorostyrene appeared to be more reactive than styrene, with a higher conversion than styrene at 40°C (entry 12).

Table 5.1 Hydroformylation of Styrene and Derivatives

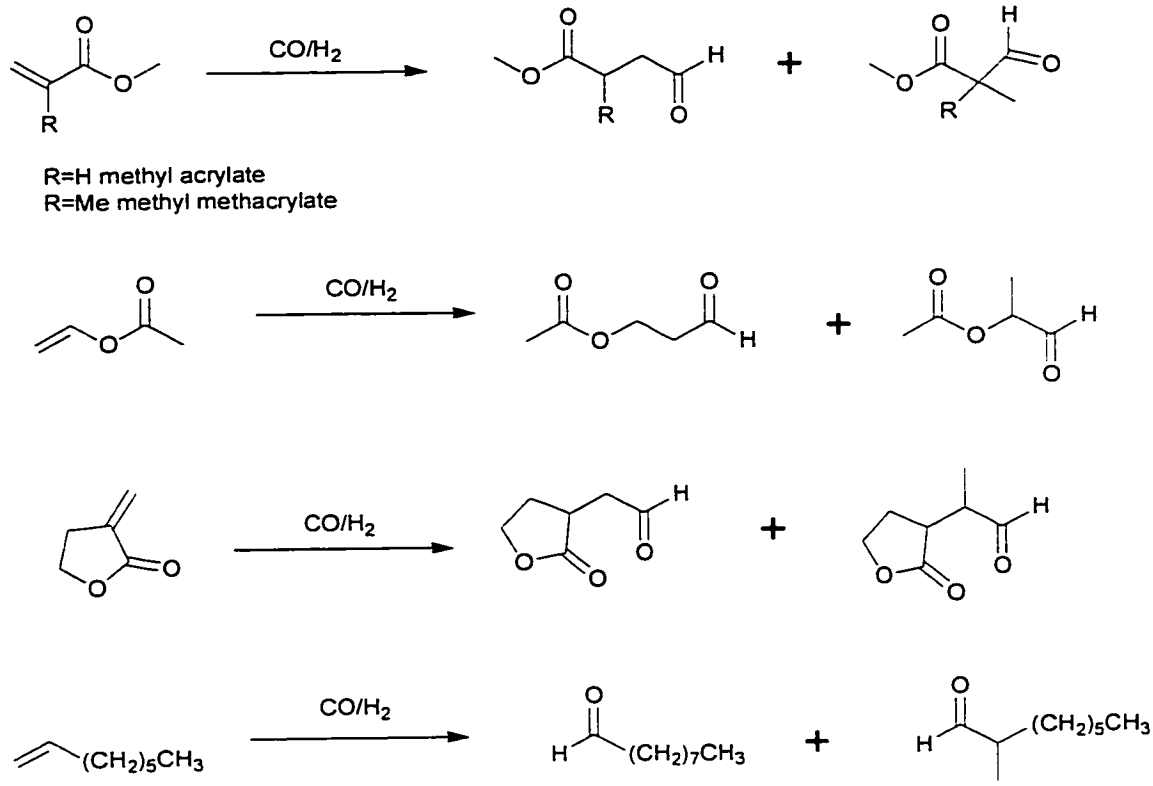


Run No.	Substrate[a]	Temp (°C)	Pressure[b] (psi)	Time (h)	Conversion[c] (%)	(% branched aldehyde)[d]
1		90	600	2	98	80
2		80	600	6	90	80
3		50	600	20	90	95
4		40	600	20	75	96
5		40	600	26	90	96
6		40	600	20	77	96
7		35	600	18	16	97
8		40	600	43	90	90
9		25	600	20	8	97
10[e]		40	600	20	2.5	95
11		60	600	22	99	94
12		40	600	20	93	97
13		60	600	20	99	93
14		40	600	20	74	95

[a]All experiments were run with 2 mmol of substrate, 2 mL of chloroform, 0.012 mmol of $[Rh(CO)_2Cl]_2$ and 0.024 mmol of ligand. [b]Total pressure for 1:1 mixture of CO and H_2. [c]Determined by ^1H NMR/GC [d]Determined by ^1H NMR/GC, remainder of which is linear aldehyde. [e]Reaction run without any ligand present.

5.2.3 Hydroformylation of alkyl substituents

(Diphenylphosphinoyl)phenyl-methanol (**91**) did not perform as well in the hydroformylation of straight chain alkyl or cyclic alkenes. The substrates and the proposed products are shown in scheme 5.5.

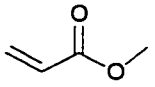
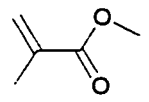
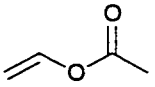
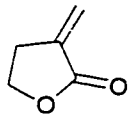


Scheme 5.5 Hydroformylation of alkyl substituents

The results of these hydroformylation reactions are shown in table 5.2. For both methyl acrylate and methyl methacrylate (entries 1-6), only when the amount of phosphine oxide was increased to four times the amount of rhodium were there any

signs of insertion of a formyl group into the olefinic bond of the substrate. The other products were hydrogenation products. With vinyl acetate, as the reactant, the ligand showed little activity. At 600 psi and 40°C, the conversion for vinyl acetate was very low (entry 7). When the temperature and pressure were increased, hydrogenation replaced any hydroformylation taking place. Methylene-butyrolactone (entries 9-11) underwent not only hydrogenation but also isomerisation of the double bond to an internal position, without any signs of aldehyde formation. In the case of 1-octene, the predicted product is *n*-nonaldehyde. Due to electronic effects, the linear aldehyde is preferentially formed. While using (diphenylphosphinoyl)phenyl-methanol as the ligand for the hydroformylation of 1-octene, *n*-nonaldehyde was indeed the major product, however, the regioselective control was poor affording no more than a 60:40 ratio of linear to branched aldehyde (entries 12-14).

Table 5.2 Hydroformylation of alkyl substituents

Run No.	Substrate[a]	Temp (°C)	Pressure[b] (psi)	Time (h)	Conversion[c] (%)	(% branched)[d]
1		60	600	20	11	e
2		60	600	27	8	e
3		80	600	25	27	e
4[f]		60	1000	28	18	Trace
5		55	1000	20	20	e
6		60	1000	20	15	e
7		40	600	22	31	97
8		50	1000	20	44	e
9		50	600	20	97	g
10		100	1000	22	99	h
11		80	1000[i]	20	60	e
12	1-octene	50	600	8	61	43
13		50	600	14	64	46
14		50	600	20	100	40

[a]All experiments were run with 2 mmol of substrate, 2 mL of chloroform, 0.012 mmol of $[Rh(CO)_2Cl]_2$ and 0.024 mmol of ligand. [b]Total pressure for a 1:1 mixture of CO and H_2. [c]Determined by ^1H NMR/GC. [d]Determined by ^1H NMR/GC, remainder of which is linear aldehyde or specified product. [e]only hydrogenated products. [f]4:1 ratio ligand:Rh. [g]79% hydrogenated, 17% isomerised. [h]63% hydrogenated, 37 % isomerised. [i]900 psi of CO, 100 psi of H_2.

5.2.3 Hydroformylation of vinyl benzoate and phenyl vinyl ether

Good regioselectivity was achieved using phenyl containing functional olefins, such as phenyl vinyl ether and vinyl benzoate (Table 5.3). With both of these substrates the regioselectivity is as high as 99% in some cases, favouring the branched aldehyde. For vinyl benzoate (entries 1-5) a minimum pressure of 1000 psi is needed to induce addition to the alkene bond. For phenyl vinyl ether (entries 6-8) a minimum temperature of 60°C is required to keep the regioselectivity at 99%. The alkenes containing aryl substituents certainly give better regioselectivities. This may be due to the formation of the stable organo-rhodium intermediate when the alkene has an aryl group present. The rhodium can be bound to the phenethyl group, in a η^3 fashion, to give a resonance-stabilised intermediate (Figure 5.3).[10] This intermediate can lead to the formation of the branched aldehyde. Presumably, this would explain why there is a strong bias for the formation of the branched aldehyde.

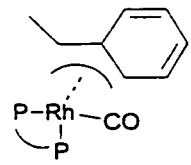
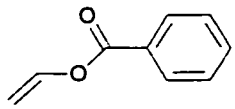
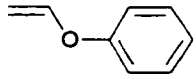


Figure 5.3 Rhodium intermediate

Table 5.3 Hydroformylation of phenyl vinyl ether and vinyl benzoate

Run No.	Substrate[a]	Temp (°C)	Pressure[b] (psi)	Time (h)	Conversion[c] (%)	(% branched)[d]
1		45	1000	15	45	99+
2		45	600	43	50	e
3		50	1000	40	70	99
4		50	1000	75	82	99
5[f]		50	1000	20	100	99
6		60	600	20	100	99
7		40	1000	20	96	93
8		60	1000	20	99	99

[a]All experiments were run with 2 mmol of substrate, 2 mL of chloroform, 0.012 mmol of $Rh[(CO)_2Cl]_2$ and 0.024 mmol of ligand. [b]Total pressure of a 1:1 mixture of CO and H_2. [c]Determined by ^1H NMR/GC [d]Determined by ^1H NMR/GC, remainder of which is linear aldehyde. [e]Mainly hydrogenated product, trace of aldehyde. [f]2:1 ligand :Rh

5.3 Active species

To hopefully gain some insight into the structure of the active species the reaction of diphenylphosphinoyl methanol and chlorodicarbonyl rhodium(I) dimer was investigated. The ligand can possibly co-ordinate to the rhodium solely through the oxygen of the phosphine oxide, or through both the phosphine oxide and the hydroxyl oxygens. A further possibility is that the ligand may be acting as a

monodenate ligand, and more than one molecule could be co-ordinated symmetrically to the rhodium. Low temperature $^{31}P\{^{1}H\}$ NMR suggests that the rhodium is in fact co-ordinating through the oxygen of the phosphine oxide bond (Appendix 5.4). All the signals are singlets with no discernible coupling to rhodium. At -70°C, the room temperature broad singlet at δ 30.9 ppm, splits into two singlets at δ 32.5 ppm and δ 48.9 ppm. This observation suggests that a fluxional process is occurring. These results were compared to those of Grim and coworkers,[11] who have reported a rhodium(I) complex with a phosphine oxide co-ordinated to (1,5-cyclooctadiene)[bis(diphenylphosphinoyl)(diphenylthiophosphinoyl)methanido] rhodium(I)-2-propanol. They observed a similar phenomenon. At room temperature the $^{31}P\{^{1}H\}$ NMR shows a broad singlet at δ 36.2 ppm, however at -50 °C, the singlet splits to give signals at δ 46.3 ppm and δ 26.5 ppm. These results were attributed to the fast exchange between the co-ordination of the phosphine oxide and then the decomplexation to give the uncoordinated phosphine oxide. The excellent regioselectivity demonstrated for certain substrates could be due in part to the lability of this ligand.

5.4 Enantioslective hydroformylation

5.4.1 Previous examples of enantioselective hydroformylation

Chiral diphosphines have been used with platinum(II) dichloride and tin chloride in the enantioselective hydroformylation of arylethenes with high enantioselectivities.[12;13] However, these reactions suffered from low reaction rates due to competitive hydrogenation reactions, and low regioselectivity. Rhodium(I) complexes have been used with both chiral diphosphite and chiral diphosphine ligands, although the enantioselectivites reported were not high.[14] The highest enantioselectivities reported in the literature for the hydroformylation of arylethenes, and in particular for styrene, is with the rhodium(I) (acac) complexes of (*R*)-2-(diphenylphosphino)-1,1'-binaphthalen-2'-yl (*S*)-1,1'-binaphthalene-2,2'-diyl phosphite [(*R,S*)-BINAPHOS].[15;16] When the reaction was carried out at 100 atm of CO/H_2 pressure and at 60°C for approximately 40 hours, 90+% conversion occurred with 90% *iso*-aldehyde and 80-95% ee. More recently, with modifications to the BINAPHOS ligand, these numbers have been improved.

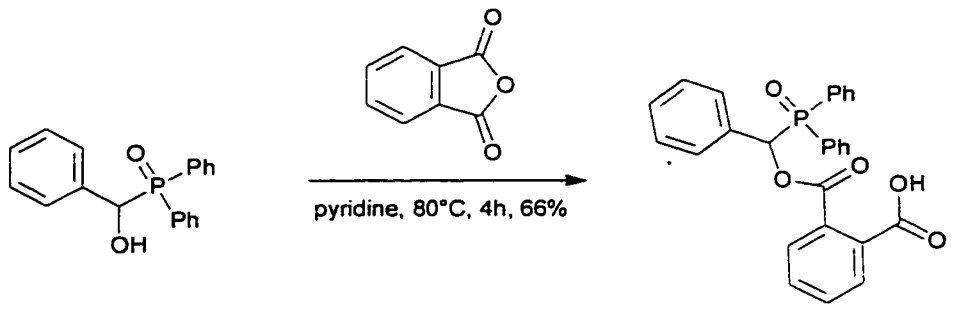
In order to use (diphenylphosphinoyl)phenyl-methanol as a ligand for enantioselective hydroformylation, it had to be first resolved into its enantiomers.

5.4.2 Methods of resolution

The conventional methods of resolution for racemic compounds involve classic techniques such as the synthesis of diastereoisomers of the compound to be resolved. Fractional crystallisation can often be used then to separate this mixture. Chiral chromatography has been used, but this technique is limited not only by the expense of the equipment but also by the limitation of the small amount of compound that can be resolved. Thirdly, kinetic resolution is another important method, this is when either a chiral catalyst or reagent is used in order to preferentially form one enantiomer.[17]

5.4.3 Resolution of (diphenylphosphinoyl)phenyl-methanol

The first method we employed was the formation of diastereoisomers. If the racemic compound has a carboxylic acid group recystallisation can be carried out with a large chiral amine such as brucine, strychnine, morphine or ephedrine.[18] The salts formed are diasteromeric and as such each diastereoisomer should possess different properties including different solubilities. In order to form these diastereoisomers with our racemic alcohol, it was first necessary to form a free carboxylic acid by reaction with phthalic anhydride (Scheme 5.5).



91 94

Scheme 5.5 Addition of phthalic anhydride to alcohol 91

Phthalic acid mono-[(diphenylphosphinoyl)phenylmethyl] ester, **94**, was then reacted with (+)-brucine hydrate (Figure 5.4). The mixture of diastereoisomers unfortunately could not be separated by preferential crystallisation.

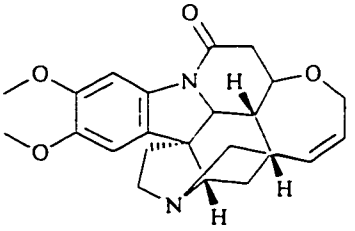
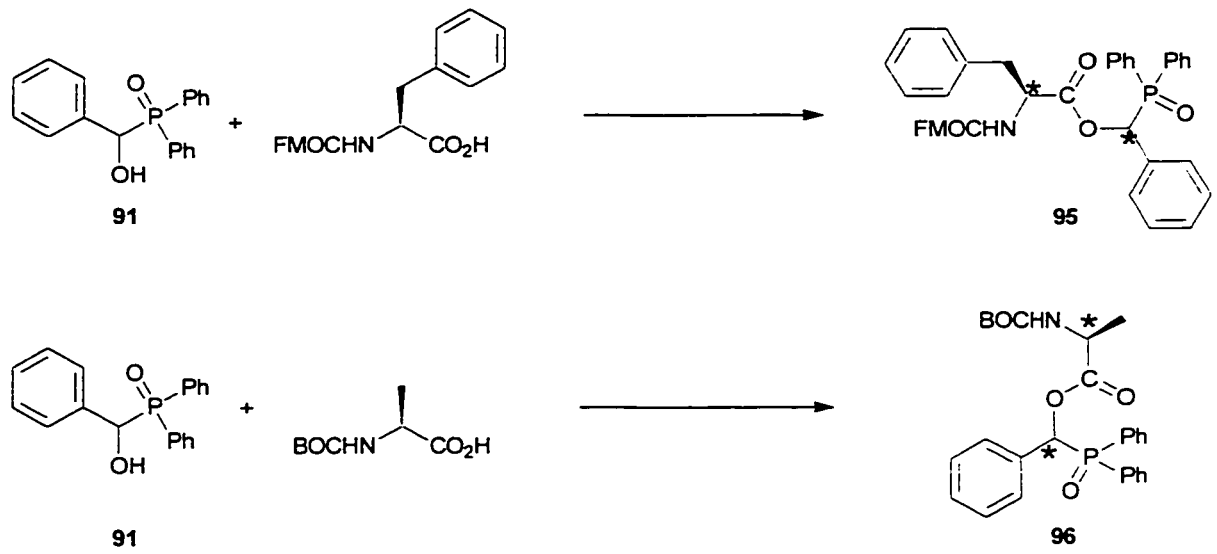


Figure 5.4 Brucine

Another method of separating diastereoisomers, other than forming a salt, is to react the racemic compound with a chiral amino acid. This again forms a mixture of diastereoisomers, which may be separated by fractional crystallisation. (Diphenyl-phosphinoyl)phenyl-methanol underwent coupling reactions both with 2-(9H-fluoren-

9-yl) phenyl alanine and *N*-(*tert*-butoxycarbonyl) alanine[a] (Scheme 5.7). These reactions suffered from low conversion and separation by recrystallisation was impractical.



Scheme 5.6 Formation of diastereoisomers of (diphenylphosphinoyl)phenyl-methanol

Finally, kinetic resolution was investigated. The alcohol (**91**) was reacted with an ester in the presence of an enzyme to affect a transesterification reaction. The first enzyme used was candida cylindacea lipase.[19] This enzyme was used under various conditions; reaction times, concentrations, solvents and using different esters. It appeared that under all of the conditions investigated no reaction occurred, and only the racemic alcohol was recovered. The second lipase used was porcine pancreatic

[a] Appendix 5.5

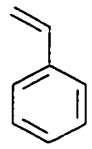
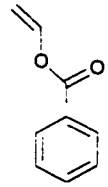
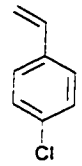
lipase.[20] This enzyme was extremely cheap and the reaction was carried out again with methyl propionate as the ester (Scheme 5.8).

Scheme 5.8 Transesterification of alcohol 91

The polarity of the alcohol hindered the separation of the enzyme cleanly from the substrate and the ester was not isolated completely pure. Also, as the reaction does not go to completion, the enantiomerically pure alcohol was not obtained, as it was mixed with the racemic starting material. Some optically active alcohol was extracted from the mixture and several preliminary hydroformylations were carried out. The alcohol was enantiomerically impure, the optical purity was determined by HPLC and optical rotation (Table 5.4), for the first batch the ligand was 18% enantiomerically pure and in the second batch the ligand was isolated in 23% enantiomeric excess.

5.4.4 Enantioslective hydroformylation using chiral alcohol

Table 5.4 Enantioselective hydroformylation

Run No.	Substrate [a]	Temp (°C)	Pressure [b] (psi)	Time (h)	Conversion[c] (%)	(% branched)[d]	% e.e of branched aldehyde[e]
1[f]		40	600	20	15	95	25
2[f]		60	800	20	22	93	35
3[g]		50	1000	20	99	97	52
4[g]		50	600	20	96	95	23

[a]All experiments were run with 2 mmol of substrate, 2 mL of chloroform, 0.012 mmol of $Rh[(CO)_2Cl]_2$ and 0.024 mmol of ligand. [b]Total pressure always a 1:1 mixture of CO and H_2. [c]Determined by ^1H NMR/GC [d]Determined by ^1H NMR/GC, remainder of which is linear aldehyde. [e]determined by the addition of chiral shift reagent into the ^1H NMR sample or chiral GC. [f]Ligand was 18% enantiomerically pure. [g]Ligand was 23% enantiomerically pure.

These reactions were carried out with two different batches of the resolved alcohol. When the resolved alcohol is used in place of the racemic ligand, the conversions are lower in the case of styrene, although the regioselectivites are comparable to previous results. In the case of vinyl benzoate neither the conversions

nor the regioselectivites are affected by the use of the resolved ligand, this is the same for *p*-chlorostyrene. However, some chiral induction has taken place, despite the ligand being only poorly resolved. This is encouraging for future work if the ligand can be synthesised optically pure. One indication from these reactions is that because the ee's are higher in the first three runs than the enantiomeric purity of the ligand, that the active catalyst is probably not a simple co-ordination of one molecule of the alcohol to the rhodium complex. This could indicate that a dimerisation of the ligand or something else occurs before co-ordination and this leads to the active catalyst.

5.5 Conclusions

Although the synthesis of (diphenylphosphinoyl)phenyl-methanol was not planned, its discovery was fortuitous as it proved a successful ligand in the rhodium-catalysed hydroformylation of a range of substrates. It was particularly effective for alkenes containing aryl substituents, exhibiting high rates and regioselectivites. It is an interesting example of a ligand which is extremely easy to make and which can be handled routinely in air. Also, it provides a novel example of a phosphine oxide ligand, which is useful in hydroformylation reactions. Unfortunately this ligand was problematic to resolve, although the results for enantioselective hydroformylation look promising.

Chapter 5 References

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Experimental Section

General Considerations

Chemicals were purchased from Aldrich, Lancaster and Strem Chemical companies and were used as received unless otherwise noted. All reactions were carried out under an atmosphere of nitrogen unless otherwise stated. During work-up procedures 'drying' refers to drying an organic phase with magnesium sulfate ($MgSO_4$) and 'concentration *in vacuo*' refers to concentration using a Büchi R-114 Rotavapor, unless otherwise stated.

Solvents were purified and dried following standard procedures.[1] Brine refers to a saturated aqueous solution of sodium chloride.

Column chromatography was performed using Silicycle silica gel 60, 230-400 mesh.

Melting points were determined in capillary tubes using a Fisher-Johns melting point apparatus and values are uncorrected.

Infrared spectra were recorded on a Bomem Michelson 100 Fourier transform spectrometer either neat on sodium chloride plates, in a Perkin Elmer sodium chloride sealed solution cell or as potassium bromide pellets. ^{1}H NMR spectra were recorded on Varian Gemini 200 (200 MHz), Varian XL-300 (300 MHz) and Bruker AMX500 (500 MHz) spectrometers. ^{13}C NMR spectra were recorded at 50 MHz (Varian Gemini 200), 75 MHz (Varian XL-300), and 125 MHz (Bruker AMX500). ^{31}P NMR spectra were recorded at 121 MHz (Varian XL-300). ^{1}H and ^{13}C NMR spectra were

reported in ppm and the residual non-deuterated solvent in the deuterated solvents served as a reference. ^{31}P chemical shifts are reported in ppm relative to the external standard 85% H_3PO_4. Chiral shift reagent used in ^{1}H NMR; ytterbium tris[3-heptafluoropropylhydroxymethylene)-(+)-camphorate]. Gas chromatography was carried out using a Hewlett Packard HP 5890 Series II chromatograph. Chiral chromatography carried out using a 10% permethylated β-cyclodextrin column in an Aglient 6890 chromatograph. Elemental analyses were carried out by MHW Laboratories, Phoenix, AZ. or by our analytical laboratories at the University of Ottawa.

FAB mass specrospcopy was carried out on a Kratos Analytical concept 2H and electrospray ionization mass spectrometry was carried out on a Micromass Quattro LC.

High pressure reactions were conducted in stainless steel autoclaves fitted with a screw cap from Parr Instruments.

Computational studies were performed on Apple Power Macintosh 8100/100 using CAChe MOPAC 6.02 software package.

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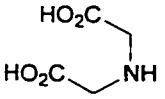
Experimental for Chapter 2

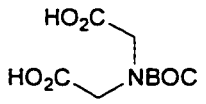
3,3′ Iminopropionic acid (27)



3,3′ Iminopropionic acid was prepared following a literature procedure.[2] ^{1}H NMR (200 MHz, D_2O) δ 3.2 (t, J=8 Hz, 2H, CH_2NH), δ 2.5 (t, J=8 Hz, CH_2CO); ^{13}C NMR (50 MHz, D_2O) 180.2 (*C*=O), 45.9 (*C*H_2NH), 34.6 (*C*H_2CO).

N-(*tert*-Butoxycarbonyl) iminopropionic acid (**28**), bis-(2-dibenzylcarbamoyl-ethyl)-carbamic acid *tert*-butyl ester (**29**) and *N,N*-dibenzyl-3-(2-dibenzylcarbamoyl-ethylamino)-propionamide (**30**) were prepared following literature procedures.[3]

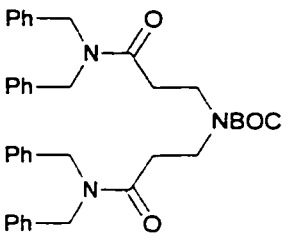
N-(*tert*-butoxycarbonyl) iminopropionic acid (28)



^{1}H NMR (200 MHz, $CDCl_3$) δ 9.3 (br s, 2H, COO*H*), δ 3.45 (br m, 4H, CH_2N), δ 2.5 (br m, 4H, CH_2CO), δ 1.4 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (50 MHz, $CDCl_3$) 174.7

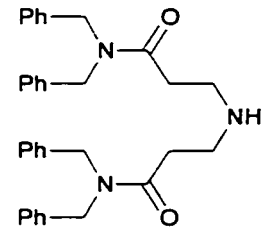
(*C*=OOH), 154.8 (*C*=ONH), 80.59 (*C*$(CH_3)_3$), 49.2 (*C*H_2N), 43.8 (*C*OOH), 27.7 (C(*C*$H_3)_3$).

Bis-(2-dibenzylcarbamoyl-ethyl)-carbamic acid *tert*-butyl ester (29)



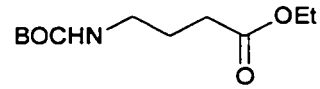
^{1}H NMR (200 MHz, $CDCl_3$) δ 7.4-7.1 (m, 20H, Ar*H*), δ 4.55 (br s, 4H, PhCH_2), δ 4.45 (br s, 4H, PhCH_2), δ 3.56 (t, J=6 Hz, 4H, CH_2N), δ 2.65 (t, J=6 Hz, 4H, CH_2C=O), δ 1.33 (s, 9H, C(C$H_3)_3$); ^{13}C NMR (50 MHz, $CDCl_3$) 171.8, 171.6, 155.3 (*C*=O), 137.2, 137.1, 136.4, 136.1, 129.0, 128.7, 127.7, 127.6, 127.4, 126.5, 126.4 (Ar*C*), 79.7 (*C*$(CH_3)_3$, 49.8 48.2, (Ph*C*H_2), 44.9, 44.6 (*C*H_2N), 32.7, 32.3 (*C*H_2C=O), 28.4 (C(*C*$H_3)_3$).

_N,N_-dibenzyl-3-(2-dibenzylcarbamoyl-ethylamino)-propionamide (30)



^{1}H NMR (200 MHz, $CDCl_3$) δ 7.3-7.1 (m, 20H, Ar*H*), δ 4.56 (s, 4H, PhCH_2), δ 4.37 (s, 4H, PhCH_2), δ 3.20 (t, J=6 Hz, 4H, CH_2N), δ 2.90 (t, J=6 Hz, 4H, CH_2C=O); ^{13}C NMR (50 MHz, $CDCl_3$) 171.0 (*C*=O), 136.2, 135.3, 129.1, 128.7, 128.4, 127.9, 127.6, 126.4 (Ar*C*), 49.7, 48.4 (Ph*C*H_2), 44.6 (*C*H_2N), 29.0 (*C*H_2C=O).

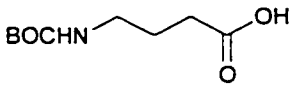
4-*tert*-Butoxycarbonylamino-butyric acid ethyl ester (33)



Ethyl-4-aminobutyrate (200 mg, 1.2 mmol), di-*t*-butyl-dicarbonate (0.41 mL, 1.8 mmol) and triethylamine (0.42 mL, 3.0 mmol) were dissolved in methylene chloride (5 mL) and left to stir overnight at room temperature. The mixture was poured into dichloromethane (10 mL) and water (5 mL) and washed with 1M hydrochloric acid (2 x 5 mL). The combined organic extracts were dried, filtered and concentrated *in vacuo*. Purification was carried out by Kughelrohl distillation (0.1

mmHg, 50°C) which afforded the product as a colourless crystalline solid (0.236 g, 92%). IR (neat, cm^{-1}) 2978, 1735, 1730, 1522, 1366, 1251, 1173; ^1H NMR (200 MHz, $CDCl_3$) δ 4.8 (br, 1H, N*H*), δ 4.0 (q, J=8 Hz, 2H, OCH_2CH$_3$), δ 3.0 (dt, J=8 Hz, 4, 2H, CH_2NH), δ 2.15 (t, J=8 Hz, 2H, CH_2C=O), δ 1.6 (m, 2H, CH$_2$CH_2CH$_2$), δ 1.25 (s, 9H, C(CH_3)$_3$), δ 1.1 (t, J=8 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) 173.5 (EtO*C*=O), 155.8 (C(CH$_3$)$_3$*C*=O) 77.0 (*C*(CH$_3$)$_3$), 60.2 (O*C*H$_2$CH$_3$), 39.7 (*C*H$_2$NH), 31.3 (*C*H$_2$C=O), 28.2 (C(*C*H$_3$)$_3$), 25.1 (*C*H$_2$), 13.9 (OCH$_2$*C*H$_3$); FAB HRMS calcd for $C_{11}H_{22}O_4N$: 232.1549, found 232.1530

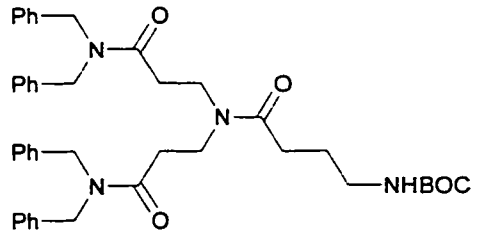
4-*tert*-Butoxycarbonylamino-butyric acid (34)



4-*tert*-Butoxycarbonylamino-butyric acid ethyl ester (**33**) (189 mg, 0.82 mmol) and sodium carbonate (210 mg, 1.64 mmol) were dissolved in an aqueous ethanol solution (70 % water, 30 % ethanol, 12 mL) and left to stir overnight. The solution was poured into ethyl acetate (10 mL) and washed with dilute hydrochloric acid (2 x 10 mL), the combined organic extracts were dried, filtered and concentrated *in vacuo*. Purification by column chromatography (100% CH_2Cl_2, increasing to 5 % methanol) afforded a white solid (84 mg, 50%). ^1H NMR (200 MHz, $CDCl_3$) δ 5.7 (br s, 1H, O*H*), δ 4.7 (br s, 1H, N*H*), δ 3.2 (m, 2H, CH_2NH), δ 2.4 (t, J=8 Hz, 2H,

CH_2C=O), δ 1.8 (m, 2H, $CH_2CH_2CH_2$), δ 1.4 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (50 MHz, $CDCl_3$) 178.3 (*C*=OOH), 155.6 (*C*=ONH), 79.1 ($C(CH_3)_3$), 39.7 (CH_2NH), 31.3 (CH_2C=O), 28.3 ($C(CH_3)_3$), 25.1 ($CH_2CH_2CH_2$).

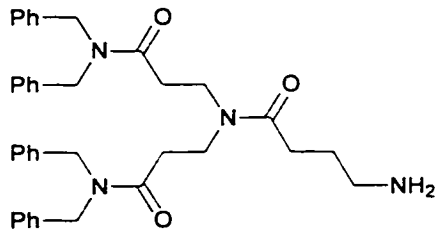
{3-[Bis-(2-dibenzylcarbamoyl-ethyl)-carbamoyl]-propyl}-carbamic acid *tert*-butyl ester (35)



4-*tert*-Butoxycarbonylamino-butyric acid (**34**) (29 mg, 0.14 mmol), *N,N*-dibenzyl-3-(2-dibenzylcarbamoyl-ethylamino)-propionamide (**30**) (74 mg, 0.14 mmol), HOBT (20 mg, 0.15 mmol) and HATU (58 mg, 0.15 mmol) were dissolved in dichloromethane (5 mL) and left to stir at room temperature for 88 hours. The mixture was washed with dilute hydrochloric acid (2 x 10 mL) and then saturated sodium bicarbonate solution (2 x 10 mL). The combined organic extracts were dried, filtered and concentrated *in vacuo*. After purification by column chromatography (dichloromethane increasing to 5% methanol/ 95% dichloromethane) a yellow oil was recovered (47 mg, 47%). IR (neat, cm^{-1}) 3357, 2974, 2927, 1700, 1648, 1170; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.15 (br s, 1H, N*H*), δ 7.4-7.0 (m, 20H, Ar*H*), δ 4.6 (s,

2H, CH_2Ph), δ 4.5 (s, 2H, CH_2Ph), δ 4.4 (s, 4H, CH_2Ph), δ 3.6 (m, 4H, C=ONCH_2CH$_2$), δ 3.1 (m, 2H, CH_2NC=O), δ 2.6 (m, 4H, CH_2C=ON), δ 2.25 (m, 2H, NC=OCH_2), δ 1.7 (m, 2H, CH$_2$CH_2CH$_2$), δ 1.4 (s, 9H, C(CH_3)$_3$; ^{13}C NMR (75 MHz, $CDCl_3$) 173.1, 172.1, 171.7, 155.4 (*C*=O), 137.5, 137.3, 136.7, 136.5, 129.5, 129.3, 129.1, 129.0, 128.9, 128.6, 128.5, 128.2, 128.0, 127.8, 126.9, 126.5 (Ar*C*), 79.1 (*C*(CH$_3$)$_3$), 50.4, 49.0 (PhCH$_2$N), 40.2 (*C*H$_2$NH) 30.5 (*C*H$_2$C=O), 28.7 (C(*C*H$_3$)$_3$), 25.5 (CH$_2$*C*H$_2$CH$_2$); Electrospray MS for $C_{43}H_{52}N_4O_5$ (M+ H$^+$) 705.1.

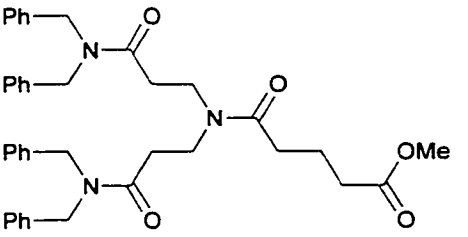
4-Amino-*N*,*N*-bis-(2-dibenzylcarbamoyl-ethyl)-butyramide (36)



Amine **35** (47 mg, 0.066 mmol) was reacted with trifluoroacetic acid (0.25 mL 3.3 mmol) and left to stir at room temperature for 15 hours, the excess trifluoroacetic acid was removed under reduced pressure and the solution was neutralised with saturated sodium bicarbonate solution. This solution was then washed with dichloromethane (10 mL), the two phases were separated and the organic phase was washed with water (2 x 10 mL). The combined organic extracts were dried, filtered and concentrated *in vacuo*. After recrystallisation, from methanol, the product was recovered as white flakes (32 mg, 81 %). IR (neat, cm^{-1})

3444, 3059, 3034, 2925, 1637, 1450, 1209, 949; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.2 (br s, 2H, NH_2), δ 7.4-7.0 (m, 20H, Ar*H*), δ 4.7-4.3 (m, 8H, CH_2Ph), δ 3.6 (m, 4H, C=ONCH_2CH$_2$), δ 2.9 (m, 2H, CH_2NH$_2$), δ 2.65 (m, 4H, CH_2C=ON), δ 2.4 (m, 2H, NC=OCH_2), δ 1.9 (m, 2H, CH$_2$CH_2CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) 173.1, 172.1, 171.6 (*C*=O), 137.4, 137.2, 136.6, 136.5, 129.5, 129.4, 129.0, 128.8, 128.5, 128.3, 128.2, 128.0, 127.8, 127.0, 126.9, 126.7 (Ar*C*), 49.2, 48.8 (*C*H$_2$Ph), 43.4 (C=ONCH$_2$CH$_2$), 31.8 (*C*H$_2$C=ON), 30.9 (NC=O*C*H$_2$), 29.5 (*C*H$_2$NH$_2$), 22.8 (CH$_2$*C*H$_2$CH$_2$); Electrospray MS for $C_{38}H_{44}N_4O_3$ 605.1 (M+ H^+), 606.1 (M+ $2H^+$).

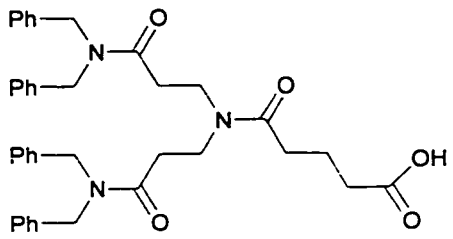
4-[Bis-(2-dibenzylcarbamoyl-ethyl)-carbamoyl]-butyric acid methyl ester (37)



Methyl-4-(chloroformyl) butyrate (0.1 mL, 0.72 mmol) was added dropwise to a solution of *N,N*-dibenzyl-3-(2-dibenzylcarbamoyl-ethylamino)-propionamide (**30**) (288 mg, 0.55 mmol), 4-dimethylaminopyridine (6.7 mg, 0.055 mmol) and triethylamine (0.23 mL, 1.65 mmol) in dichloromethane (9 mL). The reaction was left to stir at room temperature under nitrogen overnight. The solution was washed

with dilute hydrochloric acid (2 x 10 mL) and brine (2 x 10 mL), the combined organic extracts were dried, filtered and concentrated *in vacuo*. Following purification by column chromatography (dichloromethane) the product was isolated as a colourless oil (267 mg 75%). IR (neat, cm^{-1}) 3030, 2946, 1735, 1646, 1440, 1202, 1023, 702; ^1H NMR (200 MHz, $CDCl_3$) δ 7.45-7.1 (m, 20H, Ar-*H*), δ 4.6 (s, 2H, PhC*H*$_2$), δ 4.55 (s, 2H, PhC*H*$_2$), δ 4.4 (s, 4H, PhC*H*$_2$), δ 3.7 (m, 4H, C*H*$_2$N), δ 3.55 (s, 3H, OMe), δ 2.7 (m, 4H, C*H*$_2$C=ON), δ 2.3 (m, 4H, C*H*$_2$C=O), δ 1.85 (m, 2H, $CH_2CH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) 173.6, 172.2, 171.6, 170.6 (*C*=O), 129.0, 128.8, 128.5, 128.2, 128.1, 127.7, 127.5, 127.3, 126.4, 126.1 (Ar*C*), 49.9, 49.7, 48.5, 47.9 (Ph*C*H_2N), 44.7, 42.9 (*C*H_2N), 33.1, 32.9 (*C*H_2C=O), 31.8 (O*C*H_3), 20.2 ($CH_2CH_2CH_2$); FAB MS $C_{39}H_{43}N_3O_5$ (M+ H^+) 648.4.

4-[Bis-(2-dibenzylcarbamoyl-ethyl)-carbamoyl]-butyric acid (38)

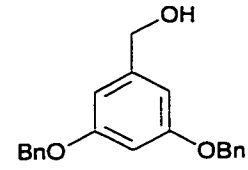


The ester **37** (1.5 g, 2.28 mmol) was dissolved in methanol (40 mL) containing sodium hydroxide (5N, 50 mL) and left to stir overnight. The methanol was removed under reduced pressure and then the residue was dissolved in

dichloromethane (30 mL) and washed with 0.5 M hydrochloric acid (2 x 20 mL). The collected organic phase was dried, concentrated *in vacuo* and the yellow solid was purified by column chromatography (dichloromethane) resulting in a yellow crystalline solid (930 mg, 65%). IR (neat, cm^{-1}) 3062, 3030, 2970, 1726, 1643, 1613, 1452, 1215, 700; ^1H NMR (200 MHz, $CDCl_3$) δ 7.4-7.0 (m, 20H, Ar*H*), δ 4.6 (s, 2H, PhC*H*$_2$N), δ 4.5 (s, 2H, PhC*H*$_2$), δ 4.4 (s, 4H, PhC*H*$_2$), δ 3.7 (s, 2H, C*H*$_2$N), δ 3.5 (s, 2H, C*H*$_2$N), δ 2.7 (s, 4H, C*H*$_2$C=O), δ 2.3 (m, 2H, C*H*$_2$CO$_2$H), δ 1.8 (m, 2H, C*H*$_2$CON), δ 1.3 (m, 2H, $CH_2CH_2CH_2$); ^{13}C NMR (50 MHz, $CDCl_3$) 173.0 (*C*=O), 171.9 (*C*=O), 171.3 (*C*=O), 137.5, 128.4, 127.3, 127.1, 126.9, (Ar*C*), 49.7 (Ph*C*H$_2$N), 43.6 (*C*H$_2$N), 32.0 (*C*H$_2$C=O), 20.5 ($CH_2CH_2CH_2$); FAB HRMS calcd for $C_{39}H_{44}N_3O_5$: 634.3281 found: 634.3210.

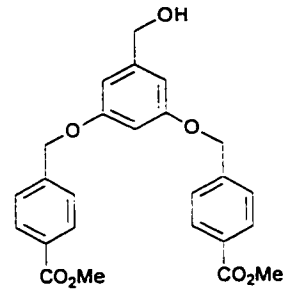
(3,5-Bisbenzyloxy-phenyl)-methanol (**41**), [3,5-bis(4-methylester-benzyloxy)-benzylalcohol] (**42**), (3,5-bisbenzyloxy) benzylbromide (**43**) and [3,5-bis(4-methylester-benzyloxy)-benzylbromide] (**44**) were all prepared accordingly to literature procedures.[4-7]

(3,5-Bisbenzyloxy-phenyl)-methanol (41)



^{1}H NMR (200 MHz, $CDCl_3$) δ 7.5-7.3 (m, 10H, Ar*H*), δ 6.65 (s, 2H, *o*-CH_2OH Ar*H*), δ 6.55 (s, 1H, Ar*H*-*p*-CH_2OH), δ 5.05 (s, 4H, OCH_2Ph), δ 4.55 (s, 2H, OCH_2OH), δ 2.7 (brs, 1H, O*H*); 13C NMR (50 MHz, $CDCl_3$) 160.0 (Ar*C*-*ipso* OR), 143.4, 136.7, 128.5, 127.9, 127.5, 105.6, 101.2 (Ar*C*), 69.9 (CH_2OPh) 65.1 (CH_2OH).

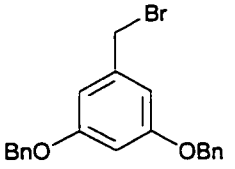
[3,5-Bis(4-methylester-benzyloxy)-benzylalcohol] (42)



^{1}H NMR (200 MHz, $CDCl_3$) δ 8.0 (d, J=8 Hz, 4H, Ar*H*), δ 7.45 (d, J=8 Hz, 4H, Ar*H*), δ 6.6 (s, 2H, *o*-CH_2OH Ar*H*), δ 6.5 (s, 1H, *p*-CH_2OH Ar*H*), δ 5.05 (s, 4H, OCH_2Ph), δ 4.6 (s, 2H, CH_2OH), δ 3.9 (s, 6H, OCH_3), δ 1.9 (brs, 1H, O*H*); ^{13}C NMR

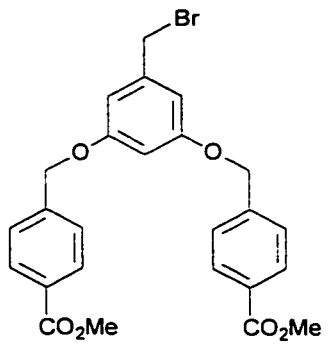
(50 MHz, $CDCl_3$) 167.2 (*C*=O), 160.2, 144.2, 142.4, 130.2, 129.9, 127.3, 106.2, 101.6 (Ar*C*), 69.7 (*C*H_2OPh), 65.4 (*C*H_2OH), 52.6 (O*C*H_3).

(3,5-Bisbenzyloxy) benzylbromide (43)



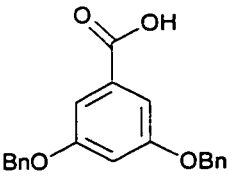
^{1}H NMR (200 MHz, $CDCl_3$) δ 7.4 (m, 10H, Ar*H*), δ 6.65 (s, 2H, *o*-CH_2Br Ar*H*), δ 6.55 (s, 1H, *p*-CH_2Br Ar*H*), δ 5.1 (s, 4H, OC*H*$_2$Ph), δ 4.4 (s, 2H, C*H*$_2$Br); ^{13}C NMR (50 MHz, $CDCl_3$) 160.1 (Ar*C*-*ipso* OR), 136.6, 128.6, 128.1, 127.5, 108.1, 102.1 (Ar*C*), 70.1 (*C*H_2OPh), 33.4 (*C*H_2Br).

[3,5-Bis(4-methylester-benzyloxy)-benzylbromide] (44)



^{1}H NMR (200 MHz, $CDCl_3$) δ 8.1 (d, J=8 Hz, 4H, Ar*H*), δ 7.45 (d, J=8 Hz, 4H, Ar*H*), δ 6.6 (s, 2H, *o*-CH_2Br Ar*H*), δ 6.5 (s, 1H, *p*-CH_2Br Ar*H*), δ 5.1 (s, 4H, OCH_2Ph), δ 4.4 (s, 2H, CH_2Br), δ 3.9 (s, 6H, OCH_3); ^{13}C NMR (50 MHz, $CDCl_3$) 163.5 (*C*=O), 159.7, 141.0, 140.0, 129.7, 126.9, 108.2, 102.0 (Ar*C*), 69.4 (CH_2OPh), 52.1 (OCH_3), 33.3 (CH_2Br).

3,5-Bisbenzyloxy-benzoic acid (45)

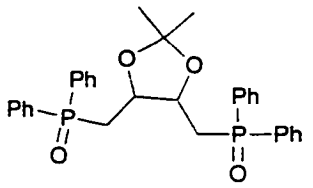


Benzyl bromide (5.1 mL, 42 mmol), 3,5-dihydroxybenzoic acid (2.0 g, 13 mmol), anhydrous potassium carbonate (2.7 g, 30 mmol) and 18-crown-6 (106 mg,

0.40 mmol) were dissolved in dry acetone (50 mL) and heated to reflux, under nitrogen for 24 hours. After cooling, the acetone was removed under vacuum, the resulting solid was dissolved in 99% ethanol (20 mL) and treated with water (6 mL) and potassium hydroxide (4.0 g). This mixture was heated to reflux overnight. The solution was allowed to cool and then concentrated *in vacuo* to 10 mL and water (80 mL) was added. The aqueous solution was acidified with glacial acetic acid. The slurry was washed with dichloromethane (6 x 30 mL). The brown solid afforded was recrystallised using acetone to give a white solid (1.9 g, 43 %). ^{1}H NMR (200 MHz, $(CD_3)_2O$) δ 7.5-7.3 (m, 12H, Ar*H*), δ 6.7 (s, 1H, *p*-CH_2Br Ar*H*), δ 5.1 (s, 4H, OCH_2Ph); ^{13}C NMR (50MHz, $(CD_3)_2O$) 167.5 (*C*=O), 160.9 (Ar*C*-*ipso* OR), 138.0, 133.5, 129.3, 128.7, 128.5, 109.3, 107.5 (Ar*C*), 70.8 (*C*H_2OPh).

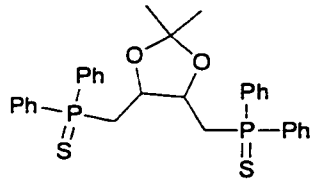
Experimental for Chapter 3

4,5-Bis(diphenyl-phosphinoylmethyl)-2,2-dimethyl-[1,3]dioxolane (52)



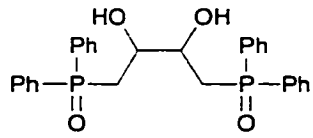
To an ice cooled solution of 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane, (DIOP) (500 mg, 1.0 mmol), in methanol (10 mL), hydrogen peroxide (50% soln., 1.1 mmol, 0.06 ml) was added. The solution was left to stir overnight, the methanol was removed *in vacuo*, then the residue was diluted with chloroform (15 mL) and washed with water (2 x 10 mL), the combined organic extracts were dried, filtered and concentrated *in vacuo*, to give the phosphine oxide as a white solid (530 mg, 100%). IR (KBr pellet, cm^{-1}) 3164, 2902, 1437, 1184, 1164, 691; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.8-7.4 (m, 20H, Ar*H*), δ 4.1 (br m, 2H, C*H*), δ 2.7 (m, 4H, CH_2), δ 1.1 (s, 6H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) 131.9, 131.6, 131.5, 131.4, 131.4, 131.3, 128.6, 128.5, 128.3 (Ar*C*), 108.6 ($O_2(C)(CH_3)_2$), 75.4 (*C*H), 75.3 (*C*H), 32.2 (CH_2), 30.8 (CH_2), 26.3 (CH_3); ^{31}P NMR (121.MHz, $CDCl_3$) δ30.0; FAB MS for $C_{31}H_{32}O_4P_2$ ($M+H^+$) 531.2.

4,5-Bis(diphenyl-phosphinothioylmethyl)-2,2-dimethyl-[1,3]dioxolane (53)



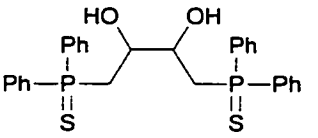
DIOP (100 mg, 0.2mmol) was mixed with crushed elemental sulfur (128 mg, 0.4 mmol) in chloroform (4 mL) and left overnight to stir at room temperature. The solvent was removed and afforded white crystals (112 mg, 100%). IR (KBr pellet, $^{cm-1}$) 3050, 2984, 1435, 1098, 1067, 800, 689; 1H NMR (200 MHz, $CDCl_3$) δ 7.8-7.4 (m, 20H, Ar*H*), δ 4.4 (m, 2H, C*H*), δ 2.9 (m, 2H, CH_2), δ 2.5 (m, 2H, CH_2), δ 1.1 (s, 6H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) 131.6, 131.5, 131.47, 131.4, 131.3, 131.2, 130.9, 130.7, 128.7, 128.5, 128.3, 128.0 (Ar*C*), 109.0 (O_2(*C*)(CH_3)$_2$), 76.1 (*C*H), 76.0 (*C*H), 36.2 (*C*H_2), 35.0 (*C*H_2), 26.7 (2*C*H_3); ^{31}P NMR (121.MHz, $CDCl_3$) δ 40.1; FAB MS for $C_{31}H_{32}O_2P_2S_2$ (M+ H^+) 563.1.

1,4-Bis(diphenylphosphoryl)-2,3-butanediol (54)



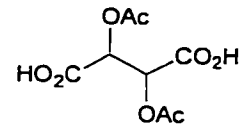
4,5-Bis(diphenyl-phosphinoylmethyl)-2,2-dimethyl-[1,3]dioxolane (**52**) (0.82 mmol, 0.44 g) was stirred in a 1:1 mixture of 1M hydrochloric acid and terahydrofuran (10 mL) for 2 hours. The solution was then diluted with dichloromethane (15 mL) and washed with saturated sodium bicarbonate solution (2 x 15 mL). The combined organic extracts were dried, filtered and concentrated *in vacuo* to give the white solid (0.43 g, 93%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.7–7.4 (m, 20H, Ar*H*), δ 4.1 (m, 2H, C*H*), δ 3.5 (br s, 2H, O*H*), δ 2.6 (m, 4H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) 132.1, 131.8, 131.2, 131.1, 131.0, 130.9, 128.5, 128.4 (Ar*C*), 76.4 (*C*H), 33.5 (*C*H_2), 32.6(*C*H_2); ^{31}P NMR (121.MHz, $CDCl_3$) δ 35.0; FAB MS for $C_{28}H_{28}O_4P_2$ (M+ H^+) 490.1.

1,4-Bis(diphenylphosphorathioyl)-2,3-butanediol (55)



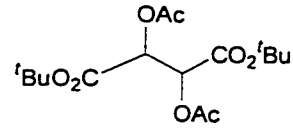
4,5-Bis-(diphenyl-phosphinothioylmethyl)-2,2-dimethyl-[1,3]dioxolane (**53**) (78 mg, 0.14 mmol) was dissolved in methanol (5 mL) and a few drops of trifluoroacetic acid were added, the mixture was heated at reflux for 5 days. The methanol was removed *in vacuo* and the excess trifluoroacetic acid was removed under high vacuum. After column chromatography (100% CH_2Cl_2, increasing to 5% methanol) the product was isolated as white crystals, (59 mg, 81%). IR (KBr, cm^{-1}) 3053, 2909, 1480, 1429, 1298, 1092, 883, 697, 610; ^1H NMR (200 MHz, $CDCl_3$) δ 8.0-7.3 (m, 20H, Ar*H*), δ 4.2 (m, 4H, C*H*, OH), δ 3.1 (m, 2H, CH_2), δ 2.5 (m, 2H, C*H*); ^{13}C NMR (50 MHz, $CDCl_3$) 131.8, 131.6, 131.5, 131.3, 130.7, 130.6, 130.5, 128.9, 128.8, 128.7, 128.6 (Ar*C*) 69.5, 69.3 (2*C*H), 34.3, 33.5 (2*C*H_2); ^{31}P NMR (121.MHz, $CDCl_3$) δ 40.1; FAB MS (M+ H^+) 523.2; Anal. Calcd for $C_{28}H_{29}O_2P_2S_2$: C 64.35, H 5.40, found C 64.16, H 5.49.

2,3-Diacetoxysuccinic acid (56)



2,3-Diacetoxysuccinic acid was prepared following a literature procedure.[2] ^{1}H NMR (200 MHz, DMSO-d_6) δ 5.5 (s, 2H, OC*H*), δ 2.1 (s, 6H, CH_3C=O); ^{13}C NMR (50 MHz, $CDCl_3$) 167.4, 165.0 (C=O), 68.5 (OC*H*), 18.2 (*C*H_3C=O).

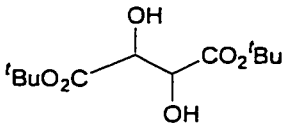
2,3-Diacetoxysuccinic acid di-*tert*-butyl ester (57)



2,3-Diacetoxysuccinic acid (0.53 g, 2.3 mmol) and concentrated sulfuric acid (0.05 mL, 0.55 mmol) in dichloromethane (10 mL) were stirred at –12°C. Isobutene (1.6 mL, 17 mmol) was condensed into the solution, the mixture was shaken vigorously, allowed to warm up to room temperature and stirred for 2 days. The mixture was poured into a beaker containing ice water (50 mL) and sodium hydroxide, (0.5 g) this was allowed to stir until it reached room temperature. More sodium hydroxide was added until the solution reached pH7. The organic layers were washed with water, and the combined organic extracts were dried, filtered and

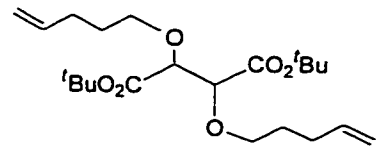
concentrated *in vacuo*. Kugelrohl distillation (0.2 mmHg/140°C) afforded 0.49 g (61%) of a colourless oil. IR (neat, cm^{-1}) 3507, 2980, 1756, 1372, 1213, 972; ^1H NMR (200 MHz, $CDCl_3$) δ 1.4 (s, 18H, $C(CH_3)_3$), δ 2.1 (s, 6H, $CH_3C=O$), δ 5.5 (m, 2H, CH); ^{13}C NMR (50 MHz, $CDCl_3$) 169.5 (C=O), 164.6 (C=O), 83.4 ($C(CH_3)_3$), 71.1 (2CH), 27.7 ($C(CH_3)_3$), 20.2 ($2CH_3C=O$); FAB MS (M+ H^+) 347.2; Anal. calcd for $C_{16}H_{27}O_8$: C, 55.48; H, 7.57, found C, 55.60; H, 7.60.

2,3-Dihydroxysuccinic acid di-*tert*-butyl ester (58)



To a stirred solution of 2,3-diacetoxysuccinic acid di-*tert*-butyl ester (1.0 g, 2.9 mmol) in methanol (10 mL) was added a methanolic solution of potassium hydroxide (0.05 g, 0.9 mmol, in 2.5 mL). After 10 minutes, sodium bicarbonate (0.2 g, 1 mmol) in water (50 mL) was added, the solution was neutralised with dilute hydrochloric acid and the methanol removed *in vacuo*. The aqueous solution was washed with dichloromethane (2 x 20 mL), the combined organic extracts were dried, filtered and concentrated *in vacuo* affording a white crystalline solid (0.76 g, 100%). ^1H NMR (200 MHz, $CDCl_3$) δ 4.25 (s, 2H, CH), δ 3.3 (br, 2H, OH), δ 1.4 (s, 18H, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 170.9 (C=O), 83.4 ($C(CH_3)_3$), 80.9 (2CH), 27.9 ($C(CH_3)_3$).

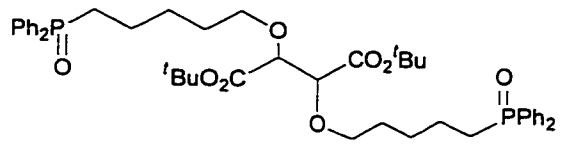
2,3-Bis-pent-4-enyloxysuccinic acid di-*tert*-butyl ester (59)



Sodium hydride (60% suspension in oil, 0.1 g, 2.5 mmol) was washed with tetrahydrofuran (3 mL) and a solution of the 2,3-dihydroxysuccinic acid di-*tert*-butyl ester (**58**) (0.26 g, 1.0 mmol) in dimethylformamide (3 mL) was added with stirring at 0°C. The solution was allowed to stir at room temperature for 1 hour before being cooled to 0°C for the addition of tetrabutyl ammonium iodide (3.7 mg, 0.01 mmol) and 5-bromo-1-pentene (0.30 mL, 2.5 mmol). The mixture was stirred at room temperature for 24 hours. To the solution was added diethyl ether (10 mL) and the mixture was washed with brine (4 x 15 mL). The combined organic extracts were dried, filtered and concentrated *in vacuo*. After purification by Kugelrohl distillation (80°C/0.1 mmHg) a colourless oil was attained (0.3 g, 77%). IR (neat, cm^{-1}) 2978, 2934, 1752, 1368, 1279, 1153, 1113, 847; ^1H NMR (200 MHz, $CDCl_3$) δ 5.8 (m, 2H, CH_2=C*H*), δ 4.9 (m, 4H, C*H*$_2$=CH), δ 4.1 (s, 2H, OC*H*), δ 3.7 (m, 2H, OC*H*$_2$), δ 3.3 (m, 2H, OC*H*$_2$), δ 2.0 (m, 4H, $CH_2CH_2CH_2$), δ 1.6 (m, 4H, C*H*$_2$CH=CH_2), δ 1.4 (s, 18H, C(C*H*$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 168.7 (*C*=O), 138.1 (*C*H=CH_2), 114.6 (CH=*C*H$_2$), 81.7 (*C*(CH$_3$)$_3$), 80.3 (O*C*H), 71.6 (O*C*H$_2$), 30.0 (OCH$_2$*C*H$_2$), 28.6

($CH_2CH=CH_2$), 28.0 ($C(CH_3)_3$); FAB MS (M+ H^+) 399.25; Anal. calcd for $C_{22}H_{38}O_6$: C 66.30, H 9.61, found C 66.52, H 9.77.

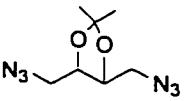
2,3-Bis[5-(diphenylphosphinoyl)pentyloxy]succinic acid di-*tert*-butyl ester (60)



2,3-Bis-pent-4-enyloxysuccinic acid di-*tert*-butyl ester (**59**) (127 mg, 0.32 mmol), AIBN (11 mg, 0.07 mmol) and diphenylphosphine (0.12 mL, 0.67 mmol) were dissolved in dry benzene (4 mL) and sealed in a glass autoclave under an argon atmosphere. The reaction vessel was heated in an oil bath at 85°C for 3 days. The solvent was removed *in vacuo*, and after purification by Kugelrohl distillation and column chromatography (75% ethyl acetate 25% pet.ether) a yellow oil was formed (0.10 g, 40%). IR (neat, cm^{-1}) 3200, 2926, 2859, 1740, 1600, 1436, 1156, 1041, 724, 699; ^1H NMR (200 MHz, $CDCl_3$) δ 7.8-7.4 (m, 20H, Ar*H*), δ 4.2 (s, 2H, OC*H*), δ 3.8 (m, 4H, OCH_2), δ 2.4 (m, 8H, OCH_2CH_2), δ 1.5 (m, 12H, $(CH_2)_3P$), δ 1.2 (s, 18H, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 167.5 (*C*=O), 132.4 (d, J=3.4 Hz), 130.4 (d, J=13.4 Hz), 128.7 (d, J=17 Hz), 128.5 (Ar*C*), 81.5 ($C(CH_3)_3$), 80.0 (OCH), 67.9 (OCH_2), 38.5 (OCH_2CH_2), 30.1 ($OCH_2CH_2CH_2$), 28.7 ($C(CH_3)_3$), 27.9 (CH_2P), 23.1

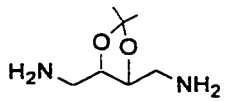
(PCH_2CH_2); ^{31}P NMR δ 33.9; Electrospray MS for $C_{46}H_{60}O_8P_2$ ($M+ H^+$) 803.1, ($M+ NH_4^+$) 820.1.

4,5-Bis-azidomethyl-2,2-dimethyl-[1,3]dioxolane (62)



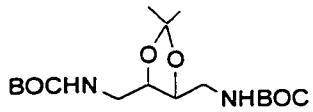
1,4-Di-*O*-tosyl-2,3-*O*-isopropylidene-*D*-threitol (4.72 g, 10 mmol) and sodium azide (5.22 g, 80 mmol) were heated to reflux in DMF (160 mL) for 5 hours. Some DMF was removed *in vacuo* then the concentrated solution was put into methylene chloride (50 mL) and washed with water (4 x 20 mL). The collected organic fractions were dried with magnesium sulfate, filtered and the solvent was removed *in vacuo*. Purification by column chromatography (10% ethyl acetate, hexane) gave a slightly yellow oil (1.64 g, 77%). IR (neat, cm^{-1}) 2988, 2933, 2104, 1465, 1237, 1090; ^1H NMR (200 MHz, $CDCl_3$) δ 4.0 (m, 2H, C*H*), δ 3.35 (m, 2H, CH_2), δ 3.25 (m, 2H, CH_2), δ 1.4 (s, 6H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) 110.2 ($C(CH_3)_2$), 76.8 (O*C*H) 51.4 (CH_2) 26.7 (CH_3).

4,5-Di(aminomethyl)-2,2-dimethyl-[1,3]dioxolane (63)



4,5-Bis-azidomethyl-2,2-dimethyl-[1,3]dioxolane (0.126 g, 0.59 mmol) in methanol (5 mL) was treated with ammonium formate (0.16 g, 2.5 mmol) and 10% palladium on carbon (0.179 g, 8.3 mmol) the reaction was left to stir at 60°C for 15 minutes. The reaction mixture was then filtered and the filtrate concentrated *in vacuo*. This afforded a colourless glassy solid (76 mgs, 81%). IR (neat, cm^{-1}) 3369, 2985, 2933, 2870, 1591, 1374, 1244, 1216, 1062, 897; ^1H NMR (200 MHz, $CDCl_3$) δ 3.65 (m, 2H, C*H*), δ 3.25 (m, 2H, CH_2), δ 2.65 (m, 2H, CH_2), δ 2.25 (br s, 4H, NH_2) δ 1.25 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 109.5 (*C*$(CH_3)_2$), 79.6 (O*C*H), 43.6 (*C*H_2), 26.9 (*C*H_3).

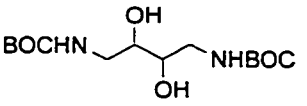
4,5-Bis[*tert*-butoxycarbonylmethyl]-2,2-dimethyl-[1,3]dioxolane (64)



4,5-Di(aminomethyl)-2,2-dimethyl-[1,3]dioxolane (**63**) (0.317 g, 2.0 mmol) was dissolved in THF (5 mL) and treated with triethylamine (0.61 mL, 4.4 mmol) and di-*t*-butyldicarbonate (1 mL, 4.4 mmol). This mixture was stirred at room

temperature overnight. The resulting mixture was washed with 1M HCl (2 x 10 mL) and brine (10 mL). The collected organic phases were dried and concentrated *in vacuo*. Purification was carried out by a Kugelrohl distillation (60°C, 0.1 mmHg) affording a yellow oil (515 mg, 71 %). IR (neat, cm^{-1}) 3357, 2979, 2933, 1714, 1367, 1248, 1169, 1085; ^1H NMR (200 MHz, $CDCl_3$) δ 5.0 (m, 2H, C*H*), δ 3.8 (m, 2H, CH_2), δ 3.3 (m, 2H, CH_2), δ 1.4 (s, 18H, C(CH_3)$_3$), δ 1.3 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 156.0 (*C*=O), 109.0 (*C*(CH_3)$_2$), 77.3 (O*C*H), 70.6 (3° *C*-BOC), 41.9 (*C*H_2), 28.3 (C(*C*H_3)$_3$), 27.1 (C(CH_3)$_2$); CI MS (M+ H^+) 361.

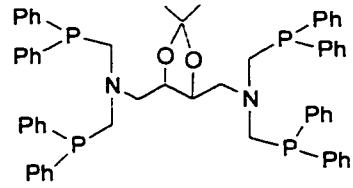
(4-*tert*-Butoxycarbonylamino-2,3-dihydroxy-butyl)-carbamic acid *tert*-butyl ester (65)



The protected diol (**64**) (95 mg, 0.26 mmol) was dissolved in methanol (4 mL) and treated with 5M HCl (4 mL) and left to stir overnight at room temperature. The methanol was removed *in vacuo* and then the oil was taken up in dichloromethane (5 mL) and water (5 mL). Sodium bicarbonate solution was added until the pH of the solution reached 7, and then the aqueous phase was washed with dichloromethane (2 x 5 mL). The combined organic extracts were dried and concentrated *in vacuo*. The product was collected as a yellow oil (82 mg, 97%). IR (neat, cm^{-1}) 3354, 2975, 1684, 1258, 117; ^1H NMR (200 MHz, $CDCl_3$) δ 5.1 (m, 2H, C*H*), δ 3.6 (br s, 2H,

N*H*), δ 3.4 (m, 2H,C*H*$_2$), δ 3.2 (m, 2H, C*H*$_2$), δ 1.4 (s, 18H, (C*H*$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 157.7 (*C*=O), 80.4 (*C*$(CH_3)_3$), 71.5 (*C*H), 43.5 (*C*H_2). 28.7 (C(*C*H_3)$_3$); CI MS (M+ H^+) 361.

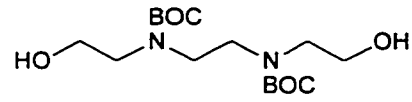
4,5-Bis(bis[{diphenyl-phosphanyl}methyl]aminomethyl)-2,2-dimethyl-[1,3]dioxolane (66)



Paraformaldehyde (800 mg, 27.5 mmol) and diphenylphosphine (4.8 mL, 27.5 mmol) were heated to reflux in toluene (125 mL) for an hour, in a Schlenk flask fitted with a reflux condenser. When the reaction mixture cooled, 4,5-di(aminomethyl)-2,2-dimethyl-[1,3]dioxolane (**63**) (1g, 6.3 mmol) in methanol (20 mL) was then added. The reactants were heated to reflux for a further 42 hours. The solvent was removed under high vacuum and the excess reactants were sublimed, affording a thick opaque gluey solid (5.84 g, 92%). IR (neat, cm^{-1}) 3054, 2979, 2933, 1578, 1477, 1433, 1094; ^{1}H NMR (300 MHz, C_6D_6) δ 7.6-6.9 (m, 40H, Ar*H*), δ 4.1 (s, 2H, C*H*), δ 4.0 (d, J=11 Hz, 4H, C*H*$_2$P), δ 3.6 (dd, J=11 Hz, $J_{P\text{-}H}$=6.4 Hz, 4H, C*H*$_2$P), δ 3.25 (m, 2H, C*H*$_2$N), δ 3.0 (m, 2H, C*H*$_2$N), δ 1.4 (s, 18H, C(C*H*$_3$)$_3$); ^{13}C NMR (75 MHz, C_6D_6) 139.1, 138.9, 134.3 (d, J=16.7 Hz), 133.7 (d, J=14.3 Hz), 133.5 (d, J=14.3 Hz), 128.8, 128.7,

128.6 (Ar*C*), 109.3 (*C*(CH_3)$_3$), 79.3 (*C*H), 60.0 (d, J=6.3 Hz, *C*H_2P), 59.9 (CH_2N), 27.4 (C(*C*H_3)$_3$); ^{31}P NMR (121 MHz, C_6D_6) δ –26.5; Electrospray MS for $C_{59}H_{60}N_2O_6P_2$ (M – CH_2PPh_2) 799, (M + 1) 800.

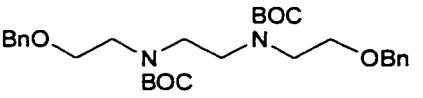
{2-[*tert*-Butoxycarbonyl(2-hydroxy-ethyl)amino]-ethyl}-(2-hydroxy-ethyl)-carbamic acid *tert*-butyl ester (67)



N,N'-bis(2-hydroxyethyl)ethylenediamine (148 mg, 1.0 mmol) was dissolved in an aqueous dioxane solution (4 mL water, 4 mL dioxane) with triethylamine (0.5 mL, 3.5 mmol) and [2-*tert*-butoxycarbonyloxyimino)-4-imidazolidinone nitrile] (540 mg, 2.2 mmol). The solution was warmed to 40 °C for 8 hours. The reaction mixture was extracted with ethyl acetate (2 x 10 mL) and the organic phase was washed with saturated sodium bicarbonate solution (10 mL). The collected organic phase was dried and concentrated *in vacuo*. After purification by column chromatography (50% ethyl acetate, 50% toluene) afforded 240 mg (69%) of a white solid. IR (KBr pellet, cm^{-1}) 3465, 2979, 2949, 1671, 1427, 1167, 1056, 1030; ^{1}H NMR (200 MHz, DMSO-d_6) δ 4.65 (br s, 2H, O*H*), δ 3.5 (m, 4H, CH_2OH), δ 3.25 (m, 4H, CH_2CH_2OH), δ 3.2 (m, 4H, CH_2N), δ 1.4 (s, 18H, C(CH_3)$_3$); ^{13}C NMR (75 MHz, DMSO-d_6) 154.6

(*C*=O), 78.5 (*C*(CH_3)$_3$), 58.9 (*C*H_2OH), 49.6 (*CH*$_2$$CH_2$OH), 45.4 (*C*$H_2$N), 28.0 (C(*C*$H_3$)$_3$; CI MS for $C_{16}H_{32}N_2O_6$ (M+1) 349.

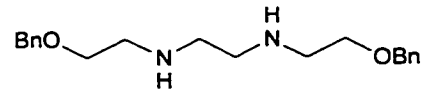
(2-Benzyloxyethyl)-{2-[(2-benzyloxyethyl)-*tert*-butoxycarbonyl-amino]-ethyl}-carbamic acid *tert*-butyl ester (68)



A THF (10 mL) solution of {2-*tert*-butoxycarbonyl-(2-hydroxyethyl)amino-ethyl}hydroxyethyl)carbamic acid *tert*-butyl ester (348 mg, 1.0 mmol) was treated with 50% sodium hydroxide solution (0.8 mL), followed by benzyl bromide (0.36 mL, 3.0 mmol) and tetrabutyl ammonium bisulphate (34 mg, 0.1 mmol) and left to stir at 40°C overnight. The mixture was then poured into water (5 mL) and washed with dichloromethane (2 x 10 mL) and brine (10 mL). The organic extracts were collected, dried with magnesium sulfate and concentrated *in vacuo*. Column chromatography was carried out (100% dichloromethane) affording a yellow oil (502 mg, 95%). IR (neat, cm^{-1}) 3030, 2973, 2864, 1692, 1412, 1365, 1244, 1164, 1120; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.3 (s, 10H, Ar*H*), δ 4.5 (s, 4H, C*H*$_2$OPh), δ 3.5 (m, 4H,OC*H*$_2$$CH_2$N), δ 3.3 (m, 8H, C*H*$_2$N), δ 1.4 (s, 18H, C(C*H*$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 155.8 (*C*=O), 138.7, 128.8, 128.7, 127.9 (Ar*C*), 73.4 (*C*H_2OAr), 72.5

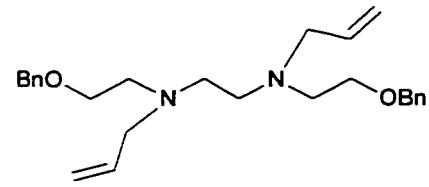
($C(CH_3)_3$), 50.9 (OCH_2CH_2N), 47.7, 47.0 (NCH_2), 28.8 ($C(CH_3)_3$; CI MS for $C_{30}H_{44}N_2O_6$ (M+1) 529.

N,N'-bis-(2-benzyloxyethyl)-ethane-1,2-diamine (69)



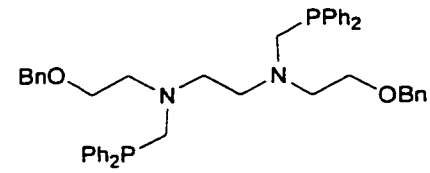
(2-Benzyloxyethyl)-{2-[(2-benzyloxy-ethyl)-*tert*-butoxycarbonyl-amino]-ethyl}-carbamic acid *tert*-butyl ester (**68**) (1.14 g, 2.1 mmol) was dissolved in dichloromethane (10 mL) and treated with trifluoroacetic acid (13 mL, 0.17 mol) and left to stir at room temperature for 4.5 hours. The excess acid was removed under high pressure and then the remaining oil was washed with sodium bicarbonate (2 x 15 mL) in dichloromethane (10 mL). The organic extracts were dried and concentrated *in vacuo*. Column chromatography (5% methanol in dichloromethane) gave a red oil (599 mg, 87%). IR (neat, cm^{-1}) 3312, 3030, 2858, 1688, 1453, 1452, 1096; ^1H NMR (200 MHz, $CDCl_3$) δ 7.3 (m, 10H,Ar*H*), δ 5.0 (br s, 2H, N*H*), δ 4.4 (s, 4H, CH_2OPh), δ 3.5 (t, J=5 Hz, 4H, CH_2CH_2O), δ 2.8 (m, 8H, CH_2N); ^{13}C NMR (75 MHz, $CDCl_3$) 137.8, 128.4, 127.8, 127.7 (Ar*C*), 73.7 (CH_2OPh), 67.9 (CH_2CH_2O), 48.1, 46.7 (CH_2N); FAB MS for $C_{20}H_{28}N_2O_2$ (M + H^+) 329 FAB HRMS cald. 329.2229, found 329.2368.

N,N'-Diallyl-N,N'-bis(2-benzyloxyethyl)ethane-1,2-diamine (70)



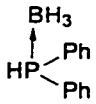
Diamine **69** (637 mg, 1.9 mmol) was dissolved in tetrahydrofuran (10 mL) and dimethylformamide (7 mL) with tetrabutylammonium iodide (7.2 mg, 0.02 mmol) and sodium hydride (116 mg, 4.9 mmol) and left to stir for 15 minutes. Allyl bromide (0.41 mL, 4.9 mmol) was added dropwise and the reaction mixture was warmed to 40°C and left to stir overnight. The solution was poured into water (20 mL) and ether (20 mL), and the organic phase was washed with brine (2 x 20 mL). The collected organic phases were dried and concentrated *in vacuo*. After purification by column chromatography (100% CH_2Cl_2 to 5% MeOH), the compound was isolated as a yellow oil (561 mg, 71 %). IR (neat, cm^{-1}) 3065, 3029, 2924, 2856, 1699, 1452, 1103, 1028, 735, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 7.4-7.2 (m, 10H, Ar*H*), δ 5.8 (m, 2H, C*H*=CH_2), δ 5.2 (m, 4H, CH_2=CH), δ 4.5 (s, 4H, CH_2OPh), δ 3.5 (t, J=6.1 Hz, 4H, OC$H_2$$CH_2$N), δ 3.15 (d, J=6.5 Hz, 4H, CH_2=CHCH_2), δ 2.7 (t, J=6.1 Hz, 4H, OCH_2CH_2N), δ 2.6 (s, 4H, NCH_2CH_2N); ^{13}C NMR (75 MHz, $CDCl_3$) 138.4 128.3, 127.6, 126.5 (Ar*C*), 135.7 (CH_2*C*H), 117.4 (*C*H_2=CH), 73.1 (Ph*C*H_2O), 68.6 (O*C*$H_2$$CH_2$), 58.3 (*C*$H_2$CH=$CH_2$), 53.6 ($OCH_2$*C*$H_2$N), 52.1 (N*C*$H_2$*C*$H_2$N); CI MS for $C_{26}H_{37}N_2O_2$ (M +H^+) 409.

***N,N'*-Bis(2-benzyloxyethyl)-*N,N'*-bis[(diphenylphosphanyl)methyl]-ethane-1,2-diamine (73)**



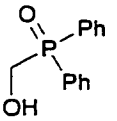
Diphenylphosphine (0.43 mL, 2.5 mmol) and paraformaldehyde (73 mg, 2.5 mmol) were combined in toluene (25 mL) and heated to reflux in a Schlenk flask fitted with a reflux condenser for 1 hour. Then *N,N'*-bis-(2-benzyloxy-ethyl)-ethane-1,2-diamine (**69**) (376 mg, 1.2 mmol) in methanol (10 mL) was added. This was heated to reflux for 60 hours. The solvent was removed under high vacuum and then the excess diphenylphosphine and diphenylphosphinyl methanol were removed by several sublimations. The pure phosphine was isolated as an amber oil (617 mg, 75%). IR (neat, cm^{-1}) 3253, 3055, 2924, 2860, 1590, 1437, 1175, 1121, 1027, 742, 696; ^1H NMR (300 MHz, C_6D_6) δ 7.6-6.9 (m, 20H, Ar*H*), δ 4.2 (s, 4H, CH_2OPh), δ 3.55 (s, 4H, NCH_2P), δ 3.45 (t, J=5.6 Hz, 4H, OCH_2CH$_2$N), δ 2.9 (m, 8H, CH_2N); ^{13}C NMR (75 MHz, C_6D_6) 139.2, 133.6 (d, J=18.1 Hz), 128.8, 128.6, 128.5, 127.9 127.7, 127.5 (Ar*C*), 73.2 (PhCH$_2$O), 69.3 (OCH$_2$CH$_2$), 59.4 (*C*H$_2$P), 55.2, 55.0 (*C*H$_2$N); ^{31}P NMR (C_6D_6, 121 MHz) δ –25.7; Electrospray MS for $C_{46}H_{50}N_2O_4P_2$ (M+ H^+) 757.

Diphenylphosphine borane (74)



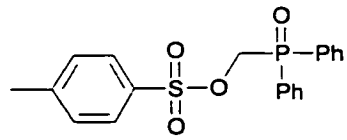
Prepared following literature procedure.[8] IR (neat, cm^{-1}) 3057, 2943, 2389, 2349, 1483, 1437, 1360, 1178, 1127, 1058; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.9 (d, J=442 Hz, 1H, P*H*), δ 7.8-7.4 (m, 10H, Ar*H*); ^{11}B NMR (160 MHz, $CDCl_3$) -40.15 (d, J=42 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 0.78 (d, J=53 Hz).

(Diphenylphosphinoyl)-methanol (75)



Diphenylphosphine (10 mL, 57 mmol), and paraformaldehyde (1.7 g, 57 mmol) were mixed in THF (50 mL) and heated to reflux overnight. The solvent was removed *in vacuo* affording an opaque thick oil (2.32 g, 100 %). IR (neat, cm^{-1}) ·3322, 3053, 2889, 1585 1481, 1434, 1158, 1025, 786; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.4-7.2 (m, 10H, Ar*H*), δ 7.8-7.2 (m, 10H, Ar*H*), δ 4.4 (d, J=8 Hz, 2H, CH_2), δ 2.8 (br s, 1H, O*H*); ^{13}C NMR (50 MHz, $CDCl_3$) 132.9 (d, J=17.6 Hz,), 132.1, 131.2 (d, J=9.3 Hz), 128.7 (d, J=14 Hz) (Ar*C*), 62.5 (d, J=13.4 Hz, CH_2).

Toluene-4-sulfonic acid diphenyl-phosphinoylmethyl ester (76)



Diphenylphosphinoyl methanol (1.0 g, 4.4 mmol) was dissolved in chloroform (8 mL) and treated with pyridine (0.71 ml, 8.8 mmol) and *p*-toluenesulfonyl chloride (1.3 g, 6.6 mmol). This solution was left to stir at room temperature for 3 hours, then washed with 2M HCl (10 mL) in diethyl ether (10 mL), and then 5% $NaHCO_3$ solution (10 mL). The organic extracts were collected and concentrated *in vacuo*. After column chromatography, (100% CH_2Cl_2 increasing to 5% MeOH, then a second column of 20% pentane 80% ethyl acetate) a white solid was obtained (420 mg, 25 %). IR (neat, cm^{-1}) 3059, 3026, 2956, 2803, 1664, 1493, 1437, 1363, 1182, 1026, 994; ^1H NMR (200 MHz, $CDCl_3$) δ 7.4-7.2 (m, 10H, Ar*H*), δ 7.8-7.2 (m, 14H, Ar*H*), δ 4.6 (d, J=7.1 Hz, 2H, C*H*$_2$), δ 2.4 (s, 3H, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 145.4, 132.7, 131.3 (d, J=10 Hz), 129.9, 128.6 (d, J=12.3 Hz), 127.9 (Ar*C*), 64.6 (d, J=82 Hz, *C*H_2), 21.5 (*C*H_3); CI MS for $C_{20}H_{19}O_4PS$ ($M+H^+$) 387.

General procedure for Hydroformylation

The following is a typical procedure: The catalyst was placed in a stainless steel autoclave with a glass liner equipped with a stirring bar, under a stream of nitrogen. The olefinic substrate (2 mmol), $[Rh(CO)_2Cl]_2$ (0.02 mmol), and a solution

of aminophosphine **66** (0.02 mmol) in CH_2Cl_2 were mixed with methylene chloride (total volume made up to 2 mL). The autoclave was purged three times with carbon monoxide, in order to displace any air, then charged with a 1:1 ratio of carbon monoxide and hydrogen gases. The autoclave was placed in an oil bath with sufficient silicone oil to cover the majority of the autoclave and heated to the appropriate temperature.

Platinum complex with 4,5-bis(bis[{diphenylphosphanyl}methyl]-aminomethyl)-2,2-dimethyl-[1,3]dioxolane (77)

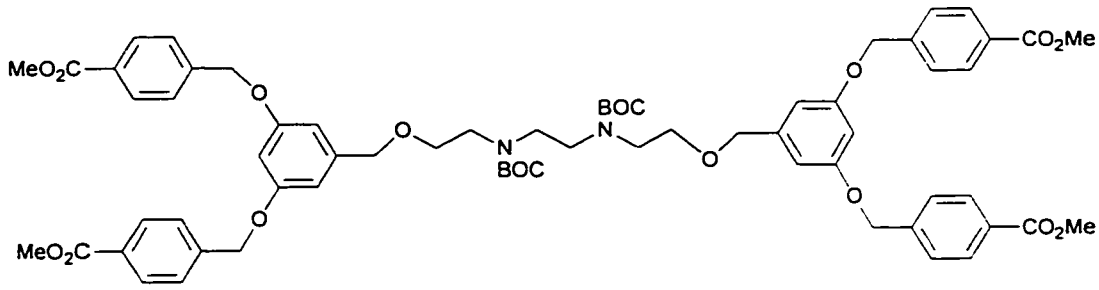
Phosphine **66** (300 mg, 0.32 mmol) was treated with dichloro(1,5-cyclooctadiene)platinum(II) (219 mg, 0.32 mmol) in methylene chloride (5 mL). The reaction was allowed to stir under an inert atmosphere for 3 hours. The solvent was removed *in vacuo*, and then the resulting white solid was washed with pentane (3 x 2 mL) (298 mg, 64%). ^{1}H NMR (300 MHz, C_6D_6) δ 8-7.2 (m, 40H, Ar*H*), δ 4.1 (m, 2H, C*H*), δ 3.6 (m, 4H, CH_2P), δ 3.4 (m, 4H, CH_2P), δ 2.6 (m, 4H, CH_2N), δ 1.4 (s, 6H, CH_3); ^{13}C NMR (75 MHz, C_6D_6) 134.3 (t, J=4.7 Hz), 133.9 (t, J=4.7 Hz), 132.7, 132.0 (d, J=7.1 Hz), 129.0, 128.7 (t, J=5.2 Hz) (Ar*C*), 110.9 (*C*(CH_3)$_2$), 77.2 (*C*H), 64.8 (*C*H_2N), 56.9 (?, J=? Hz, *C*H_2P), 28.3 (*C*H_3); ^{31}P NMR (121 MHz, C_6D_6) δ -7.6 (s, $J_{Pt\text{-}P}$=3396 Hz); Elemental Anal. Calcd C 47.72, H 4.07, N 1.89, found C 47.90, H 4.18, N 1.68.

Platinum complex of *N,N'*-bis(2-benzyloxyethyl)-*N,N'*-bis-[(diphenylphosphanyl)-methyl]-ethane-1,2-diamine (78)

Phosphine **73** (71 mg, 9.8 x 10^{-5} mol) was treated with dichloro(1,5-cyclooctadiene)platinum (II) (36 mg, 9.8 x 10^{-5} mol) in methylene chloride (2 mL). The reaction was allowed to stir under an inert atmosphere for 3 hours. The solvent was removed *in vacuo*, and then the resulting yellow solid was washed with pentane (3 x 2 mL) (43 mg, 44%). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.9-7.0 (m, 30H, Ar*H*), δ 4.5 (s, 4H, C*H*$_2$P), δ 4.2 (m, 4H, C*H*$_2$OPh), δ 3.5 (m, 4H, C*H*$_2$O), δ 3.2 (m, 4H, C*H*$_2$N), δ 2.4 (s, 4H, C*H*$_2$N); ^{13}C NMR (75 MHz, CD_2Cl_2) 137.9, 134.2, 132.7, 131.7, 130.8, 129.5, 129.2, 128.9, 128.6, 128.3, 128.2, 128.1 (Ar*C*), 73.5 (d, J=15 Hz, P*C*H$_2$), 67.7 (OCH_2Ph), 66.2 (CH_2O), 31.3 (CH_2N), 28.4 (CH_2N); ^{31}P NMR (121 MHz, C_6D_6) δ 0.8 (s, $J_{Pt\text{-}P}$=3644 Hz).

Experimental for Chapter 4

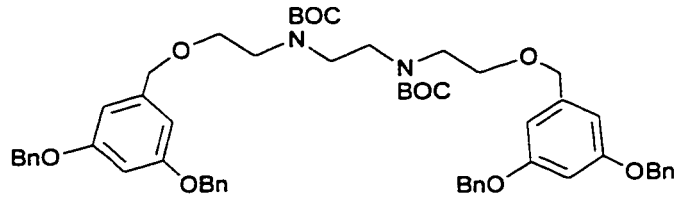
[2-(3,5-Bisbenzyloxy-4'-methyl ester-benzyloxy-4'-methyl ester)-ethyl]-(2-{[2-(3,5-bisbenzyloxy-benzyloxy)-ethyl]-*tert*-butoxycarbonyl-amino}-ethyl)-carbamic acid *tert*-butyl ester (83)



The alcohol **69** (131 mg, 0.38 mmol), bromide **44** (430 mg, 0.87 mmol) and silver (II) oxide (70 mg, 0.30 mmol) were dissolved in dimethylformamide (40 mL). The reaction was carried out in dark conditions at 60 °C for 72 hours. The reaction mixture was filtered, dissolved in chloroform, then washed with water (3 x 20 mL). The collected organic phases were dried and condensed *in vacuo*. Recrystallisation from methanol gave a white precipitate (180 mg, 40 %). IR (KBr, cm^{-1}) 3351, 3057, 2975, 1722, 1595, 1436, 1277, 1157, 843, 755; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.9, 7.3 (m, 16H, Ar*H*), δ 6.6-6.4 (m, 6H, Ar*H*), δ 4.9 (s, 8H, ArCH_2OAr), δ 4.6 (s, 4H, PhCH_2OCH_2), δ 3.8 (s, 12H, OCH_3), δ 3.6 (br s, 4H, CH_2O), δ 3.3 (br s, 8H, CH_2N), δ 1.4 (s, 18H, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 166.8 (*C*=O), 159.8, 143.7, 141.9, 129.8, 129.6, 105.8, 101.2 (Ar*C*), 76.4 (*C*(CH_3)$_3$), 69.3 (ArCH_2OAr), 65.0

(CH_2OPh), 61.9 (CH_2O), 52.1 (OCH_3), 46.6 (CH_2N), 28.4 ($C(CH_3)_3$); Electrospray MS for $C_{67}H_{76}N_2O_{18}$ (M- BOC) 1083.

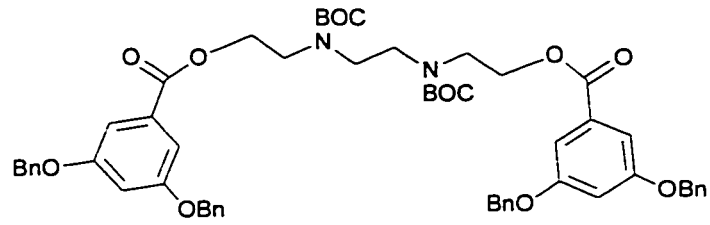
[2-(3,5-Bisbenzyloxy-benzyloxy)-ethyl]-(2-{[2-(3,5-bisbenzyloxy-benzyloxy)-ethyl]-*tert*-butoxycarbonyl-amino}-ethyl)-carbamic acid *tert*-butyl ester (83)



(3,5-Bis-benzyloxy) benzylbromide (160 mg, 0.42 mmol) and {2-*tert*-butoxycarbonyl-(2-hydroxyethyl)-amino-ethyl}-hydroxyethyl)-carbamic acid *tert*-butyl ester (49 mg, 0.14 mmol) were dissolved in tetrahydrofuran (5 mL) and treated with 50% sodium hydroxide solution (0.13 mL) and tetrabutylammonium bromide (4.8 mg, 0.015 mmol). The reaction mixture was stirred at room temperature for 29 hours, washed with diethyl ether (2 x 10 mL) and washed with brine (10 mL). The organic extracts were collected, dried and concentrated *in vacuo*. The residue was purified by column chromatography (100% dichloromethane increasing to 5% methanol, a yellow oily solid was afforded (530 mg, 40%). IR (neat, cm^{-1}) 3064, 3032, 2973, 2930, 2870, 1692, 1595, 1453, 1294, 1160, 1057, 737, 697; ^1H NMR (200 MHz, $CDCl_3$) δ 7.5-7.2 (m, 20H, Ar*H*), δ 6.6 (s, 6H, Ar-*H*), δ 5.0 (s, 8H, PhOCH_2Ar), δ 4.4 (s, 4H, CH_2OAr), δ 3.6 (m, 4H, NCH_2CH_2O), δ 3.5 (m, 8H,

CH_2CH_2N), δ 1.4 (s, 18H, $C(CH_3)_3$); ^{13}C NMR (50 MHz, $CDCl_3$) 160.0 (Ar-*C*), 155.0 (N*C*=O), 141.0, 137.0, 128.5, 127.9, 127.5, 106.4, 101.1 (Ar-*C*), 80.0 ($C(CH_3)_3$), 73.2 ($PhCH_2O$), 70.0 ($ArCH_2OPh$), 69.0 (OCH_2CH_2N), 62.9 (OCH_2CH_2N), 46.5, 46.4 (NCH_2CH_2N), 28.4 ($C(CH_3)_3$); Electrospray MS for $C_{58}H_{68}N_2O_{10}$ ($M+ H^+$) 953, (M(-BOC) + H^+) 853.

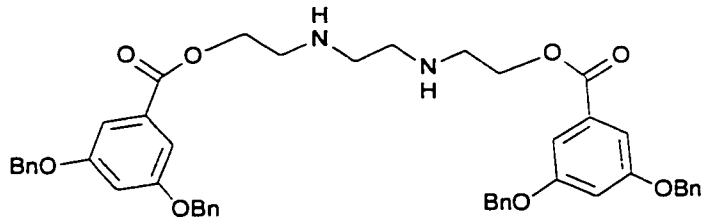
3,5-Bisbenzyloxybenzoic acid 2-(*tert*-butoxycarbonyl-{2-[*tert*-butoxycarbonyl-(2-{3,5-bisbenzyloxy}-ethyl)-amino]-ethyl}-amino)-ethyl ester-(84)



3,5-Bis-benzyloxybenzoic acid (101 mg, 0.30 mmol), 4-dimethylaminopyridine (37 mg, 0.30 mmol) and dicyclohexylcarbodiimide (62 mg, 0.30 mmol) were dissolved in dichloromethane (8 mL) and left to stir for 45 minutes before adding {2-*tert*-butoxycarbonyl-(2-hydroxyethyl)-aminoethyl}-hydroxyethyl)-carbamic acid *tert*-butyl ester (48 mg, 0.14 mmol) (**67**). After 17 hours, the solution was washed with water (2 x 10 mL) and brine (10 mL), the organic extracts were dried and concentrated *in vacuo*. Purification was carried out by column chromatography (5% methanol in dichloromethane) affording a yellow oil (111 mg,

83%). IR (neat, cm^{-1}) 3327, 2929, 2851, 1718, 1686, 1540, 1226, 1052, 736; ^1H NMR (300 MHz, $CDCl_3$) δ 7.6-7.2 (m, 24H, Ar*H*), δ 6.8 (s, 2H, *p*-$ArCO_2$-) δ 5.1 (s, 8H, OCH_2Ar), δ 4.4 (s, 4H, CH_2O), δ 3.6 (m, 4H, NCH_2CH_2O), δ 3.5 (m, 4H, CH_2CH_2N), δ 1.4 (s, 18H, $(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 165.9 (Ar-*C*=O), 159.7 (Ar-*C*), 155.1 (N*C*=O), 136.4, 128.5, 128.1, 127.5, 108.3, 107.1 (Ar-*C*), 80.0 ($C(CH_3)_3$), 76.6 (CH_2OPh), 70.2 (OCH_2CH_2N), 62.9 (OCH_2CH_2N), 46.5, 46.4 (NCH_2CH_2N), 28.3 ($C(CH_3)_3$); Electrospray MS for $C_{58}H_{64}N_2O_{12}$ ($M+ H^+$) 981.

3,5-Bisbenzyloxy-benzoic acid 2-[2-(2-{3,5-bisbenzyloxy}-ethylamino)-ethylamino]-ethyl ester-(85)

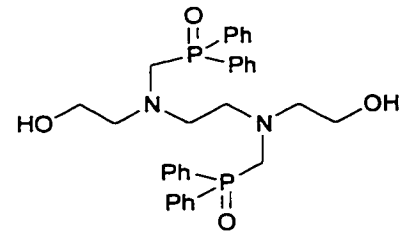


BOC amine (**84**) (216 mg, 0.2 mmol) was treated with trifluoroacetic acid (0.068 mL, 0.88 mmol) in dichloromethane (5 mL) and 1,3-dimethoxybenzene (0.02 mL, 0.16 mmol). The solution was left to stir for 7 hours. The excess acid was removed under high pressure and then the remaining oil was washed with sodium bicarbonate (2 x 15 mL) in dichloromethane (10 mL). The organic extracts were dried and concentrated *in vacuo*. Column chromatography (5% methanol in

dichloromethane) afforded a yellow oil (156 mg, 35%). IR (neat, cm^{-1}) 3326, 2928, 2851, 1717, 1626, 1593, 1158, 1051; ^1H NMR (300 MHz, ($CDCl_3$) δ 7.5-7.2 (m, 24H, Ar*H*), δ 6.8 (s, 2H, *p*-ArCO_2-), δ 5.1 (s, 8H, OCH_2Ar), δ 4.4 (t, J=5.6 Hz, 4H, CH_2C=O), δ 3.4 (br s, 2H, N*H*), δ 3.0 (t, J=5.6 Hz, 4H, NCH_2CH_2O), δ 2.7 (m, 4H, CH_2CH_2N); ^{13}C NMR (75 MHz, $CDCl_3$) 166.5 (Ar-*C*=O), 160.1, 138.7, 132.3, 129.0, 128.5, 128.0, 108.9, 103.9 (Ar-*C*), 77.6 (CH_2OPh), 70.7 (OCH_2), 64.8 (NCH_2CH_2O), 49.5, 48.8 (NCH_2CH_2N); Electrospray MS for $C_{48}H_{48}N_2O_8$(M+ H^+) 781.

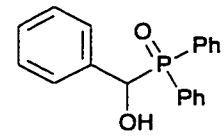
Experimental for chapter 5

2-((Diphenylphosphinoylmethyl)-{2-[(diphenylphosphinoylmethyl)-(2-hydroxyethyl)-amino]-ethyl}-amino)-ethanol (88)



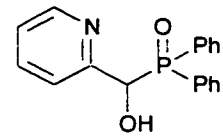
N,N'-bis(hydroxyethyl) ethylene diamine (148 mg, 1.0 mmol) and paraformaldehyde (63 mg, 2.0 mmol) were stirred at 50°C for 15 minutes. Ethyl diphenylphosphinite (0.43 mL, 2.0 mmol) was added slowly maintaining the temperature at 50°C over 20 minutes. This mixture was left stirring for a further 90 minutes. The solvent was removed *in vacuo* leaving an oily residue. Addition of dichloromethane afforded a white solid (289 mg, 50%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.8-7.4 (m, 20H, Ar*H*), δ 3.6 (br s, 2H, O*H*), δ 3.45 (m, 4H, CH_2OH), δ 3.4 (m, 4H, CH_2CH$_2$OH), δ 2.4 (s, 8H, CH_2N); ^{13}C NMR (50 MHz, $CDCl_3$) 132.4, 131.9, 131.1 (d, J=2.9 Hz), 128.7 (d, J=3.8 Hz), 60.1 (*C*H$_2$OH), 58.8 (*C*H$_2$CH$_2$OH), 55.4 (*C*H$_2$N), 54.9 (*C*H$_2$P); ^{31}P NMR (121 MHz, $CDCl_3$) δ 30.9.

(Diphenylphosphinoyl)phenyl-methanol-(91)



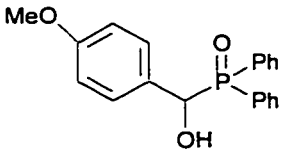
Benzaldehyde (1 ml, 10 mmol) and diphenylphosphine (1.75 mL, 10 mmol) were stirred in a THF (10 mL) solution overnight. The solvent was removed *in vacuo* and the resulting off white solid was recrystallised in methanol affording a white crystalline solid (2.1 g, 67%). IR (KBr, cm^{-1}) 3210, 3059, 1435, 1163, 722, 693; ^{1}H NMR (200 MHz, DMSO-d6) δ 7.9-7.0 (m, 15H, Ar*H*), δ 5.5 (d, J=4.6, 1H, C*H*); ^{13}C NMR (75 MHz, DMSO-d6) 138.1, 131.9 (d, J=8.5 Hz), 131.6 (m), 131.3 (d, J=8.8 Hz), 128.3 (d, J=10.7 Hz), 128.1 (d, J=10.7 Hz), 127.7 (d, J=4.4 Hz), 127.5 (d, J=2.2 Hz), 127.4 (d, J=2.7 Hz), (Ar*C*), 72.1 (d, J=86.4 Hz, *C*H); ^{31}P NMR δ 33.2; Electrospray MS for $C_{19}H_{17}O_2P$ (M+ H^+) 309, (2M+ H^+) 617; m.pt. 154-157 °C.

(Diphenylphosphinoyl)-pyridin-2-yl-methanol-(92)



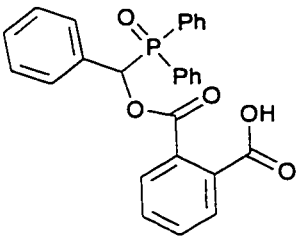
IR (KBr, cm^{-1}) 3211, 3059, 1584, 1433, 1156, 1060, 722, 691; ^{1}H NMR (200 MHz, CD_3OD) δ 8.4-7.1 (m, 14H, Ar*H*), δ 5.6 (d, J=8 Hz, 1H, C*H*); Elemental anal. calcd C 69.89, H 5.21, N 4.53, found C 69.12, H 5.04, N 4.28; melting point 167-168°C, FAB MS for $C_{18}H_{17}NO_2P$ (M+ H^+) 311.

(Diphenylphosphinoyl)-(4-methoxyphenyl)-methanol-(93)



^{1}H NMR (200 MHz, CD_3OD) δ 7.9-6.7 (m, 14H, Ar*H*), δ 6.3 (dd, J_{P-H}=18.6 Hz, J_{H-H} =5.1 Hz, 1H, C*H*), δ 5.5 (br s, 1H, O*H*), δ 3.6 (s, 3H OCH_3); ^{13}CNMR (300 MHz, CD_3OD) 160.0, 132.7, 132.3 (d, J=10.4 Hz), 131.8 (d, J=9.3 Hz), 131.6 (d, J=9.3 Hz), 131.3 (d, J=9.6 Hz), 129.1, 129.0, 128.9, 128.6 (d, J=11.8), 128.4, 128.3, 113.3 (Ar*C*), 72.7 (d, J=89.5 Hz), 54.6 (OCH_3); melting point 152-155°C; Electrospray MS for $C_{20}H_{19}O_3P$ ($M + H^+$) 339.

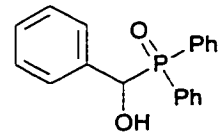
Phthalic acid mono-[(diphenylphosphinoyl)-phenylmethyl] ester-(94)



(Diphenylphosphinoyl)phenyl-methanol (836 mg, 2.7 mmol) was dissolved in pyridine (20 mL) and then treated with phthalic anhydride (987 mg, 6.7 mmol). The mixture was heated to 80°C for 4 hours, then allowed to cool. This solution was then poured into dilute HCl (30 mL) and washed with dichloromethane (3 x 20 mL). The organic extracts were collected, dried and concentrated *in vacuo*. Recrystallisation in

methanol afforded a white solid (780 mg, 66% yield). IR (KBr, cm^{-1}) 3064, 2800, 1748, 1701, 1275, 1248, 1146, 1060, 780; ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.0-6.9 (m, 19H, Ar*H*), δ 5.55 (d, J=6 Hz, 1H, C*H*); ^{13}C NMR (50 MHz, DMSO-d_6) 167.5 (*C*=O), 165.7 (*C*=O, d, J=9.2 Hz), 132.3, 131.5 (d, J=7 Hz), 131.2 (d, J=7.4 Hz), 131.1, 129.0, 128.7 (d, J=4 Hz), 128.5 (d, J=4 Hz), 128.2, 128.1 (d, J=4.4 Hz), 127.8, 127.7 (ArC), 73.6 (d, J=82.4 Hz, *C*H); ^{31}P NMR δ 32.7; Electrospray MS for $C_{27}H_{21}O_5P$ (M) 456, ($M + H^+$) 457.

Transesterification of (Diphenylphosphinoyl)phenyl-methanol



(Diphenylphosphinoyl)phenyl-methanol (0.1 g, 0.325 mmol), methyl propionate (0.035 ml, 0.36 mmol) and porcine pancreatic lipase (0.2 g) were added to diethyl ether (10 ml). This suspension was stirred in a water bath at 30°C for 3 days. The mixture was then filtered to remove the enzyme and washed with methanol and then ethanol. The washings were concentrated *in vacuo* to give a white solid, compound **91**.

General procedure for the hydroformylation reaction using (diphenyl-phosphinoyl)phenyl-methanol

The following is a typical procedure: The catalyst was placed in a stainless steel autoclave with a glass liner equipped with a stirring bar, under a stream of nitrogen. The olefinic substrate (2 mmol), $[Rh(CO)_2Cl]_2$ (0.012 mmol), (diphenylphosphinoyl)phenyl methanol (0.024 mmol) were mixed with chloroform (2 mL). The autoclave was purged three times with carbon monoxide, in order to displace any air, then charged with a 1:1 ratio of carbon monoxide and hydrogen gases. The autoclave was placed in an oil bath with sufficient silicone oil to cover the majority of the autoclave and heated to the appropriate temperature.

Experimental References

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Appendix

3.1 Method for alkylation of diol 54

Diol **54** (217 mg, 0.44 mmol), tetrabutyl ammonium bromide (3 mg, 9 $x10^{-6}$ mmol) and sodium hydride (23 mg, 0.90 mmol) were dissolved in DMF (4 mL) at 0°C and treated with ethyl bromoacetate (0.11 mL, 0.90 mmol) in THF (4 mL). The reaction mixture was allowed to stir overnight, then poured into ethyl acetate (10 mL) and washed with water (2 x 5 mL) and brine (5 mL). The collected organic extracts were dried and concentrated *in vacuo*.

4.1 Method of carboxylic acid activation with trifluoroacetic anhydride

Carboxylic acid **38** (492 mg, 0.80 mmol) in benzene (20 mL) was treated with trifluoroacetic anhydride (0.4 mL, 2.8 mmol) at 35°C for 30 min before alcohol **67** (123 mg, 0.40 mmol) was added as a solution in benzene (7 mL). After stirring overnight, the reaction mixture was washed with 5M NaOH solution (2 x 10 mL), the organic phase was dried and the solvent removed *in vacuo*.

4.2 Typical method for ester formation under Mitsonobu conditions

Typical procedure: PPh_3 (130 mg, 0.48 mmol) and DEAD (0.07 mL, 0.48 mmol) were mixed together at 0°C in THF (20 mL) and allowed to stir for 10 minutes, alcohol **67** (7 mg, 0.2 mmol) was then added and the reaction mixture was stirred for 30 min before the addition of carboxylic acid **38** (210 mg, 0.48 mmol). The resulting mixture was stirred for a further 20 hours. The THF was removed *in vacuo* and a standard work-up procedure was carried out.

4.3 Formation of Acid Chloride 82

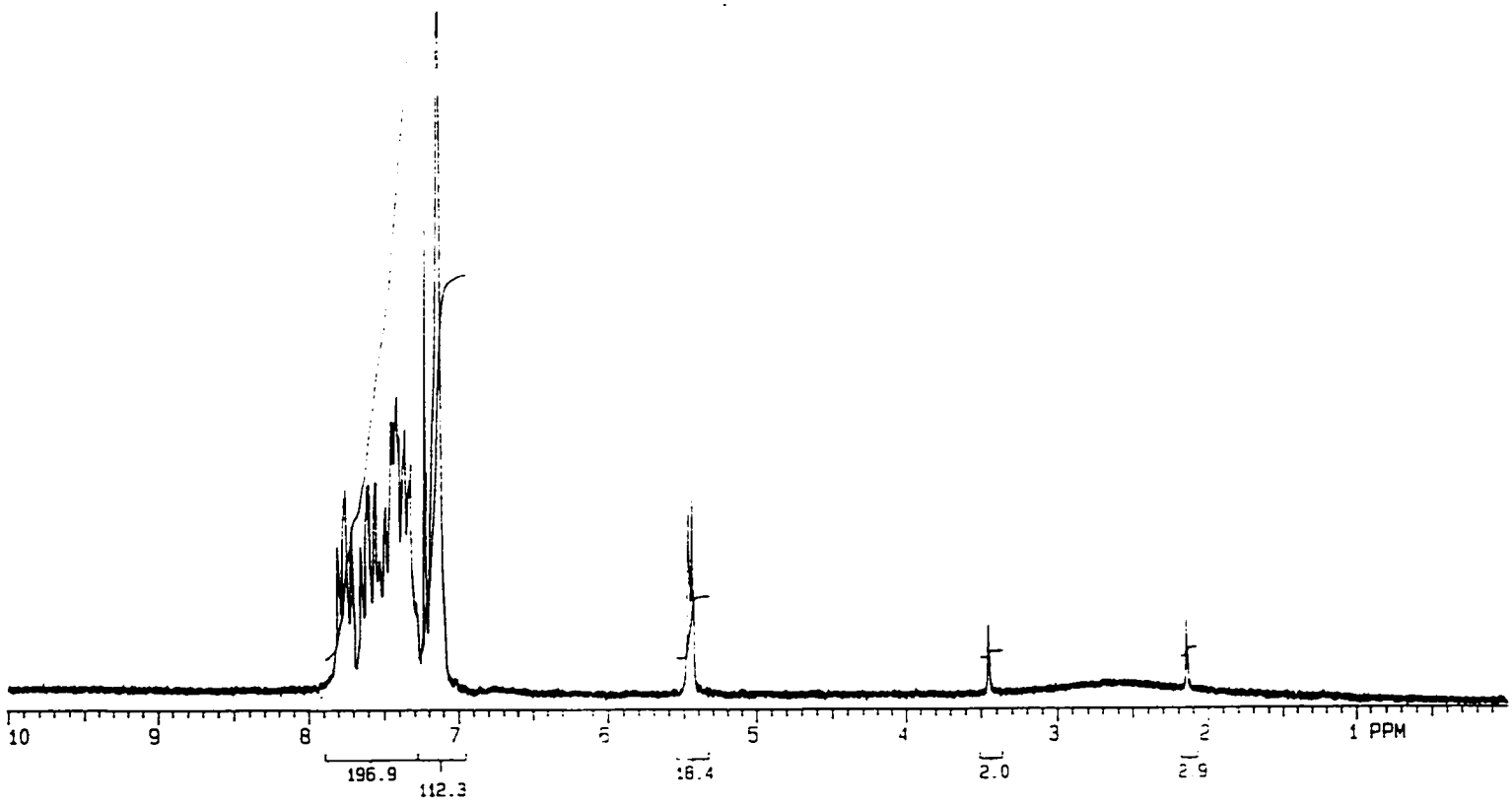
Carboxylic acid **38** (380 mg, 0.60 mmol) and $SOCl_2$ (0.5 mL, 3.8 mmol) were heated in benzene (3 mL) to 40°C for 40 min. The excess $SOCl_2$ was removed *in*

vacuo. The residue was then treated with alcohol **67** (70 mg, 0.30 mmol) in CH_2Cl_2 (4 mL) and Et_3N (0.2 mL, 1.2 mmol). After stirring at room temperature overnight, the mixture was passed down a small column of florisil affording a red oil.

4.4 Reaction of bromide 44 and 1,6-hexanediol

Bromide **44** (58 mg, 0.12 mmol) and 1,6-hexanediol (59 mg, 0.05 mmol) were stirred in DMF (25 mL) with Ag_2O (180 mg, 0.04 mmol), in darkness at 60°C for 72 hours. The reaction mixture was filtered and the DMF removed *in vacuo*.

5.1 ^{1}H NMR of (diphenylphosphinoyl)phenyl-methanol (91)



5.2 Data for Crystal Structure of (diphenylphosphinoyl)phenyl-methanol (91)

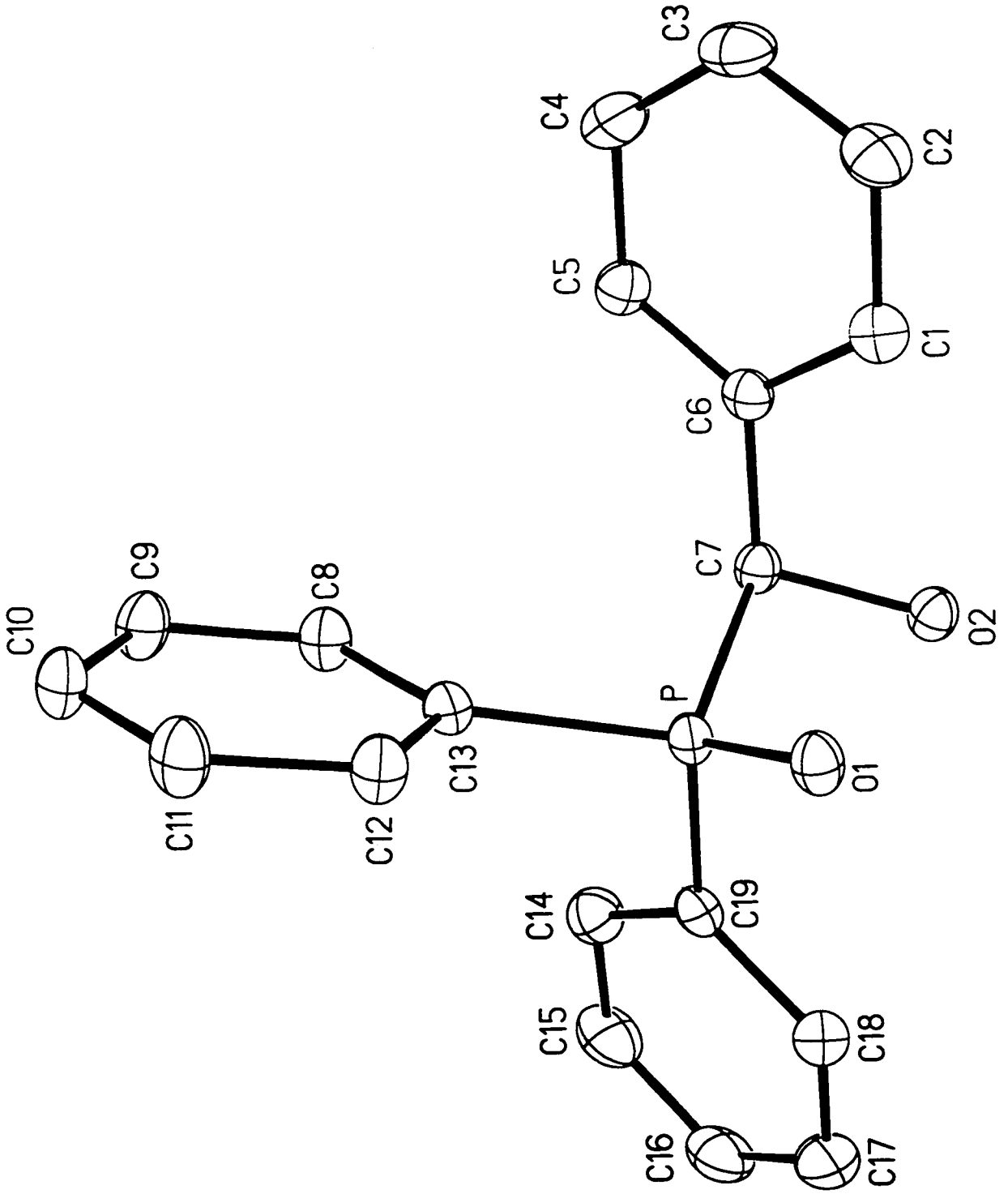

C3
C4
C2
C5
C1
C6
C7
O2
C9
C8
C10
P
C13
O1
C11
C12
C14
C19
C15
C18
C16
C17

Table 1. Crystal data and structure refinement for ha043.

Identification code	ha043
Empirical formula	C19 H17 O2 P
Formula weight	308.30
Temperature	203(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)/n
Unit cell dimensions	a = 11.1921(10) A alpha = 90 deg. b = 6.2930(6) A beta = 92.136(2) deg. c = 21.8388(19) A gamma = 90 deg.
Volume	1537.1(2) A^3
Z, Calculated density	4, 1.332 Mg/m^3
Absorption coefficient	0.183 mm^-1
F(000)	648
Crystal size	0.30 x 0.14 x 0.12 mm
Theta range for data collection	1.87 to 28.78 deg.
Limiting indices	-14<=h<=15, 0<=k<=8, 0<=l<=29
Reflections collected / unique	12010 / 3661 [R(int) = 0.0227]
Completeness to theta = 28.78	91.4 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.928075 and 0.811057
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3661 / 0 / 199
Goodness-of-fit on F^2	1.060
Final R indices [I>2sigma(I)]	R1 = 0.0373, wR2 = 0.1001
R indices (all data)	R1 = 0.0492, wR2 = 0.1042
Largest diff. peak and hole	0.350 and -0.311 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for ha043.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
P	5528(1)	4779(1)	1822(1)	24(1)
O(1)	5874(1)	7073(2)	1796(1)	31(1)
O(2)	7295(1)	3800(2)	2515(1)	30(1)
C(1)	8430(1)	4772(2)	1362(1)	33(1)
C(2)	9270(2)	4745(3)	911(1)	39(1)
C(3)	9385(2)	2981(3)	542(1)	43(1)
C(4)	8660(2)	1232(3)	623(1)	40(1)
C(5)	7818(1)	1242(2)	1073(1)	32(1)
C(6)	7694(1)	3013(2)	1445(1)	26(1)
C(7)	6808(1)	3001(2)	1950(1)	25(1)
C(8)	4578(1)	1850(2)	945(1)	32(1)
C(9)	3903(2)	1391(2)	416(1)	37(1)
C(10)	3361(2)	3010(3)	76(1)	38(1)
C(11)	3503(2)	5090(3)	258(1)	42(1)
C(12)	4182(2)	5564(2)	783(1)	35(1)
C(13)	4719(1)	3950(2)	1133(1)	25(1)
C(14)	4062(2)	2253(3)	2537(1)	39(1)
C(15)	3344(2)	1907(3)	3033(1)	50(1)
C(16)	3154(2)	3535(4)	3442(1)	51(1)
C(17)	3664(2)	5493(3)	3363(1)	50(1)
C(18)	4383(2)	5857(3)	2871(1)	38(1)
C(19)	4585(1)	4234(2)	2455(1)	29(1)

Table 3. Bond lengths [A] and angles [deg] for ha043.

P-O(1)	1.4961(10)
P-C(19)	1.8024(15)
P-C(13)	1.8040(14)
P-C(7)	1.8315(14)
O(2)-C(7)	1.4208(16)
C(1)-C(2)	1.386(2)
C(1)-C(6)	1.396(2)
C(2)-C(3)	1.380(3)
C(3)-C(4)	1.382(3)
C(4)-C(5)	1.388(2)
C(5)-C(6)	1.389(2)
C(6)-C(7)	1.5111(19)
C(8)-C(9)	1.388(2)
C(8)-C(13)	1.3911(19)
C(9)-C(10)	1.386(2)
C(10)-C(11)	1.375(2)
C(11)-C(12)	1.384(2)
C(12)-C(13)	1.394(2)
C(14)-C(15)	1.389(2)
C(14)-C(19)	1.392(2)
C(15)-C(16)	1.381(3)
C(16)-C(17)	1.372(3)
C(17)-C(18)	1.385(2)
C(18)-C(19)	1.391(2)

O(1)-P-C(19)	111.85(7)
O(1)-P-C(13)	111.72(6)
C(19)-P-C(13)	107.13(7)
O(1)-P-C(7)	113.14(6)
C(19)-P-C(7)	104.11(6)
C(13)-P-C(7)	108.44(6)
C(2)-C(1)-C(6)	120.12(14)
C(3)-C(2)-C(1)	120.29(16)
C(2)-C(3)-C(4)	119.89(15)
C(3)-C(4)-C(5)	120.27(15)
C(4)-C(5)-C(6)	120.20(15)
C(5)-C(6)-C(1)	119.22(14)
C(5)-C(6)-C(7)	120.37(13)
C(1)-C(6)-C(7)	120.37(13)
O(2)-C(7)-C(6)	113.07(11)
O(2)-C(7)-P	100.90(8)
C(6)-C(7)-P	114.56(9)
C(9)-C(8)-C(13)	119.76(13)
C(10)-C(9)-C(8)	120.37(14)
C(11)-C(10)-C(9)	120.18(14)
C(10)-C(11)-C(12)	119.82(14)
C(11)-C(12)-C(13)	120.66(14)
C(8)-C(13)-C(12)	119.19(14)
C(8)-C(13)-P	124.68(11)
C(12)-C(13)-P	116.11(11)
C(15)-C(14)-C(19)	120.00(16)
C(16)-C(15)-C(14)	119.67(18)
C(17)-C(16)-C(15)	120.69(17)
C(16)-C(17)-C(18)	120.14(17)
C(17)-C(18)-C(19)	119.94(16)
C(18)-C(19)-C(14)	119.55(15)

C(18)-C(19)-P	118.39(12)
C(14)-C(19)-P	122.06(12)

Symmetry transformations used to generate equivalent atoms:

5.3 Data for Crystal Structure of (diphenylphosphinoyl)pyridin-2-yl-methanol-(92)

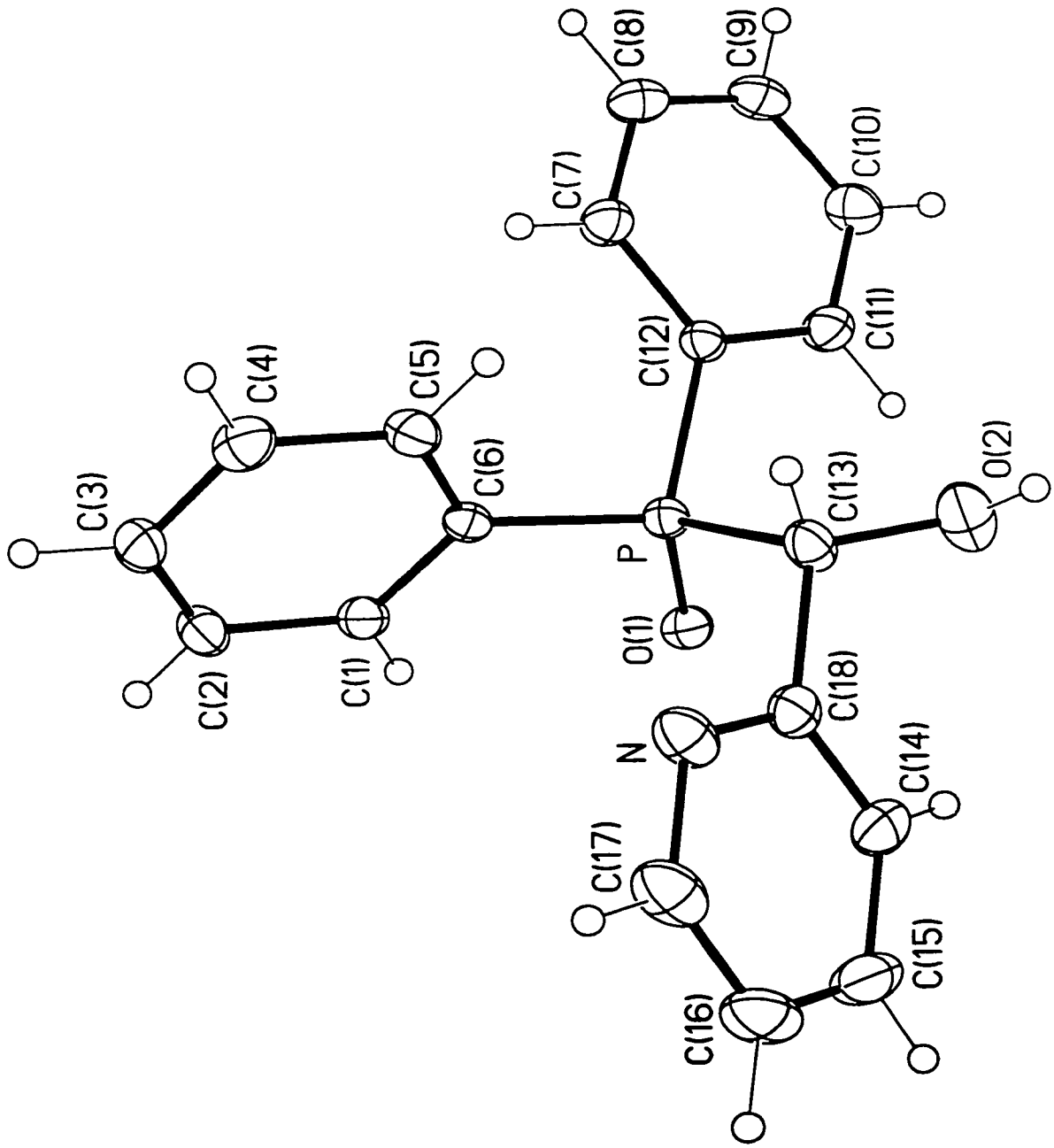

C(8)
C(9)
C(10)
C(7)
C(11)
C(12)
C(4)
C(5)
C(6)
C(3)
C(13)
O(2)
P
O(1)
C(2)
C(1)
C(18)
N
C(14)
C(17)
C(15)
C(16)

Table 1. Crystal data and structure refinement for ha028.

Identification code	ha028
Empirical formula	C18 H16 N O2 P
Formula weight	309.29
Temperature	203(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)
Unit cell dimensions	a = 9.146(1) A alpha = 90 deg. b = 8.926(1) A beta = 105.147(2) deg c = 9.639(1) A gamma = 90 deg.
Volume	759.5(2) A^3
Z, Calculated density	2, 1.352 Mg/m^3
Absorption coefficient	0.187 mm^-1
F(000)	324
Crystal size	0.4 x 0.3 x 0.3 mm
Theta range for data collection	2.19 to 28.81 deg.
Limiting indices	-12<=h<=11, -11<=k<=11, 0<=l<=12
Reflections collected / unique	5997 / 3428 [R(int) = 0.0403]
Completeness to theta = 28.81	91.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.928076 and 0.733458
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3428 / 1 / 199
Goodness-of-fit on F^2	1.026
Final R indices [I>2sigma(I)]	R1 = 0.0474, wR2 = 0.1141
R indices (all data)	R1 = 0.0584, wR2 = 0.1178
Absolute structure parameter	0.05(12)
Largest diff. peak and hole	0.782 and -0.254 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for ha028.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
P	1431(1)	8318(1)	3660(1)	26(1)
O(1)	1050(2)	6693(2)	3622(2)	34(1)
O(2)	22(3)	9133(3)	5590(3)	52(1)
N	-2022(3)	10012(3)	1991(3)	43(1)
C(1)	1431(3)	7963(3)	846(3)	32(1)
C(2)	1481(3)	8436(4)	-516(3)	40(1)
C(3)	1671(3)	9931(4)	-787(3)	42(1)
C(4)	1808(3)	10956(3)	310(3)	39(1)
C(5)	1746(3)	10506(3)	1663(3)	33(1)
C(6)	1565(3)	8996(3)	1940(3)	28(1)
C(7)	4345(3)	9571(4)	4719(3)	36(1)
C(8)	5710(3)	9708(4)	5749(4)	41(1)
C(9)	5941(3)	8983(3)	7040(3)	39(1)
C(10)	4799(3)	8122(4)	7322(3)	42(1)
C(11)	3440(3)	7983(3)	6300(3)	37(1)
C(12)	3189(3)	8697(3)	4979(3)	28(1)
C(13)	-31(3)	9473(4)	4156(3)	34(1)
C(14)	-2444(3)	7944(4)	3427(4)	46(1)
C(15)	-3850(4)	7724(4)	2490(5)	57(1)
C(16)	-4321(4)	8639(5)	1328(4)	56(1)
C(17)	-3387(4)	9737(4)	1105(4)	53(1)
C(18)	-1575(3)	9115(3)	3152(3)	35(1)

Table 3. Bond lengths [A] and angles [deg] for ha028.

P-O(1)	1.491(2)
P-C(6)	1.799(3)
P-C(12)	1.802(3)
P-C(13)	1.848(3)
O(2)-C(13)	1.403(3)
N-C(18)	1.350(4)
N-C(17)	1.338(4)
C(1)-C(6)	1.382(4)
C(1)-C(2)	1.391(4)
C(2)-C(3)	1.379(5)
C(3)-C(4)	1.379(5)
C(4)-C(5)	1.380(4)
C(5)-C(6)	1.392(4)
C(7)-C(8)	1.382(4)
C(7)-C(12)	1.389(4)
C(8)-C(9)	1.369(5)
C(9)-C(10)	1.380(5)
C(10)-C(11)	1.375(4)
C(11)-C(12)	1.388(4)
C(13)-C(18)	1.523(4)
C(14)-C(18)	1.380(4)
C(14)-C(15)	1.379(4)
C(15)-C(16)	1.362(5)
C(16)-C(17)	1.354(5)
O(1)-P-C(6)	112.15(12)
O(1)-P-C(12)	111.09(11)
C(6)-P-C(12)	108.94(12)
O(1)-P-C(13)	111.64(14)
C(6)-P-C(13)	106.19(13)
C(12)-P-C(13)	106.55(12)
C(18)-N-C(17)	116.7(3)
C(6)-C(1)-C(2)	119.9(3)
C(3)-C(2)-C(1)	120.6(3)
C(2)-C(3)-C(4)	119.1(3)
C(5)-C(4)-C(3)	120.9(3)
C(4)-C(5)-C(6)	119.9(3)
C(1)-C(6)-C(5)	119.4(3)
C(1)-C(6)-P	117.7(2)
C(5)-C(6)-P	122.9(2)
C(8)-C(7)-C(12)	120.5(3)
C(9)-C(8)-C(7)	120.5(3)
C(8)-C(9)-C(10)	119.8(3)
C(11)-C(10)-C(9)	119.9(3)
C(10)-C(11)-C(12)	121.1(3)
C(7)-C(12)-C(11)	118.2(2)
C(7)-C(12)-P	124.0(2)
C(11)-C(12)-P	117.7(2)
O(2)-C(13)-C(18)	111.6(2)
O(2)-C(13)-P	107.02(19)
C(18)-C(13)-P	109.4(2)
C(18)-C(14)-C(15)	117.9(3)
C(16)-C(15)-C(14)	119.6(3)
C(15)-C(16)-C(17)	119.2(3)
N-C(17)-C(16)	123.6(4)
N-C(18)-C(14)	123.0(3)

N-C(18)-C(13)	115.6(3)
C(14)-C(18)-C(13)	121.5(3)

Symmetry transformations used to generate equivalent atoms:

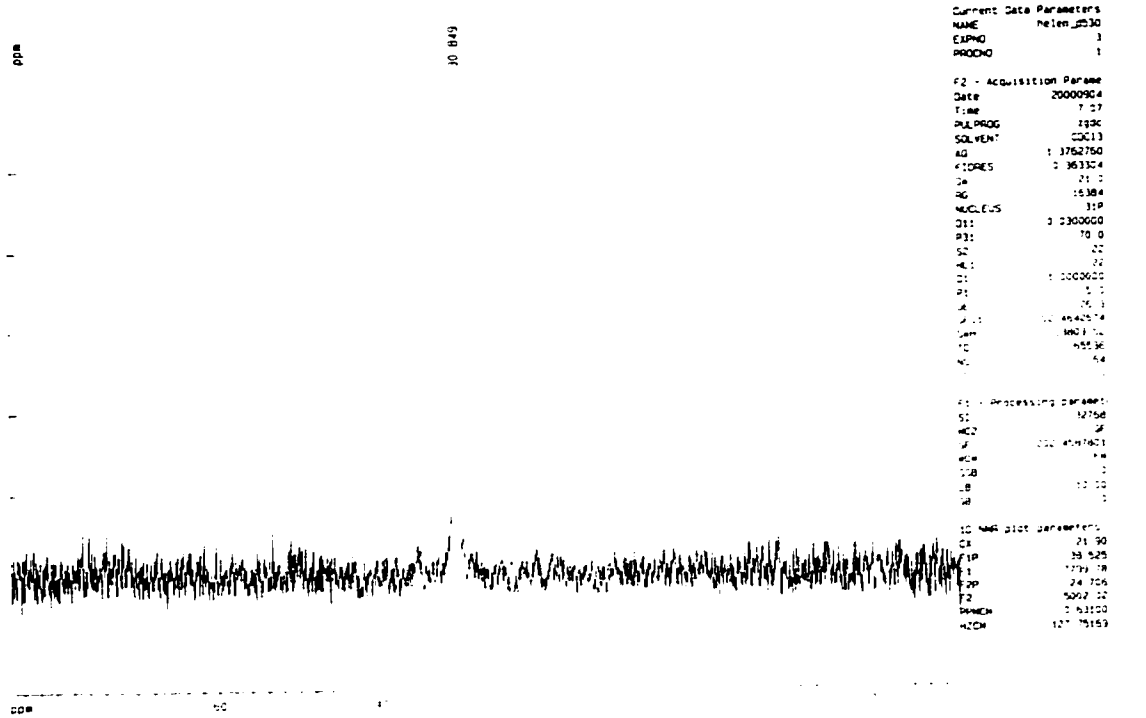
Table 4. Anisotropic displacement parameters (A^2 x 10^3) for ha043. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

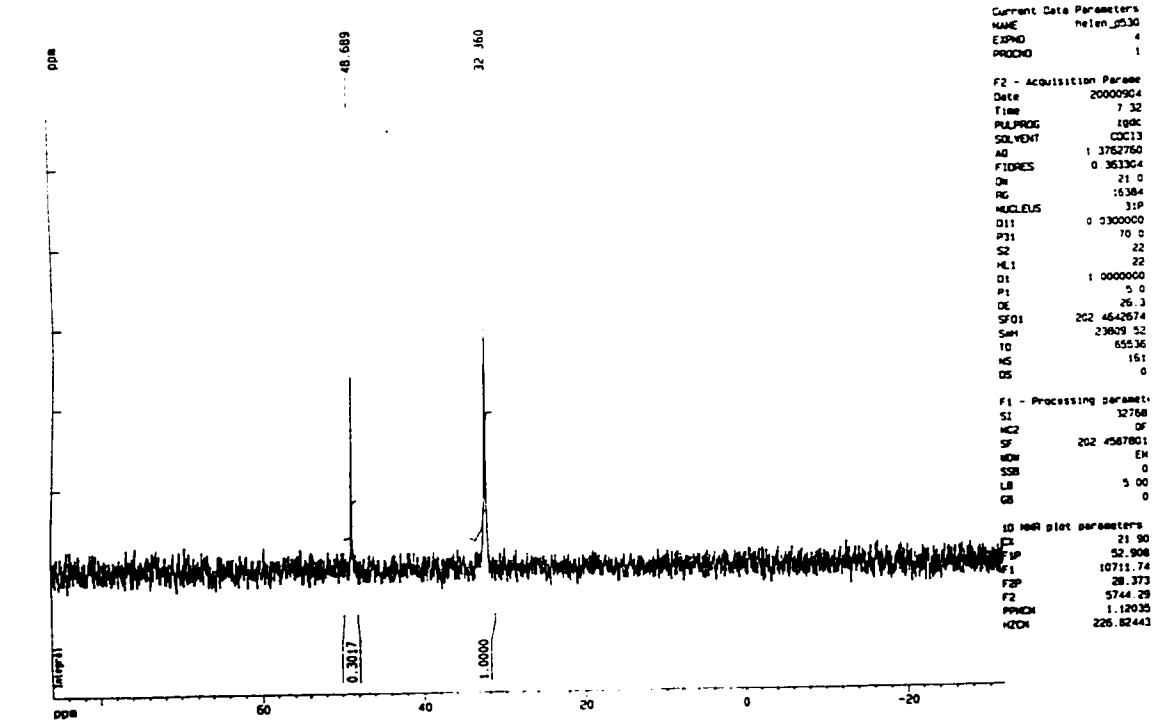
	U11	U22	U33	U23	U13	U12
P	24(1)	21(1)	27(1)	-1(1)	-5(1)	0(1)
O(1)	32(1)	22(1)	38(1)	0(1)	-10(1)	-1(1)
O(2)	30(1)	30(1)	28(1)	-2(1)	-9(1)	5(1)
C(1)	34(1)	31(1)	33(1)	2(1)	-2(1)	0(1)
C(2)	37(1)	42(1)	39(1)	9(1)	2(1)	-4(1)
C(3)	41(1)	55(1)	33(1)	7(1)	9(1)	7(1)
C(4)	46(1)	42(1)	33(1)	-5(1)	4(1)	9(1)
C(5)	34(1)	31(1)	32(1)	-1(1)	-2(1)	2(1)
C(6)	25(1)	28(1)	26(1)	3(1)	-5(1)	3(1)
C(7)	27(1)	23(1)	24(1)	0(1)	-5(1)	1(1)
C(8)	38(1)	24(1)	34(1)	3(1)	-10(1)	0(1)
C(9)	47(1)	27(1)	36(1)	-4(1)	-10(1)	-5(1)
C(10)	42(1)	39(1)	31(1)	-2(1)	-13(1)	-2(1)
C(11)	51(1)	32(1)	41(1)	3(1)	-20(1)	6(1)
C(12)	42(1)	24(1)	38(1)	-1(1)	-12(1)	4(1)
C(13)	24(1)	25(1)	26(1)	0(1)	-4(1)	-1(1)
C(14)	37(1)	39(1)	41(1)	-2(1)	2(1)	-6(1)
C(15)	37(1)	59(1)	53(1)	11(1)	4(1)	-10(1)
C(16)	35(1)	78(1)	42(1)	4(1)	8(1)	1(1)
C(17)	42(1)	68(1)	40(1)	-13(1)	5(1)	3(1)
C(18)	33(1)	43(1)	38(1)	-8(1)	-1(1)	-1(1)
C(19)	23(1)	34(1)	31(1)	0(1)	-4(1)	1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for ha043.

	x	y	z	U(eq)
H(2A)	7833	2994	2646	45
H(1A)	8356	5978	1612	39
H(2B)	9764	5933	856	47
H(3A)	9955	2968	237	51
H(4A)	8738	32	371	48
H(5A)	7330	45	1127	39
H(7A)	6517	1533	2011	30
H(8A)	4938	747	1176	39
H(9A)	3812	-27	287	44
H(10A)	2896	2685	-279	45
H(11A)	3139	6187	26	50
H(12A)	4282	6988	904	42
H(14A)	4195	1150	2258	47
H(15A)	2989	571	3089	59
H(16A)	2669	3299	3778	62
H(17A)	3526	6591	3644	60
H(18A)	4734	7198	2818	46

5.4 Variable ^{1}H NMR of (diphenylphosphinoyl)-methanol-(84) and chlorodicarbonyl rhodium (I) dimer





5.5 Attempted formation of diastereoisomers of (diphenylphosphinoyl)phenyl-methanol and *N*-(*tert*-butoxycarbonyl) alanine

(Diphenylphosphinoyl)phenyl-methanol (**84**) (440 mg, 1.3 mmol), DMAP (194 mg, 1.6 mmol), HATU (602 mg, 1.6 mmol) and *N*-(*tert*-butoxycarbonyl) alanine (300 mg, 1.6 mmol) were dissolved in CH_2Cl_2 (10 mL) and DMF (20 mL) and left to stir for 24 hours. The reaction mixture was washed with water (2 x 10 mL) and chloroform (2 x 10 mL), the organic extracts were collected, dried and concentrated *in vacuo*.

Claims to Original Research

1) The synthesis of a new tetra-phosphine, 4,5-bis(bis[{diphenyl-phosphanyl}methyl]aminomethyl)-2,2-dimethyl-[1,3]dioxolane and a new bis-phosphine, *N,N'*-bis-(2-benzyloxyethyl)-*N,N'*-bis-[(diphenylphosphanyl)methyl]-ethane-1,2-diamine, were carried out.

2) The hydroformylation reactions of several olefin substrates were undertaken using rhodium(I) complexes of 4,5-bis(bis[{diphenyl-phosphanyl}methyl]aminomethyl)-2,2-dimethyl-[1,3]dioxolane and *N,N'*-bis-(2-benzyloxyethyl)-*N,N'*-bis-[(diphenylphosphanyl)methyl]-ethane-1,2-diamine

3) A novel phosphine oxide ligand, (diphenylphosphinoyl)phenyl-methanol, was synthesised and employed, as a ligand, in the rhodium-catalysed hydroformylation and enantioselective hydroformylation reactions of a range of aryl and alkyl alkenes.