Rhodium Catalyzed Hydroformylation: Adventures in Heterogeneous and Recyclable Systems
Rhodium Catalyzed Hydroformylation: Adventures in Heterogeneous and Recyclable Systems

by

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Canada
To my family
and to Joe.
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ABSTRACT

The synthesis of dendritic ligands supported on silica gel and polymers, and their use in the rhodium catalyzed hydroformylation reaction is presented in this thesis. In building a softer, more organic moiety on the surface of a heterogeneous support, the potential of uniting the advantages of heterogeneous catalysis with that of homogeneous systems is explored.

The synthesis of polyamidoamine (PAMAM) dendrimers anchored on silica, via the iterative additions of methylacrylate and ethylenediamine to aminopropyl silica, is carried out. A series of C₄, C₆ and C₁₂ diamines were also used to construct PAMAM dendrimers with longer diamine linkers. Phosphorylation of the various PAMAM dendrimers on silica was accomplished and the supported bis–(diphenylphosphanylmethylated) ligands were complexed to rhodium.

The heterogeneous complexes were found to be effective catalysts for the hydroformylation of various aryl olefins and vinyl esters, showing good to excellent regio–selectivity for the branched aldehydes. Aliphatic olefins were also easily converted into the corresponding aldehydes, however, only a slight excess of the linear product was observed.

Rhodium complexes of bis–(diphenylphosphanylmethylated) pseudopeptide based ligands immobilized on resin were prepared and studied in the hydroformylation of various olefins. The effect of relocating the metal centers from the periphery to the interior of the dendrimer was also examined.
The recyclability of the aforementioned heterogeneous catalysts was investigated, however, leaching of the metal from the support and the accompanying loss of activity is observed.

The synthesis of PAMAM and polyarylether ligand supported on PEG was attempted. The preparation of a soluble triphenylphosphite supported on PEG was also attempted and the crude system was evaluated as a recyclable ligand for the hydroformylation of 1-octene. Preliminary investigations into the activity of the zwitterionic \((\eta^6-C_6H_5BPh_3)^\text{-Rh}(\,1,5\text{-cyclooctadiene})\) complex with phosphite under mild hydroformylation conditions resulted in a surprising regioselective outcome where the industrially more important linear aldehyde of 1-octene was favoured with high selectivity.
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**LIST OF ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Å</td>
<td>Angstrom</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl (−COCH₃)</td>
</tr>
<tr>
<td>Ac₂O</td>
<td>acetic anhydride</td>
</tr>
<tr>
<td>AcOH</td>
<td>acetic acid</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl (−C₆R₅) or argon</td>
</tr>
<tr>
<td>ATR</td>
<td>attenuated total reflectance</td>
</tr>
<tr>
<td>atm</td>
<td>atmosphere</td>
</tr>
<tr>
<td>BET</td>
<td>Brunauer, Emmett, and Teller Method (for measuring the surface area of solid catalysts and other high surface area materials using adsorption of nitrogen gas)</td>
</tr>
<tr>
<td>B:L</td>
<td>branched:linear</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl (−CH₂C₆H₅)</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butoxycarbonyl (−COOC(CH₃)₃)</td>
</tr>
<tr>
<td>C</td>
<td>Celcius</td>
</tr>
<tr>
<td>Cbz</td>
<td>carbobenzoxy (−OCOCH₂C₆H₅)</td>
</tr>
<tr>
<td>cod</td>
<td>1,4-cyclooctadiene (C₈H₁₂)</td>
</tr>
<tr>
<td>cm⁻¹</td>
<td>wavenumbers</td>
</tr>
<tr>
<td>CPMAS</td>
<td>cross polarization magic angle spinning</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Cy</td>
<td>cyclohexyl, (−C₆H₁₁)</td>
</tr>
<tr>
<td>DAB</td>
<td>poly(propylene imine)–diaminobutane</td>
</tr>
<tr>
<td>DCC</td>
<td>dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane, (CH₂Cl₂)</td>
</tr>
<tr>
<td>DIC</td>
<td>diisopropylcarbodiimide</td>
</tr>
<tr>
<td>DIEA</td>
<td>diisopropylethylamine</td>
</tr>
<tr>
<td>DIPEA</td>
<td>diisopropylethylamine</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide, (HCON(CH₃)₂)</td>
</tr>
<tr>
<td>DMSO–d₆</td>
<td>deuterated dimethylsulfoxide, (CD₃SOCD₃)</td>
</tr>
<tr>
<td>EDA</td>
<td>ethylenediamine, (NH₂CH₂CH₂NH₂)</td>
</tr>
<tr>
<td>e⁻</td>
<td>electron</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>e.g.</td>
<td><em>exempli gratia</em></td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionization</td>
</tr>
<tr>
<td>Equiv.</td>
<td>equivalent</td>
</tr>
<tr>
<td>EtOH</td>
<td>ethanol, (CH₃CH₂OH)</td>
</tr>
<tr>
<td>FAB</td>
<td>fast atom bombardment</td>
</tr>
<tr>
<td>Fmoc</td>
<td>9-fluorenlymethyl carbamate</td>
</tr>
<tr>
<td>FT–IR</td>
<td>Fourier–transform infra red</td>
</tr>
<tr>
<td>F.Wt.</td>
<td>formula weight</td>
</tr>
</tbody>
</table>
G generation
G_{x.5} half generation
GC gas chromatography
Gly glycine
GPC gel permeation chromatography
h hours
HATU [0–(7–azabenzotriao-l–yl)–1,1,3,3–tetramethyluronium hexafluorophosphate]
HBTU 2–(1H–benzotriazol–1–yl)–1,1,3,3–tetramethyluronium hexafluorophosphate
HOBT 1-hydroxybenzotriazole
HPLC high performance liquid chromatography
Hz Hertz
ICP inductive coupled plasma
J coupling in Hz
Kg kilogram
L ligand
LRMS low resolution mass spectrometry
MA methylacrylate
MALDI-TOF matrix assisted Laser desorption ionization time of flight
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBHA</td>
<td>4-methylbenzhydrylamine (polystyrene resins)</td>
</tr>
<tr>
<td>MCM</td>
<td>mobile crystalline material</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MeOH</td>
<td>methanol (CH₂OH)</td>
</tr>
<tr>
<td>mg</td>
<td>milligram</td>
</tr>
<tr>
<td>MHz</td>
<td>megahertz</td>
</tr>
<tr>
<td>ml</td>
<td>millimeter</td>
</tr>
<tr>
<td>mmol</td>
<td>millimole</td>
</tr>
<tr>
<td>Mol. Wt.</td>
<td>molecular weight</td>
</tr>
<tr>
<td>MPEG</td>
<td>mono-methoxy poly(ethylene glycol)</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>mtorr</td>
<td>millitorr</td>
</tr>
<tr>
<td>MW</td>
<td>molecular weight</td>
</tr>
<tr>
<td>nm</td>
<td>nanometer</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>n.r.</td>
<td>no reaction</td>
</tr>
<tr>
<td>NRC</td>
<td>National Research Council of Canada</td>
</tr>
<tr>
<td>OH</td>
<td>hydroxyl</td>
</tr>
<tr>
<td>OMe</td>
<td>methoxy</td>
</tr>
<tr>
<td>oz</td>
<td>ounce</td>
</tr>
</tbody>
</table>

xxvi
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$p$</td>
<td>para, 1,4-</td>
</tr>
<tr>
<td>PAMAM</td>
<td>poly(amidoamine)</td>
</tr>
<tr>
<td>Pd/C</td>
<td>palladium on carbon</td>
</tr>
<tr>
<td>PDI</td>
<td>polydispersity index</td>
</tr>
<tr>
<td>PEG</td>
<td>poly(ethyleneglycol)</td>
</tr>
<tr>
<td>PG</td>
<td>Protecting group</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl ($-C_6H_5$)</td>
</tr>
<tr>
<td>Phe</td>
<td>phenylalanine</td>
</tr>
<tr>
<td>PPI</td>
<td>poly(propyleneimine)</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>psi</td>
<td>pounds per square inch</td>
</tr>
<tr>
<td>psig</td>
<td>pounds per square inch (gauge pressure)</td>
</tr>
<tr>
<td>R</td>
<td>radical</td>
</tr>
<tr>
<td>rbf</td>
<td>round bottom flask</td>
</tr>
<tr>
<td>RI</td>
<td>refractive index</td>
</tr>
<tr>
<td>RT</td>
<td>room temperature ($21 , ^{\circ}C$)</td>
</tr>
<tr>
<td>$t$</td>
<td>tert-, tertiary</td>
</tr>
<tr>
<td>SAPC</td>
<td>supported aqueous phase catalyst</td>
</tr>
<tr>
<td>SBA</td>
<td>A high surface area, highly ordered nanoporous silicate</td>
</tr>
<tr>
<td>SEC</td>
<td>size exclusion chromatography</td>
</tr>
</tbody>
</table>
SPS  solid phase synthesis
SiO₂  silica
TADDOL  ααα’-tetraaryl-1,3-dioxolane-4,5-dimethanol
TEA  Triethylamine (NE₃)
TFA  Trifluoroacetic acid (CF₃COOH)
téo  theoretical
THF  tetrahydrofuran
TPP  triphenylphoshine
UHP  ultra high purity
w.r.t.  with respect to
X  heteroatom
zw  zwitterionic
°  degree
δ  chemical shift
η  eta
µm  micrometers
CHAPTER 1: INTRODUCTION

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1.0 GENERAL INTRODUCTION: THE SEARCH FOR THE IDEAL CATALYST

In a world where limited resources and the bottom line dictate just about every facet of life much can be said about the value of efficiency, versatility and capability. The field of catalysis is an excellent example with regards to these principles and remarkable efforts have been extended toward the development of the ideal catalyst. Such a catalyst would be both selective and efficient for the desired transformation but also be highly active and stable. Of course one must keep in mind the budget of the process and the practical issues involved in the industrial development of any catalytic system. Of major concern for any team implementing catalysis into their process is the cost versus economic payoff. In this respect, the ideal catalyst should be cheap, durable and reusable as well as selective, incredibly efficient, and operate under mild conditions.

With respect to durability and reusability, heterogeneous systems promise us stability, ease of recovery via simple phase separation, and the opportunity for recycling. However, heterogeneous systems are typically accompanied by a loss in activity as well as selectivity. Research in this field has diverged into many areas of study including the use of soluble dendrimers as an interface between the well-defined science of homogeneous catalysis and the black box realm of heterogeneous catalysis. This thesis is the result of one such study and details our efforts to develop new catalytic systems that efficiently combine the advantages of both heterogeneous and homogeneous catalysis with regard to the hydroformylation reaction.
1.1 DENDRIMERS: A BRIEF REVIEW

Also known as fractal polymers, arborols, or cascade molecules, dendrimers are globular macromolecules that are characterized by a highly branched structure radiating from a central core (Figure 1.1). A variety of central core moieties have been employed in literature ranging from a single multivalent atom such as silicon, carbon, or nitrogen to multi-substituted benzene rings or porphyrins to more complicated centres such as the corners of a cubic silsesquioxane moiety or a polymer backbone. Emanating from the core are the successive generations, each separated by a multivalent branching point. Typically, each generational segment is constructed by the iteration of two steps, addition of the branching monomer followed by either addition of a second linear monomer or activation of the previously added functional group. At the

![Diagram of a Dendrimer](Figure 1.1 Anatomy of a Dendrimer)
surface or periphery, dendrimers are characterized by a high number of terminal
groups that are usually functionalised according to the intended use of the
dendrimer. Also, in the interior of the dendrimer, we find voids or cavities that can
accommodate back folding portions of the dendrimer itself or small guest
molecules as an endo host.

On paper, dendrimers are usually drawn in a 2 dimensional aspect,
characterized by all the growth tiers aligning properly forcing all the end groups to
crowd together at the surface. In fact, dendrimers are known to take a more
spherical shape with as many end groups as possible back folding into the less
dense areas of the spherical entity.

1.1.1 The Genesis of Dendrimer Science

Vögtle reported the first successful synthesis of a cascade molecule in
1978.\(^4\) Nearly 40 years prior to Vögtle’s seminal report, Nobel Laureate Paul
Flory presented a series of theoretical articles discussing the properties of
gelation.\(^32\)-\(^36\) Flory was actually proposing a statistical model to predict the
likelihood of hyperbranched polymers but some of the diagrams in his papers
bare a striking resemblance to dendrimers. In the past two decades, dendrimers
have become the fastest growing area of polymer science. The field continues to
flourish with well over 5000 research articles and patents already published or
filed.

Early on in the dendrimer revolution, new molecular architectures and the
synthesis of various dendrimers motifs attracted considerable attention from a
fundamental research aspect. More recently, emphasis has been placed on developing the properties of dendrimers and investigating their potential in a variety of applications.

1.1.2 Synthetic Strategies

There are two conceptually different synthetic strategies for the construction of dendrimers. They are the divergent approach and the convergent approach. Other strategies include combinations or slight variations on the two aforementioned methods. Each synthetic strategy for dendrimer construction involves the repetition of alternating growth reactions followed by an activation reaction.

1.1.2.1 The Divergent Approach

In the divergent approach,\textsuperscript{4,20,21} the dendrimer is induced to grow from the core outward with the addition of successive generations. Using this methodology, dendrimers can be grown on large scale (Kg), with the use of excess reagents. One serious disadvantage of this approach is the difficulties associated with purification. The accumulation of similar functional groups creates problems with polarity-based chromatography and the slight difference in the size and shape of the defective products and pure targets compounds complicates size exclusion chromatography (SEC). Limited success in this endeavour has been achieved via gel permeation chromatography (GPC) for low generation products.
Convenience dictates that each reaction in the synthesis of a divergently grown dendrimer needs to be very clean and be able to achieve a high yield. However, incomplete reactions are inevitable and mistakes in earlier generations are propagated and magnified in the later generations. Statistics determines the dendrimer purity. For example a DAB (Poly(propylene imine) from a 1,4-diaminobutane core) dendrimer with 64 terminal amine groups has had a total of 248 reactions from the initiator core. At 99.5 % reaction efficiency for each step, the 5th generation dendrimer would be only \((0.995^{248})\) 29% defect free. Since every new generation of dendrimer cannot be purified these statistical defects cannot be avoided.

![Divergent and Convergent Approaches](image)

**Figure 1.2** The Divergent and Convergent Strategies of Dendrimer Synthesis.
1.1.2.2 THE CONVERGENT APPROACH

In response to the weaknesses of the divergent approach, Fréchet and co-workers\textsuperscript{37-43} developed the convergent approach. Using this method, the difficulties associated with many reactions preformed on one molecule are overcome by starting the synthesis at the periphery. By gradually linking the external units together with an interior unit, a dendritic wedge is grown from the surface inward. When the wedge is completed, several of them are attached to the core unit to produce the complete dendrimer. In this manner, a manageable number of reaction sites is maintained to avoid the problems associated with the statistical propagation of errors prevalent in the divergent approach. As a consequence, only a small number of side products can be formed. Also, every new generation can be purified more easily than in the divergent route. In this respect, the convergent approach also allows for the synthesis of \textit{perfect} or essentially defect free dendrimers, as purification, although tedious, can be done at each step.

From the convergent approach, the higher generations are not readily available due to the difficulties associated with coupling the focal point of the large wedge to the core. Dendrimers based on structurally rigid building blocks, \textit{e.g.} aromatic monomers, as well as more flexible building blocks, such as aliphatic polyethers, are accessible \textit{via} this method.\textsuperscript{44}
1.1.3 Characterization

An inherent problem with dendrimers is the difficulty associated with their characterization, which is complicated by the size of the macromolecules and multiplicity of functional groups. The polymeric nature of dendrimers generally leaves their solid-state structure without any long-range order, thus X-Ray crystallography is unable to provide the ultimate proof of the dendritic structure except in rare cases.\textsuperscript{45-47} Standard organic synthesis characterization techniques such as IR, \textsuperscript{1}H, \textsuperscript{13}C and \textsuperscript{7}X-NMR spectroscopies provide insight into the functional groups present and can be very useful for detecting side reactions as well as other defects within the sample. However IR and NMR\textsuperscript{48,49} can be ambiguous about the overall structure of the dendrimer. Mass Spectrometry,\textsuperscript{45,50} Matrix Assisted Laser Desorption Ionization Time of Flight (MALDI-TOF) and Electrospray Ionization (ESI) are also valuable characterization methods which reveal the molecular weights of dendrimer products. The molecular weight or size of the dendrimers may also be obtained by employing standard polymer techniques such as SEC, viscosity and light scattering measurement. GPC also gives a measure of dendrimer purity via the polydispersity index (PDI).

1.1.4 Applications of Dendrimers

As the principles of dendrimer synthesis became generally accepted, many groups modified the focus of their research to consider the properties and potential applications\textsuperscript{7,10,44,45,51-56} of this particular class of macromolecules.
In the field of medicinal chemistry, Roy and co-workers\textsuperscript{57-61} investigated the binding properties of glycodendrimers and their use as viral inhibitors. Other medicinal applications include the use of dendritic chelates as magnetic resonance imaging (MRI) contrast agents,\textsuperscript{62,63} gene therapy vectors\textsuperscript{64} and drug delivery agents.\textsuperscript{8,65}

1.1.4.1 Dendrimers as Catalysts

Very early on in the development of dendrimer science, the multiple site topologies of these macromolecules inspired many to envision the potential for incorporating transition metal complexes within the dendrimer scaffold.\textsuperscript{14,18,66,67} With the aid of coordinating anions, such as carboxylates, and Lewis base type ligands, such as amines, and especially phosphines, metals have been successfully placed at the core, the periphery, and all points in between. Dendrimers have been shown to incorporate metal ions, such as ruthenium, osmium, platinum, palladium, iron, cobalt, nickel, copper, gold, rhodium, titanium, and manganese, within their structures.

The idea that dendrimers could be used as catalysts is an obvious extension of the preparation of these metalldendrimer complexes.\textsuperscript{45,67-72} In 1994, Tomalia and Dvornic\textsuperscript{12} proposed that dendritic catalysts would provide a unique opportunity to bridge the interface between classical homogeneous and heterogeneous catalysis providing advantages from both spheres. From the large size inherent to dendrimers, their heterogeneous nature should simplify separation of the catalyst from the products \textit{via} straightforward separation
techniques such as dialysis, ultra-filtration and centrifugation. Many dendrimer molecules are nanoscopic and can be molecularly dissolved and precipitated after use. Also due to the regularity of the catalytic sites, mechanistic oriented characterizations should be possible to allow for fine-tuning of the environment around the metal centre. A comprehensive review by Astruc would suggest that we have had limited success in this area already but there is much more to investigate.

Several practical issues should also be raised before embarking in the area of dendritic catalysis. In order to produce an effective catalyst, it is beneficial to have some insight into the binding proprieties of the catalyst and its active site. In principle at least, dendritic catalysis would be expected to behave in a similar manner to the conventional homogeneous systems after which they were modeled, showing similar selectivity as well as kinetic behaviour.

1.1.4.2 Placement of the Metals Centres

As mentioned before, metals centres can be located at the core, the periphery, and all points in between. The placement of the active site in a well isolated position, such as the core, can result in beneficial interactions between the substrate and the catalyst. One can easily envision the protection that the bulk of the dendrimer would provide a sensitive metal centre by limiting access to it from decomposing and deactivating forces. Reaction rates would also be expected to be slower for core centred catalysts due to the diffusion rate of the substrate through the bulk of the dendrimer. Placement of multiple active sites on
the exterior of the dendrimer would be expected to demonstrate comparable
catalytic behaviour to the homogeneous analogue. Also interactions between the
metal centres in close proximity to each other might have a beneficial or
unexpected result.

Although there are countless examples of core centred and peripherally
placed metal complexes acting as catalysts, only a few of each type will be
illustrated.

1.1.4.3 Catalysis at the Core

Core centred catalysts have been applied as size, shape selective or
enantioselective catalysts. A common theme amongst many core centred
dendrimer catalysts is to compare them to enzymes as biomimetics. The size of
the dendrimer can be similar to that of some enzymes and with careful planning,
the microenvironment surrounding the active site has the potential to be
manipulated by way of electronic and steric factors. It is possible to create a
discriminating microenvironment in terms of regio- and enantioselectivity as well
as orchestrating the site isolation of the metal centres from each other.

Moore and Suslick$^{24,73}$ reported a substituted polyphenylester manganese
porphyrin (1.1) as a regio- and shape selective metallo-dendrimer catalyst (Figure
1.3). Their system demonstrated the influence of dendron size, and the steric
environment, on the epoxidation of alkenes with iodosylbenzene as the oxygen
source. When compared to the non-substituted manganese porphyrin complex,
the dendritic species showed a greater preference for the less hindered double
bond in a 1:1 mixture of linear and cyclic alkenes. Also the terminal double bond was transformed 4 times faster than the internal double bond in 1,4-octadiene. Epoxidation of the less electron rich 1-alkenes is generally slower than that of the internal alkenes however steric influences have been known to reverse this trend. A remarkable increase in the shape selectivity of the catalyst was noted for the higher generations.

1.1
Figure 1.3 A poly(arylester) dendrimer attached to a chloro manganese (III) porphyrin core.
A significant increase in the stability of the manganese centre towards oxidation was observed in the dendrimer species and was attributed to the protective bulk of the dendrimer. This trend was also witnessed in several other studies involving oxidative systems showing a general shielding effect at higher generations.26

Brunner and co-workers were amongst the first to report dendrimer type molecules containing internal catalytic sites. These catalysts, which were labelled as *dendrizymes*,74-76 were designed to induce asymmetric discrimination via a chiral backbone. The prepared pyridine-containing Schiff-base (1.2) with a Cu(I) binding moiety surrounded by (1S,2S)-2-aminopropyl-1,3-propanediol, (1R,2S)-ephedrine, or L-aspartic acid units was employed in the cyclopropanation of styrene with ethyl diazoacetate; however, the catalyst exhibited very little asymmetric induction (<10% ee).

Figure 1.4 Brunner's diphosphine and diimine dendrizyme ligands.
Brunner also prepared a new class of diphosphine based ligands that were functionalised with menthyl containing dendritic branches (1.3).\textsuperscript{77} Unfortunately, the observed enantioselectivities for the hydrogenation of acetamidocinnamic acid to N–acetylphenylalanine with the rhodium (I) dendrimer complex were fairly low. Upon inspecting the presented figures, it can be easily assumed that the chiral elements were too far removed from the active site at the core to impact the enantioselective outcome of the reaction.

An elegant example of a core centred enantioselective dendrimer catalyst is Seebach’s $\alpha,\alpha,\alpha',\alpha'$-tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL) (1.4) system.\textsuperscript{78,79} Four generations of Fréchet’s polyarylether dendrons were constructed around a TADDOL core and employed in the enantioselective nucleophilic addition to aldehydes. Both the dendrimer based and the model catalyst showed high enantioselectivities for the diethylzinc addition to benzaldehyde yielding the secondary alcohols in greater than 96 % ee. A cross-linked version of this dendrimer system has been recycled and reused for up to 20 cycles with only minimal degradation of the catalyst observed. Further incorporation of chiral building blocks into the backbone of the dendrimer did not influence the enantioselectivities as the additional chiral building blocks were sufficiently removed from the metal centre. Also, only a slight drop in the rate was observed up to and including the third generation catalyst while a significant drop off was observed for the fourth generation.
Figure 1.5 Seebach's Titanium TADDOL as an enantioselective dendritic catalyst.

The introduction of regio- or stereocontrol in a catalytic reaction using core centred metallo dendrimers is far from straightforward however proximity of the directing groups to the active site is significant. The bulky dendritic branches around the core centred catalytic site often lowers the turnover numbers significantly however dendrimers seem to be flexible enough to limit the desired spatial constraints on the course of the reaction.
1.1.4.4 CATALYSIS AT THE PERIPHERY

Dendrimers are by their very nature multivalent and periphery derived dendritic catalysts take advantage of this aspect by increasing the loading of metal centres at the surface of the dendrimer.

Dubois\textsuperscript{56} reported the preparation of the first organophosphine dendrimers, containing 12 or 15 phosphorus atoms located both in the interior of the dendrimer as well at the periphery. These dendritic ligands (1.5 and 1.6) were complexed to $[\text{Pd(CH}_3\text{CN)}_2][\text{BF}_4]$ and employed as catalysts for the electrochemical reduction of $\text{CO}_2$ to $\text{CO}$. An estimation of the activity at each palladium site showed similar kinetics as those observed by the parent monomeric species. The result suggests that no cooperative effect was observed between the palladium sites within the dendrimer. The formation of an inactive Pd (I) species in the form of a Pd–Pd bond suggests the one electron reduction of Pd (II) during bulk electrolysis. From the observation of the Pd(I) species, one

![Diagram](image1.png)

Figure 1.6 Dubois's organophosphine palladium dendrimer complexes.
can presume that better separation of the Pd (II) centres from each other on the dendrimer, *i.e.* via site isolation, would avoid this sort of Pd–Pd deactivation.

In their seminal work, van Leeuwen and van Koten reported the use of a soluble carbosilane complex containing pendant arylnickel(II) complexes (Figure 1.7) as a catalyst for the Kharasch addition of tetrachloromethane to

![Figure 1.7 A soluble carbosilane nickel complex.](image_url)
methacrylate. The catalytic activity of the dendritic catalyst was observed to be slightly lower (80%) than that of the parent monomeric or polymeric bound analogues. It was proposed that the lower rates were due to high local concentrations of Ni(II) centres at the surface of the dendrimer, which are particularly sensitive to oxidation and subsequent Ni(II)/Ni(III) interactions. Interactions of the active Ni(II) with neighbouring inactive Ni(III) sites is supported by EPR measurements. The selectivity proved to be independent of the dendrimer backbone as regio-selectivity of the addition products was consistently observed to be 1:1.

Reetz modified a poly(propylene imine) dendrimer with chelating diphenylphosphine ligands (Figure 1.18). Complexation with a variety of metals such as palladium, iridium, nickel and rhodium was facilitated by the presence of the terminal \(-\text{N(CH}_2\text{PPh}_2\text{)}_2\) groups. In catalytic studies with the palladium complexed dendrimer, the authors reported the Heck reaction of styrene with bromobenzene proceeds with significantly higher activity than for the discrete parent complex. Added thermal stability of the palladium species arising from the dendrimer framework was cited as a contributing factor in the increased activity. Reetz also probed the rhodium dendrimer complex from \([\text{Rh(cod)}_2]\text{BF}_4\) as a catalyst for the hydroformylation of 1-octene and styrene and reported a 62% selectivity favouring the linear aldehyde.
Figure 1.8 The fourth generation bisphosphinomethylated poly(propylene imine) dendrimer.
Togni prepared a series of chiral ferrocenyl diphosphine ligands (Figure 1.9) using the Josiphos unit. Rhodium complexes, prepared from [Rh(cod)$_2$]BF$_4$, were used as catalysts for the mild hydrogenation of dimethylitaconate. The dendritic catalysts gave 98 % ee or higher which is comparable to the monomeric Rh–Josiphos complex (99 % ee).

A variety of phosphine containing metalloendrimer complexes prepared

---

Figure 1.9 Togni’s chiral ferrocenyl diphosphine ligands.
in the group of Majoral$^{85-89}$ have been described extensively in the literature however only a few of their Ru and Pd metallodendrimers have been screened as catalysts for Stille couplings, Knoevenagel condensations, and Michael additions.$^{88}$

1.1.4.5 DENDRIMER CATALYSTS FOR INDUSTRY

Practical use of dendritic catalysts in industry can be easily envisaged to employ membrane reactors that are designed to separate the reaction components from the catalyst via nanofiltration in a continuous flow process. Quantitative retention of the catalyst (> 99.9 %) is desired for any realistic use of such a catalyst in any industrial process.

The real potential of dendrimers as supports for industrial catalysis was first explored by Kragi$^{90,91}$ in an experiment involving the palladium catalyzed allylic substitution reaction. The preparation of N–[3–phenyl–2–propenyl]–morpholin was carried out in a continuous flow reactor$^{92}$ with a generation 4 poly(propylene imine) dendrimer bearing 32 diphosphine groups (1.8) complexed to palladium. The conversion was reported to be 75 % after 100 residence times however the product was contaminated with palladium (0.14 % Pd per residence time) and decomposition of the metal centres was also observed. A similar experiment with the generation 3 poly(propylene imine) dendrimer bearing 16 diphosphine groups bound to palladium was found to be much less active under similar conditions. The authors reported that while palladium leaching was observed to a similar extent as the generation 4 catalyst, the smaller dendrimer...
was easily retained by the membrane. Subsequent characterization attempts revealed that the lower generation system seemed to have more inactive palladium centres suggesting a dendrimer effect in the stability of the active species.

1.2 Carbonylation

The incorporation of carbon monoxide into an organic substrate, via a metal carbonyl complex, is an elegant method to create a new carbon-carbon bond. This transformation can involve either an insertion of CO into a C–X bond or addition of CO along with H₂, H₂O, ROH or RR'NH across an unsaturated double bond. Perhaps the most prominent industrial example of carbonylation chemistry is the Monsanto process which produces millions of tons annually of acetic acid from methanol and CO with a Rh (I) complex and methyl iodide. The addition of CO and R'H across a double bond includes useful transformations such as hydroformylation (R' = H), hydrocarboxylation (R' = OH) and hydroesterification (R' = OR).

1.2.1 The Hydroformylation Reaction

First observed by Otto Roelen⁹³ in 1938, the addition of formaldehyde, derived from carbon monoxide and hydrogen gas, across a carbon-carbon double bond is known as the hydroformylation reaction (eq. 1.1). The early industrial processes all used cobalt as the basis for their hydroformylation catalyst and required high temperatures (up to 180°C) and pressures (up to 5000
psi). Based on the seminal research of the Wilkinson group, a transition to rhodium-phosphine based catalysts was started in the 1960’s where the hydroformylation of a wide variety of substrates could be carried out at 25°C and 1 atm. Cobalt, rhodium, iridium, platinum, and ruthenium complexes have all been reported as catalysts for the hydroformylation process, however the activity of the platinum and ruthenium species is too low to be of any industrial significance.

1.2.2 USES OF ALDEHYDES

The hydroformylation reaction is one of the most industrially important reactions involving homogeneous catalysts and produces millions of tons of aldehydes from alkenes every year. The resulting mixtures of branched (1.10) and linear (1.11) aldehydes can be chemically transformed into many different functional groups (Figure 1.10). Branched aryl aldehydes are useful intermediates in the pharmaceutical industry while straight chain linear aldehydes have been produced on megaton scales annually. Butanal from propene is further transformed to either butanol by reduction, or to 2–ethylhexanol via an aldol condensation and subsequent reduction. Butanol, (as are other small alkenes C₅–C₁₁) is used as an industrial solvent while 2–ethylhexanol is further
Figure 1.10 Industrial uses of linear and branched aldehydes.

converted to phthalate esters, which are used as plasticizers in the polymer industry.94 The hydroformylation products of higher olefins (C_{12}–C_{16}) are typically reduced to the corresponding alcohol, which can be used in the manufacturing of biodegradable detergents.

1.2.3 MECHANISTIC CONSIDERATIONS

The mechanism depicted in figure 1.11 is the dissociative mechanism proposed by Wilkinson and is very similar to that proposed by Heck and Breslow for the corresponding cobalt system.99,100 Wilkinson’s associative mechanism which involves a 20 electron species has been rejected by the academic community101 however some industrial chemists still consider it possible at high pressures and ligand concentrations.94
Figure 1.11 Wilkinson's dissociative hydroformylation mechanism showing the α (left) and β (right) insertion paths.

The dissociative mechanism here is simplified (here \( L = CO \) or \( PR_3 \)) as many other species are in equilibrium depending on the conditions. Starting from the \( 18 \) e\(^-\) \( L_4\)RhH species (1.12), the first step is dissociation of a CO or phosphine ligand to generate the active \( L_3\)RhH species (1.13). Olefin coordination (1.14) followed by hydride insertion via the α or β pathway leads to the alkyl complex 1.15 or 1.16 respectively. Subsequent coordination of a CO ligand followed by insertion generates the branched or linear acyl complex 1.19 or 1.20.
respectively. Oxidative addition of $\text{H}_2$, prior to the reductive elimination of aldehyde 1.10 or 1.11 regenerates 1.13.

1.2.4 FACTORS AFFECTING SELECTIVITY AND ACTIVITY

The main factors affecting selectivity and activity in the hydroformylation reaction depend on reaction conditions such as pressure, temperature and concentration as well as the metal/ligand complex. Electronic effects from the substituents off the vinylic carbons on the substrate are also extremely important in the selectivity, as are steric factors.

1.2.4.1 LIGAND EFFECTS

Systematic studies of ligand effects in the hydroformylation reaction are often made more difficult by the presence of several catalytically active species since the whole system is in a dynamic equilibrium (Figure 1.12). All active in the hydroformylation reaction, these complexes can be found in various concentrations in the reaction mixture depending on the pressure and temperature of the medium. Each active complex demonstrates its own activity and selectivity at different rates. This complex equilibrium in solution with ligand

$$\begin{align*}
\text{RhH(CO)}_4 & \rightleftharpoons \text{RhH(CO)}_3\text{L} \\
\text{CO} & \rightleftharpoons \text{CO} \\
\text{RhH(CO)}_2\text{L}_2 & \rightleftharpoons \text{RhH(CO)}\text{L}_3 \\
\text{CO} & \rightleftharpoons \text{CO} \\
\text{RhH(L)}_4 & \rightleftharpoons \text{RhH(L)}_4
\end{align*}$$

Figure 1.12 The dynamic equilibrium of $\text{RhH(CO)}_n\text{L}_m$ under hydroformylation conditions.
exchange obscures a defining mechanistic understanding of the role that each species plays.\textsuperscript{102}

1.2.4.1.1 **Ligand Effects: Phosphines and Phosphites**

Both phosphines and phosphites have been extensively investigated as ligands for the rhodium catalyzed hydroformylation reaction. $\text{RhH(PPh}_3\text{)}_3\text{CO}$, first reported by Vaska in 1963, was studied as a hydroformylation catalyst by Wilkinson\textsuperscript{96-98} a few years later and is undoubtedly the best known catalyst for the reaction. In 1969, Pruett and Smith reported the first examples of phosphite ligands in the rhodium-catalyzed hydroformylation.\textsuperscript{102} Phosphites are better $\pi$ acceptors than are phosphines and result in an increased rate. Phosphites are also generally easier to prepare than phosphines as they are much less sensitive to oxidizing agents however they are especially sensitive to hydrolysis and alcoholysis. Also, alkyl phosphites often suffer the Arbuzov rearrangement.\textsuperscript{103}

1.2.4.1.2 **Ligand Effects: Electronic Factors**

Electronic factors are known to play a very important role in the rate and selectivity of the hydroformylation reaction. Electron-donating ligands, such as alkylphosphines, generally reduce conversion rates and require higher temperatures. Electron-withdrawing substituents on the ligands increase reaction rates as a result of the increased lability of CO dissociation and stronger alkene association. This observation is not surprising since $\pi$ back bonding contributes
significantly to the strength of the metal ligand bond, especially for carbonyl ligands.

Also, an increase in the electron-withdrawing properties of the ligands results in a higher propensity to direct the formation of the linear aldehyde of 1-octene and other aliphatic olefins. Strongly electron-withdrawing ligands create a higher positive charge on the metal, which favours the formation of the linear metal alkyl complex.

1.2.4.1.3 Ligand Effects: Steric Factors

When comparing ligands of similar electronics for aliphatic olefins, steric effects also affect the regio-selective outcome of the reaction. Bulkier ligands promote the formation of the unsaturated HRh(CO)₂L species via ligand dissociation. This results in a less crowded active species, and an increase in the ratio of the branched aldehyde is typically observed.¹⁰⁴

Using extremely bulky phosphites,¹⁰⁵ monoligated rhodium phosphite species are observed to have high reaction rates with unreactive alkenes such as 2-methyl-1-hexene when compared to triphenylphosphine (tpp). Using a diphosphite ligand resulted in a decrease in the catalyst activity, however a marked increase in the selectivity towards the linear aldehyde from 1-alkenes is observed.
1.2.4.2 Temperature Effects

Temperature has a dramatic effect on the rate and selectivity of the hydroformylation reaction. In the case of vinlyc and allylic alkenes, the alkyl rhodium intermediates are known to behave differently at higher temperatures. The branched alkyl intermediate is more likely to undergo β-hydride elimination back to the alkene or isomer while the linear alkyl intermediate is converted to the acyl species via the migratory insertion process. For 1-hexene, linearity was observed to increase from 52% to 72% when raising the temperature from 20°C to 100°C. Typically in the case of styrene as the substrate, a strong increase in the rate as well as formation of the linear aldehyde is observed with an increase in reaction temperature.

1.2.4.3 Effect of Carbon Monoxide and Hydrogen Pressure

The concentrations of CO and H₂ also have a remarkable effect on the observed regioselectivity. It is commonly observed that in the case of styrene, a decrease in CO pressure is accompanied by an increase in linear isomer. In the case of hexene and octene, CO pressure does not affect the regioselectivity at any temperature.⁹⁴,¹⁰¹

1.2.4.4 Effect of Substrate

Substituents off the vinlyc carbons on the substrate greatly affect the rate and selectivity of the reaction. Phenyl rings and electron withdrawing groups
such as esters, favour branched aldehyde formation while bulkier substrates tend to direct linear aldehyde formation.

1.2.5 THE HETEROGENEOUS HYDROFORMYLATION REACTION

It is generally accepted that the development of routinely recoverable and recyclable catalysts has the potential to play a more dominant role in chemical research as industry strives to find an economically feasible means to overcome the environmental challenges put forth by public sentiment. With this goal in mind, considerable research has been devoted to the development of recyclable catalyst systems for the hydroformylation of alkenes.

1.2.5.1 POLYMER SUPPORTED HYDROFORMYLATION

Nozaki and co-workers have described a recoverable cross-linked polystyrene phosphine-phosphite complexed rhodium catalyst (1.21) based on their effective \((R,S)\)-BINAPHOS ligand\(^{106,107}\). This polymer supported hydroformylation catalyst has demonstrated excellent enantio-selectivity yielding up to 90% ee and is recovered via precipitation and removal of the supernatant.

![Figure 1.13 Nozaki's crosslinked polystyrene supported Rh–BINAPHOS.](image)
fluid. Mechanical stirring was observed to degrade the polymer matrix. Also, significant loss of activity was observed upon reuse of recovered catalyst.

1.2.5.2 Silica supported catalysts

In 1979, rhodium monophosphine complexes were covalently anchored on commercially available silica and used as hydroformylation catalysts for 1-hexene.\textsuperscript{108} Leaching of the metal was observed from the support under the conditions used (100°C, benzene and 68 bar) and the resulting carbonyl species were thought to be responsible for the observed activity and low selectivity.

1.2.5.3 Sol-Gel immobilization

Another interesting alternative to silica-anchored catalysts involves use of the Sol-Gel process to immobilize ligands in a silicate matrix. The Sol–Gel process is a very attractive avenue for such modifications due to its mild nature and diversity.\textsuperscript{109-111} Recycling of a rhodium phosphine catalyst trapped in the silicate matrix prepared \textit{via} the Sol-Gel method was carried out 8 times with only minimal leaching reported (<1% per cycle).

1.2.5.4 Supported aqueous phase catalyst

The intriguing concept of supported aqueous phase catalysts (SAPC), by Davis and co-workers, involves the immobilization of the catalyst in a thin layer of water adhered to the pores of a high surface area silicate.\textsuperscript{112-115} The catalyst is not tethered to the surface \textit{via} any covalent bonds, instead, sulfonated
Figure 1.14 Davis' supported aqueous phase catalyst.

substituents that solubilize the ligands in the water layer are incorporated. Since the water layer on the surface of the silica is very thin, a large contact layer between the organic solvent and the aqueous catalyst film is ensured. Under this system, alkenes are converted into aldehydes at a high rate; however, low selectivity for the linear product is observed using the monophosphine that they employed. Davis did not report the recyclability of his SAPC catalysts.

A more recent report by van Leeuwen, presents the use of a water soluble ligand, the disodium salt of 2,7-bissulfonate-4,5-bis(diphenylphosphino)-9,9-dimethylxanthene under SAPC conditions. The rhodium complex was very selective towards the linear aldehyde (40:1) of 1-octene, however the turnover frequency was extremely slow at a rate of 15/h. The authors also reported recycling their SAPC catalyst 10 times without significant loss of selectivity or activity. ¹¹⁶,¹¹⁷
1.2.5.5 Silica as a Support

Silica is a popular matrix to use as an inorganic support for catalysis due to its relative inertness, stability and neutrality.\textsuperscript{118} Also, modification techniques of the surface siloxane groups are well explored and numerous derivatives are commercially available. Unfortunately, leaching of the metal from the support and low reactivities are often observed.

1.3 Research Objectives

It is always desirable to strive towards the development of an ideal catalyst. With this lofty goal in mind, it was proposed that building a more homogeneous, mobile, organic moiety on the surface of a heterogeneous support would offer the means of uniting the advantages of heterogeneous systems with those of the homogeneous counterparts.

More specifically, we intended to develop a dendrimer based hydroformylation catalyst anchored on an inorganic support and investigate the effect of dendrimer generation on activity and selectivity. With recyclability in mind, it was decided that silica would be a cheap support and allow for facile catalyst recovery \textit{via} filtration or centrifugation. The silica is expected to add robustness to the system as well.

With respect to the hydroformylation reaction, access to either the branched or linear aldehyde would be desirable depending on the utility of the products. Providing a rhodium centre with coordinating phosphines or phosphites is expected to enhance selectivity and conversion in the catalytic reaction.
CHAPTER 2: SUPPORTED DENDRIMERS

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2.0 SUPPORTED DENDRIMERS

With the goal of designing a new catalyst that would effectively combine the advantages of both heterogeneous and homogeneous systems, a series of supported dendrimers were chosen as ligands. In our system, it was imagined that the soft organic periphery of the dendrimer would be soluble in solution and allow for homogeneous–like activity while the heterogeneous core would offer catalyst stability and simplify recovery. In the design of these supported ligands, several options for the heterogeneous core and dendrimer backbone were considered.

With regards to the catalyst support, silica gel was chosen as the core because it is relatively cheap and readily available as well as durable, especially when compared to organic supports such as polymers. With its large particle size (μm), silica would facilitate catalyst recovery via simple filtration. Another contributing factor in this decision was the interest industry shows in silica–supported systems.

A variety of dendrimer motifs are prevalent in the literature, and were considered with respect to the choice of the dendrimer backbone. The early poly(propyleneimine)\textsuperscript{4,119} and poly(amidoamine)\textsuperscript{20,21,120-122} systems from Vögtle and Tomalia respectively are perhaps the best known and most researched. Other popular motifs are Newkome’s polyol,\textsuperscript{3} Fréchet’s poly(arylether),\textsuperscript{37,38} poly(arylester)\textsuperscript{123} and the carbosilane dendrimers\textsuperscript{16,124} popularized by van Leeuwen and van Koten.\textsuperscript{18}
2.0.1 Poly(propyleneimine) and Poly(amideamine) Dendrimers

Vögtle's initial report regarding the double Michael-type addition of acrylonitrile (2.2) to benzyl amine (2.1) followed by the reduction of the resulting bis-nitrile (2.3) to the bis-amine (2.4) reported fairly low yields (Scheme 2.1). This method was later greatly improved by Meijer to afford a commercially viable means for the preparation of these poly(propyleneimine) dendrimers (PPI) up to at least generation 5.

Scheme 2.1 Vögtle's original synthesis of a cascade molecule.

In 1985, the first of Tomalia's prolific repertoire of papers and patents regarding the preparation of Starburst™ or poly(amideamine) dendrimers (PAMAM) described the double Michael-type addition of methyl acrylate (2.8) to ammonia (2.7) followed by amidation of the resulting tri-ester (2.9) with an
excess of ethylenediamine (2.10) to afford the triamine (2.11) (Scheme 2.2). These dendrimers are now commercially available up to generation 10,\textsuperscript{128} and are undoubtedly the most widely studied series available. As with all divergently grown dendrimers, both the PPI and the PAMAM dendrimers have a characteristic polydispersity that arises from the magnification of statistically unavoidable missed reactions or side reactions.

Scheme 2.2 The synthesis of Tomalia’s PAMAM dendrimers.
2.0.2 Initial investigation of silica supported dendrimers

Initial attempts in our lab involved the construction of a PPI dendrimer on the surface of silica. Aminopropyl groups grafted to the surface would serve as the dendritic core with the silica particle as the heterogeneous support. The relatively large size of the particles (35 – 70 μm) would allow for the opportunity of simple recovery via filtration resulting in the potential to recycle the used catalyst multiple times.

Vögtle's method was applied to the construction of PPI dendrimers starting from commercially available aminopropyl silica (2.14) with a loading of 0.9 mmol NH₂/g SiO₂ (Scheme 2.3). An exhaustive Michael type addition of 2.2 to the primary amines yielded the bis-nitrile on silica (2.15). A cobalt/sodium borohydride in methanol system was then used to reduce 2.15 to the bis-amine yielding the first generation PPI dendrimer on silica (2.16). Repetition of these two steps toward the second-generation tetraamine (2.18) was attempted but failed at the reduction step. At the time, it was thought that the heterogeneous nature of the reducing agent coupled with the heterogeneous nature of the silica support was not conducive for a meaningful reaction. Subsequent to the findings described in the present chapter, it was concluded that the second generation PPI on silica likely suffered a similar fate to that of the PAMAM on silica, in that a threshold of dendrimer growth is reached at around generation 2.
Scheme 2.3 The construction of a poly(propylene imine) dendrimer on silica.

2.1 PAMAM DENDRIMERS ON SILICA.

Learning from the initial investigation, it was proposed that clean homogenous reagents needed to be used for the construction of dendrimers on a heterogeneous surface. Upon surveying the literature, Tomalia's PAMAM
dendrimer building steps, which promised to be both efficient and cleaner, prompted the investigation of their use with 2.14 as the heterogeneous core.

2.1.1 The Synthesis of PAMAM on Silica

Starting from 2.14, the same silica core that was used in the previous attempt for PPI construction, four generations of PAMAM dendrimers were constructed on the surface of the silica (Scheme 2.4). Standard Starburst dendrimer building methods, as reported by Tomalia and co-workers, were modified to propagate the dendrimer generation on the surface. A double Michael–type addition of the pre-existing primary amine group to excess methyl acrylate (2.8) forms the bis-amine propionate ester on silica (2.19). Subsequent amidation of the ester moieties with a large excess of ethylenediamine (2.10) completes the first generation (2.20). Repetition of these two reactions produces the higher generations of the dendrimer esters (2.21, 2.23 and 2.25) and amines (2.22, 2.24 and 2.26) on silica. As a crude purification method, simple vacuum filtration and solvent rinsing served to remove excess reagents. Any further purification techniques would be futile due to the heterogeneous nature of the silica gel core.
Scheme 2.4 The synthesis of the PAMAM dendrimers on silica.
At higher amine terminated generations (2.24 and 2.26), filtrations became more tedious, sometimes taking days to complete, due to clogging of the fritted glass filter with diamine. In such instances, silica product was sacrificed as the solid particles were allowed to settle and compact at the bottom of the flask prior to decanting the overlying solution. Methanol and ether were then added and the filtration started anew. Filtration of the half generations (2.23 and 2.25), were much more facile as the methyl ester groups tended to be less 'sticky' than the amine groups.

Figure 2.1 The proposed structures of the third (2.24) and fourth (2.26) generation PAMAM dendrimers on Silica.
2.1.2 THE CHARACTERIZATION OF PAMAM ON SILICA

It is statistically probable that during the preparation of these dendrimers, several branches may not have reacted completely resulting in amputated versions of the proposed structures. Also, since purification of these supported dendrimers is impossible, an incomplete reaction at one stage will only propagate itself in the higher generations. Another likely complication can arise from the condensation of neighbouring terminal amines. An evaluation of the purity of these supported dendrimers would be useful however, one can easily imagine the difficulties encountered with any attempts to characterize these compounds on silica.

It must be recognized that the heterogeneity of the dendrimers constructed on silica does not allow for simple proton and carbon NMR characterization. The heterogeneity of these compounds and the nature of silica make it unrealistic to assume any characterization technique found in an organic chemists repertoire would serve to elucidate much useful information.\textsuperscript{127} Mass spectrometric techniques are not available, nor is GPC for a molecular mass determination.

We were gratified to have access to a solid state NMR for $^{13}$C determination. Very little variance in the assignment of the $^{13}$C NMR spectra (Figure 2.2) is noticed for the various amine terminated generations: $\delta = 173$, N–C(O); $\delta = 50$, N–CH$_2$; $\delta = 28$, C(O)CH$_2$; $\delta = 10$ ppm, SiCH$_2$CH$_2$. Solid state $^{15}$N NMR was also attempted, but after 4 days on the machine, any peaks present were still buried in the baseline. $^{15}$N NMR was expected to provide
characterization information regarding the relative environments around the amine and amide nitrogens. Enriching the sample with $^{15}$N isotopes is possible, though an expensive experiment, especially considering that excess $^{15}$N labelled diamine would be needed.

Figure 2.2 Representative $^{13}$C NMR (CPMAS) of a PAMAM dendrimer anchored on silica.

2.1.3 The Threshold of Dendrimer Growth

As with any exponential growth strategy, there is a threshold at which the surface area to volume ratio of the sphere becomes insufficient to encourage useful growth. A threshold has been reached in which there is no further room to expand. On silica, one can easily imagine that the dendritic wedges in the pores
would fill the pore quickly, while those on the exterior surface would have more room to grow until steric hindrance from neighbouring groups prove to be too significant for further reaction. In another effort to characterize the various generations, an attempt to determine the amine content via titration was made.\textsuperscript{128} The results obtained (Table 2.1) agreed generally with the NMR data that third and fourth generation dendrimers were not complete.

Tsubokawa and co–workers\textsuperscript{129} explored the grafting of the same PAMAM dendrimers onto the surface of ultrafine silica via a similar procedure to ours. By measuring the amino content at each generation, they concluded that the resulting product was more likely to be a highly branched polymer rather than a true dendrimer especially at higher generations. Unfortunately, the information provided in Tsubokawa’s paper is incomplete and neglects to mention data for the lower generations.\textsuperscript{130}

Table 2.1 Amine content of PAMAM dendrimers on Silica

<table>
<thead>
<tr>
<th>Dendrimer</th>
<th>Generation</th>
<th>Theoretical (mmol NH\textsubscript{2}/g SiO\textsubscript{2})</th>
<th>Determined (mmol NH\textsubscript{2}/g SiO\textsubscript{2})</th>
<th>Tsubokawa (mmol NH\textsubscript{2}/g SiO\textsubscript{2})</th>
</tr>
</thead>
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<tr>
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<td>0</td>
<td>0.9</td>
<td>0.97</td>
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<tr>
<td>2.22</td>
<td>1</td>
<td>1.5</td>
<td>1.34</td>
<td>NR</td>
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<td>4</td>
<td>3.6</td>
<td>1.92</td>
<td>2.5</td>
</tr>
</tbody>
</table>

NR = not reported
2.1.4 The Phosphorylation of the PAMAM Dendrimers on Silica

The utility of phosphines in the complexation of transition metals is of major significance in catalysis. Consequently, a clean and soluble method for modifying the prepared dendrimers on silica to be attractive coordination sites for rhodium as well as other metals was investigated.

Majoral was the first to make use of diphenylphosphanyl methanol (2.29) as a simple yet effective tool in the preparation of bis-(diphenylphosphanyl methyl) terminated dendrimers from a hydrazine precursor.\textsuperscript{131} Concurrently, Reetz published a very similar procedure outlining the phosphorylation of the primary amine groups on the periphery of a soluble PPI dendrimer (1.8).\textsuperscript{81} By extending reaction times and increasing the reagent to substrate ratio, a heterogeneous procedure was developed towards the phosphorylation of the PAMAM dendrimers attached to the silica gel support.

![Scheme 2.5 The phosphorylation of the PAMAM dendrimer on silica.](image)
Double phosphonimethylation of each terminal amine was carried out using 2.29 prepared in situ from paraformaldehyde (2.27) and diphenylphosphine (2.28) (Scheme 2.5). The resulting phosphonylated dendrimers (2.30 – 2.34) were characterized by $^{31}$P solid state NMR, with chemical shifts of −27 to −28 ppm (Ph$_2$P–CH$_2$N–) for the various generations (Figure 2.3). These experimental results compared well with the published result of −28 ppm for the homogeneous phosphonylated poly(propylene imine) dendrimer described by Reetz.$^{81}$

Figure 2.3 $^{31}$P NMR (CPMAS) of a bis(diphenylphosphonomethyl) terminated PAMAM dendrimer on silica.
As in the $^{13}$C NMR spectra of the amine terminated dendrimers, very little variance in the $^{31}$P NMR spectra was observed with the different generations of the phosphorylated species, save that the third and fourth generations (2.33 and 2.34 respectively) required longer acquisition times on the machine to achieve similar baselines observed in the lower generations (2.31 and 2.32).

The $^{13}$C NMR spectra of 2.31 – 2.34 show the new aromatic carbons from the phenyl rings ($\delta = 130$, P–C$_6$H$_5$) as well as the carbon in between the nitrogen and phosphorous atoms ($\delta = 88$, N–CH$_2$–P) (Figure 2.4).

Figure 2. 4 $^{13}$C NMR (CPMAS) of a bis(diphenylphosphanylmethyl) terminated PAMAM dendrimer on silica.
2.1.5 COMPLEXATION TO RHODIUM

The bis-phosphanylated amino group can act as a bidentate ligand for coordination with many transition metals. One can envision the formation of a six membered ring upon complexation with the metallic species. The phosphorylated dendrimers were readily complexed by reaction with half an equivalent of chloro(dicarbonyl)rhodium (I) dimer ([Rh(CO)$_2$Cl]$_2$) in hexanes and easily isolated by microporous membrane filtration. The resulting complexed dendrimers (2.35 – 2.39) were characterized by $^{31}$P solid state NMR (Figure 2.5). A broad signal for the complexed phosphorous ([Ph$_2$PCH$_2$N–]Rh) is observed at a chemical shift centred at 24 ppm.

![Figure 2.5 Representative $^{31}$P NMR (CPMAS) of a Rh Complexed phosphonated PAMAM dendrimer anchored on a silica support.](image)

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The phosphanylated dendrimers (2.30 – 2.34) can be handled in air, however partial oxidation of the phosphine, detected by $^{31}$P NMR analysis ($\delta \approx 29$ ppm; $\text{Ph}_2\text{P(OMe)}_2\text{N}$), occurs after exposure to atmospheric oxygen for one month. This decomposition is expedited if filtration of the phosphanylated dendrimers and complexes is not carried out under a flow of inert gas such as argon or nitrogen. Storage of the dendrimers and complexes under argon is sufficient to avoid oxide formation.

2.1.5.1 Rhodium Determination

The rhodium complexed dendrimers (2.35 – 2.39) were digested with hydrofluoric acid or Aqua–regia by microwave heating and analyzed for Rh content by ICP analysis. The degree of complexation decreases significantly beyond the second generation. This is believed to be due to the lower amine content resulting from the threshold of dendrimer growth being reached as well as incomplete phosphanylation reaction of any amines present due to steric crowding.
### Table 2.2 Rhodium content of the various dendrimers.\(^a\)

<table>
<thead>
<tr>
<th>Generation</th>
<th>Catalyst</th>
<th>g Rh / g Si</th>
<th>μmol Rh / 25 mg SiO(_2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2.35</td>
<td>0.046</td>
<td>11.2</td>
</tr>
<tr>
<td>1</td>
<td>2.36</td>
<td>0.029</td>
<td>7.0</td>
</tr>
<tr>
<td>2</td>
<td>2.37</td>
<td>0.039</td>
<td>9.5</td>
</tr>
<tr>
<td>3</td>
<td>2.38</td>
<td>0.0018</td>
<td>0.44</td>
</tr>
<tr>
<td>4</td>
<td>2.39</td>
<td>0.0026</td>
<td>0.63</td>
</tr>
</tbody>
</table>

\(^a\)Average ICP result from two independent laboratories for the same sample.

### Table 2.3 Compound Index for the various generations of dendritic amines, bis- (diphenylphosphanyl)methyl)amines and rhodium complexes on silica.

<table>
<thead>
<tr>
<th>Generation</th>
<th>NH(_2)</th>
<th>(\text{PPh}_2)</th>
<th>(\text{RhL}_3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2.14</td>
<td>2.30</td>
<td>2.35</td>
</tr>
<tr>
<td>1</td>
<td>2.20</td>
<td>2.31</td>
<td>2.36</td>
</tr>
<tr>
<td>2</td>
<td>2.22</td>
<td>2.32</td>
<td>2.37</td>
</tr>
<tr>
<td>3</td>
<td>2.24</td>
<td>2.33</td>
<td>2.38</td>
</tr>
<tr>
<td>4</td>
<td>2.26</td>
<td>2.34</td>
<td>2.39</td>
</tr>
</tbody>
</table>
2.2 THE HYDROFORMYLATION OF OLEFINS

The catalytic activities of the prepared dendrimer catalysts were investigated with regards to the hydroformylation reaction. Initial trials with styrene (eq 2.1) under various hydroformylation conditions were attempted and all the prepared catalysts gave successful results.

\[
\text{C}_8\text{H}_8\text{CH} = \text{C} + \text{CO/H}_2 \xrightarrow{2.35 - 2.39} \text{C}_8\text{H}_8\text{CH} = \text{C} - \text{CH} = \text{C} - \text{CH}_2\text{C}_6\text{H}_4\text{O} - \text{CH}_2\text{C}_6\text{H}_4\text{O} \quad [2.1]
\]

2.40 2.41 2.42

These early experiments coupled with the available characterization data hinted that the activity of the second generation catalyst (2.37) was superior to the other generations. Consequently, most experiments investigating the effect of the reaction parameters were carried out under that expectation with 2.37 as the illustrative catalyst.

2.2.1 PRESSURE DEPENDENCE

As expected, a pressure dependence of the regio–selectivity was noted when styrene (2.40) was used as the substrate. The general trend observed was that increasing the total pressure of the reaction increased the branched to linear ratio of aldehydes while decreasing the total pressure also decreases activity of the catalyst. Reactions carried out under bubbling CO and H\textsubscript{2} or at 50 psi (Table 2.4, entries 1 and 2 respectively) yielded only trace aldehydes. At 75 °C, quantitative yields were obtained at higher pressures and selectivities favouring
2-phenylpropionaldehyde (2.41) over 3-phenylpropionaldehyde (2.42) ranged from 3:1 at 500 psi (Table 2.4, entry 3) to 9:1 at 1200 psi (Table 2.4, entry 6).

Table 2.4 The pressure dependence on the hydroformylation of styrene.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pressure(^b) (psi)</th>
<th>Conversion(^c) (%)</th>
<th>Selectivity(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bubbling</td>
<td>Trace</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>5</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>500</td>
<td>&gt;99</td>
<td>3:1</td>
</tr>
<tr>
<td>4</td>
<td>800</td>
<td>&gt;99</td>
<td>6:1</td>
</tr>
<tr>
<td>5</td>
<td>1000</td>
<td>&gt;99</td>
<td>8:1</td>
</tr>
<tr>
<td>6</td>
<td>1200</td>
<td>&gt;99</td>
<td>9:1</td>
</tr>
</tbody>
</table>

\(^a\) 2.0 mmol of styrene, 25 mg catalyst 2.37, 10 ml CH\(_2\)Cl\(_2\), 22 h 75 °C, \(^b\) Total pressure using a 1:1 ratio of CO:H\(_2\). \(^c\) Determined by GC. \(^d\) Determined by \(^1\)H NMR.

2.2.2 SOLVENT EFFECT

Changing the solvent had a slight effect on the regioselectivity and activity of the hydroformylation reaction. A variety of solvents were used for the hydroformylation of 2.40, with THF, CH\(_2\)Cl\(_2\) and chloroform (Table 2.5, entries 4, 5 and 6 respectively) giving very similar selectivities and yields. However CH\(_2\)Cl\(_2\) was chosen as the solvent of choice due to its lower vapour pressure and simple NMR spectrum. Benzene, pentane and hexane (Table 2.5, entries 1, 2 and 3)
were also tried but lower yields and selectivities were observed and attributed to the lower solubility of the dendrimer bulk in the non-polar hydrocarbon solvents while use of sulfolane (Table 2.5, entry 7) resulted in very low conversions. The reaction in methanol (Table 2.5, entry 8) generated the acetal forms of the aldehydes.

Table 2.5 The hydroformylation of styrene using 2.37 in various solvents. a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Conversion b (%)</th>
<th>Selectivity c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>benzene</td>
<td>93</td>
<td>5:1</td>
</tr>
<tr>
<td>2</td>
<td>pentane</td>
<td>78</td>
<td>4:1</td>
</tr>
<tr>
<td>3</td>
<td>hexane</td>
<td>82</td>
<td>4:1</td>
</tr>
<tr>
<td>4</td>
<td>CHCl₃</td>
<td>&gt;99</td>
<td>7:1</td>
</tr>
<tr>
<td>5</td>
<td>CH₂Cl₂</td>
<td>&gt;99</td>
<td>8:1</td>
</tr>
<tr>
<td>6</td>
<td>THF</td>
<td>&gt;99</td>
<td>8:1</td>
</tr>
<tr>
<td>7</td>
<td>sulfolane</td>
<td>14</td>
<td>4:1</td>
</tr>
<tr>
<td>8</td>
<td>methanol</td>
<td>&gt;99</td>
<td>- d</td>
</tr>
</tbody>
</table>

a 2.0 mmol of styrene, 10 ml Solvent, 25 mg Catalyst 2.37, 22 h 75 °C, Total pressure 1000 psi using a 1:1 ratio of CO:H₂. b Determined by GC. c Determined by ¹H NMR. d Acetal products observed.
2.2.3 TEMPERATURE DEPENDENCE

A very significant temperature effect was observed for the hydroformylation reaction using the dendrimer catalysts on silica. As expected, lowering the temperature significantly increases the regio-selectivity towards the branched product 2.41. At temperatures above 110 °C (Table 2.6, entries 9 and 10), the catalyst starts to decompose to a black precipitate however complete conversion is still observed. These reactions were allowed to run to completion for 22 hours however, it was noted that when shorter reaction times are tried, a notable decrease in the activity is observed at lower temperatures. Also only trace conversion of styrene occurred after 96h at 4°C (Table 2.6, entry 1).
Table 2.6 The effect of temperature on the regioselectivity of the hydroformylation of styrene$^a$.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature ($^\circ$C)</th>
<th>Conversion$^b$ (%)</th>
<th>Selectivity$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^d$</td>
<td>4</td>
<td>trace</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>&gt;99</td>
<td>&gt;25:1</td>
</tr>
<tr>
<td>3</td>
<td>35</td>
<td>&gt;99</td>
<td>&gt;25:1</td>
</tr>
<tr>
<td>4</td>
<td>45</td>
<td>&gt;99</td>
<td>20:1</td>
</tr>
<tr>
<td>5</td>
<td>55</td>
<td>&gt;99</td>
<td>15:1</td>
</tr>
<tr>
<td>6</td>
<td>65</td>
<td>&gt;99</td>
<td>13:1</td>
</tr>
<tr>
<td>7</td>
<td>75</td>
<td>&gt;99</td>
<td>8:1</td>
</tr>
<tr>
<td>8</td>
<td>90</td>
<td>&gt;99</td>
<td>3:1</td>
</tr>
<tr>
<td>9$^e$</td>
<td>110</td>
<td>&gt;99</td>
<td>2:1</td>
</tr>
<tr>
<td>10$^e$</td>
<td>130</td>
<td>&gt;99</td>
<td>2:1</td>
</tr>
</tbody>
</table>

$^a$2.0 mmol of 2.40, 25 mg catalyst 2.37, 10 ml CH$_2$Cl$_2$, 22 h. Total pressure using a 1:1 ratio of CO:H$_2$. $^b$ Determined by GC. $^c$ Determined by $^1$H NMR. $^d$ 96 h. $^e$ Catalyst decomposed to black at higher temperatures.
2.2.4 The Hydroformylation of Various Olefins

Table 2.7 describes the versatility of catalyst 2.37 for the hydroformylation of a variety of olefins. 1-Decene (Table 2.7, entry 1) and 1-octene (Table 2.7, entries 2 – 4) react to form the linear aldehydes in slight excess. In the case of 1-octene, increasing the reaction temperature from 75 to 110 °C does not improve the selectivity however lowering the temperature to 40 °C decreases the formation of the linear aldehyde and prevents the isomerization reaction. 4-Isobutylstyrene (Table 2.7, entries 5 – 7) gives excellent regioselectivity at room temperature (entry 7); however, the presence of the isobutyl group in the para position slows down the reaction considerably when compared to styrene. Excellent selectivity was also observed from the reaction of vinyl acetate (Table 2.7, entries 8 – 11) at room temperature (entry 11) with 52 % conversion. Increasing the temperature to 35°C (entry 10) decreases the selectivity slightly; however the conversion is nearly complete. When vinyl benzoate (Table 2.7, entries 12 – 14) is employed as the substrate, the observed selectivities are excellent regardless of the temperature of the reaction. A notable temperature dependence on the activity is also witnessed. Other aromatic substrates such as 4-methoxystyrene (Table 2.7, entry 15) and 6-methoxyvinylnaphthalene (Table 2.7, entry 16) give very similar selectivities to styrene. Use of 9-vinlanthracene (Table 2.7, entry 17) afforded only the branched aldehyde.
Table 2.7 The hydroformylation of various olefins using **2.37**.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Temperature (°C)</th>
<th>Conversion (%)</th>
<th>Selectivity Branched:Linear</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-decene</td>
<td>75</td>
<td>&gt;99</td>
<td>1(^b):1.8</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>110</td>
<td>&gt;99</td>
<td>1(^b):1.5</td>
</tr>
<tr>
<td>3</td>
<td>1-octene</td>
<td>75</td>
<td>&gt;99</td>
<td>1(^b):1.6</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>40</td>
<td>&gt;99</td>
<td>1:1.2</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>75</td>
<td>&gt;99</td>
<td>8:1</td>
</tr>
<tr>
<td>6</td>
<td>4-isobutylstyrene</td>
<td>65</td>
<td>&gt;99</td>
<td>11:1</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>25</td>
<td>60</td>
<td>26:1</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>75</td>
<td>&gt;99</td>
<td>7:1</td>
</tr>
<tr>
<td>9</td>
<td>vinyl acetate</td>
<td>65</td>
<td>&gt;99</td>
<td>13:1</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>35</td>
<td>96</td>
<td>18:1</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>25</td>
<td>52</td>
<td>20:1</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>75</td>
<td>&gt;99</td>
<td>19:1</td>
</tr>
<tr>
<td>13</td>
<td>vinyl benzoate</td>
<td>35</td>
<td>56</td>
<td>21:1</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>25</td>
<td>29</td>
<td>21:1</td>
</tr>
<tr>
<td>15</td>
<td>4-methoxystyrene</td>
<td>75</td>
<td>&gt;99</td>
<td>7:1</td>
</tr>
<tr>
<td>16</td>
<td>6-methoxy-2-vinylphenanthrene</td>
<td>75</td>
<td>&gt;99</td>
<td>7:1</td>
</tr>
<tr>
<td>17(^c)</td>
<td>9-vinylanthracene</td>
<td>75</td>
<td>72</td>
<td>1:0</td>
</tr>
<tr>
<td>18</td>
<td>allylphenylether</td>
<td>75</td>
<td>&gt;99</td>
<td>2:1</td>
</tr>
</tbody>
</table>

\(^a\)2.0 mmol of substrate, 25 mg of **2.37**, 10 ml CH\(_2\)Cl\(_2\), 22 h, 75 °C, total pressure 1000 psi using a 1:1 ratio of CO:H\(_2\). \(^b\)Sum of branched aldehyde isomers. \(^c\)92h.
2.2.5 Recycling Study

The recyclability of 2.36 – 2.39 was investigated after recovery of the silica from the product solutions via microporous filtration, and subsequent reuse with a fresh aliquot of styrene. The best results were obtained for catalyst 2.37 (Table 2.8, entries 3–6), which was washed with distilled hexanes after filtration and used a total of four times without significant loss of activity or selectivity.

Table 2.8 The hydroformylation of styrene using 2.36 – 2.39: A recycling study.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Cycle(^b)</th>
<th>Conversion (%)</th>
<th>Selectivity (^2.41:2.42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.36</td>
<td>1</td>
<td>&gt;99</td>
<td>7:1</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>2</td>
<td>&gt;99</td>
<td>6:1</td>
</tr>
<tr>
<td>3</td>
<td>2.37</td>
<td>1</td>
<td>&gt;99</td>
<td>6:1</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>2</td>
<td>&gt;99</td>
<td>8:1</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>3</td>
<td>&gt;99</td>
<td>7:1</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>4</td>
<td>98</td>
<td>7:1</td>
</tr>
<tr>
<td>7</td>
<td>2.38</td>
<td>1</td>
<td>&gt;99</td>
<td>8:1</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>2</td>
<td>5</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>2.39</td>
<td>1</td>
<td>&gt;99</td>
<td>8:1</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>2</td>
<td>12</td>
<td>–</td>
</tr>
</tbody>
</table>

\(^a\) 0.3 mmol of styrene, 10 ml CH\(_2\)Cl\(_2\), 25 mg catalyst, 22 h 75 °C, Total pressure 1000 psi using a 1:1 ratio of CO:H\(_2\). \(^b\) catalyst filtered, washed with distilled hexanes and reused in subsequent cycle.
Recycling of catalysts 2.38 and 2.39 (Table 2.8, entries 7–8 and 9–10 respectively) was also attempted, however, very low conversions were obtained for the second cycles. The wash solution was colourless after the second cycle, consistent with little, if any, leaching.

2.2.6 Rhodium Leaching and the Background Reaction

It should also be noted that after the hydroformylation reaction with the 2.35, 2.36 and 2.37 catalysts, the product solution is slightly yellowish in colour suggesting that some leaching of the rhodium metal occurs. This leaching is less evident when using 2.38 and 2.39 as the catalyst and is likely due to the lower metal content of the compounds.

Difficulties in characterization prevent us from knowing the environment of all the rhodium. From $^{31}$P NMR we can see that all the phosphorus is complexed, however, the compounds are likely to have some rhodium atoms adsorbed to the surface of silica, as well as in the pores. This rhodium may contribute to a background reaction. Experiments with rhodium/ aminopropyl silica reveal that these are active hydroformylation catalysts. The rate is significantly lower and susceptible to leaching to a much greater extent. It should also be noted that the background reaction is negligible at room temperature.
2.2.7 Turnover Numbers

The hydroformylation of styrene was affected using various generations of dendrimer catalysts and the results including turnover numbers are presented in Table 2.9. At room temperature, the turnover numbers for the lower generations 2.35, 2.36 and 2.37 (Table 2.9, entries 1, 3 and 5) are generally of the order of 10 to 20 mmol substrate to mmol Rh/h while the higher generations 2.38 and 2.39 (Table 2.9, entries 10 and 12) afford 78 and 84 /h respectively. At 70 °C, complexes 2.38 and 2.39 (Table 2.9, entries 11 and 13 respectively) gave relatively high turnover frequencies of 180 and 200 /h while the TON for the lower generations (Table 2.9, entries 2, 4 and 9) are of the order of 100 /h. Note that catalyst 2.36 and 2.37 converted 23 and 21 mmol of styrene in 22 h (Table 2.9, entries 4 and 9 respectively). The time dependence of the turnover rate is also demonstrated in entries 6–9 where the highest turnover frequency occurs within the first two hours of the reaction (Table 2.9, entry 6). The turnover frequency drops by half between 4 and 8 hours (Table 2.9, entries 7 and 8 respectively) of reaction.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Temperature$^b$</th>
<th>Time</th>
<th>Conversion</th>
<th>Turnover</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.35</td>
<td>25</td>
<td>22</td>
<td>32</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>2.35</td>
<td>70</td>
<td>22</td>
<td>92</td>
<td>102</td>
</tr>
<tr>
<td>3</td>
<td>2.36</td>
<td>25</td>
<td>22</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>2.36</td>
<td>70</td>
<td>22</td>
<td>60</td>
<td>96</td>
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<tr>
<td>5</td>
<td>2.37</td>
<td>25</td>
<td>22</td>
<td>37</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td>2.37</td>
<td>70$^c$</td>
<td>2</td>
<td>44</td>
<td>230</td>
</tr>
<tr>
<td>7</td>
<td>2.37</td>
<td>70$^c$</td>
<td>4</td>
<td>74</td>
<td>200</td>
</tr>
<tr>
<td>8</td>
<td>2.37</td>
<td>70$^c$</td>
<td>8</td>
<td>88</td>
<td>120</td>
</tr>
<tr>
<td>9</td>
<td>2.37</td>
<td>70</td>
<td>22</td>
<td>82</td>
<td>100</td>
</tr>
<tr>
<td>10</td>
<td>2.38</td>
<td>25</td>
<td>72</td>
<td>25</td>
<td>78</td>
</tr>
<tr>
<td>11</td>
<td>2.38</td>
<td>70$^c$</td>
<td>22</td>
<td>18</td>
<td>180</td>
</tr>
<tr>
<td>12</td>
<td>2.39</td>
<td>25</td>
<td>72</td>
<td>38</td>
<td>84</td>
</tr>
<tr>
<td>13</td>
<td>2.39</td>
<td>70$^c$</td>
<td>22</td>
<td>28</td>
<td>200</td>
</tr>
</tbody>
</table>

$^a$ 25 mg Catalyst, 1000 psi total pressure using a 1:1 ratio of CO:H$_2$. $^b$ 10.0 mmol styrene at 25 °C, 25.0 mmol except where indicated. $^c$ 10.0 mmol.
Chapter 2: Supported Dendrimers

2.3 Summary

Four generations of bis-(diphenylphosphanyl)methyl–PAMAM dendrimers anchored on silica were prepared and complexed to rhodium. These heterogeneous catalysts were found to be effective for the hydroformylation of various aryl olefins and vinyl esters showing good to excellent regio–selectivity for the branched aldehydes. Aliphatic olefins were also easily converted into the corresponding aldehydes, however, only a slight excess of the linear product was observed.

Significant pressure and temperature effects in terms of regio–selectivity were observed for aryl olefins and vinyl esters. Lower pressures of CO/H₂ decreased the branched to linear aldehyde ratio, while decreasing the temperature increased the propensity for branched aldehyde formation.

In terms of activity, the third and fourth generation complexes suffered lower rhodium loadings and were significantly less active then their first and second generation counterparts. The higher generations had a lower amine content than expected and it was proposed that a threshold of dendrimer growth had been reached and was propagated in the phosphonation step.

We were prompted to wonder whether steric crowding on the surface or the heterogeneous support hindered the growth of the dendrimer and the subsequent phosphonation step.

63
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3.0 SUPPORTED DENDRIMERS: SPACER GROUPS AND OTHER ISSUES

In the previous chapter, it was reported that the third (2.38) and fourth (2.39) generation catalysts displayed lower activities compared to the earlier generations (2.35 – 2.37) for the hydroformylation of olefins. It was believed that incomplete dendrimer growth in the higher generations was a serious problem, which expressed itself with a lower rhodium loading.

The amine groups on the original amorphous aminopropyl silica are spread out over the outer surface of the silica particle as well as within the pores and micro-pores (average pore diameter of 7.7 nm; total surface area of 300 m²/g SiO₂). Construction of the dendrimer within the pores would be affected more easily by steric hindrance and mass transfer difficulties than on the outer surface as the available space for growth is quickly consumed by the bulky dendrimers and the accessibility of the reaction sites decreases.

A lower observed amine content develops as the threshold of dendrimer growth is reached somewhere around the second generation. Subsequent difficulties in the phosphonation step caused by steric hindrance or lack of amine substrates would translate into a lower metal content after complexation.

Another contributing factor that cannot be ignored is the unfavourable accumulation of incomplete reactions as mentioned in the introductory chapter. Despite efforts to ensure reactions are as complete as possible, statistics dictate that with so many reaction sites, unsuccessful reactions are inevitable and any errors will propagate themselves in the higher generations.
3.1 Improving Dendrimer Purity: The Strategies Considered

Several options to improve the completion and thus purity of the dendrimers constructed on silica were considered. One obvious avenue of tackling this challenge would be to grow the dendritic wedge via the convergent synthesis approach and later attach the complete dendrimer to the silica support. This idea was quickly discarded, as the entropic demands for coupling the single focal point of the huge PAMAM dendritic wedge to the heterogeneous silica core seemed insurmountable.

Several potential routes to alleviate the steric congestion were also proposed and considered. One method that was contemplated was lowering the initial amine content of the aminopropyl silica to increase the surface space available per dendritic wedge. In Tsubokowa's report, this approach was attempted by preparing aminopropyl silica with a loading of 0.4 mmol NH₂/g SiO₂. Indeed he found that lowering the amine content of the silica allowed for a more complete reaction at the higher generations, however nowhere near the theoretical amine content was achieved. Again, data for the lower generations were not discussed in his paper but the amine content of the fourth generation PAMAM dendrimer was reported to be less than 50% of the theoretical expectation.

Another possibility would be to change the silica core to something more homogeneous as it is expected that the heterogeneity of the silica support encumbers reaction completion considerably.
The final proposal was to decrease the steric crowding at the surface of the dendrimer by choosing a diamine linker with a longer chain length than ethylenediamine. It was thought that increasing the length of the monomeric unit would greatly reduce the amine content per weight of silica thus giving the dendrimers more room to grow on the silica support.

In some smaller soluble dendrimer systems, steric crowding around the metal centres at the periphery was found to have a negative dendritic effect on the activity of the catalyst.\textsuperscript{23,66,80,132} This result was particularly noticeable in atom transfer and redox systems where metal–metal interactions are deactivating and when steric hindrance causes problems with accessibility. This detrimental effect was reduced by employing longer spacer groups that decreased the congestion on the surface of the dendrimer.

3.2 Extending the Diamine Linker

In an attempt to relieve the steric crowding and allow for increased catalyst loading at higher generations, it was decided that extending the chain length of each generation was a worthwhile avenue to investigate. In theory at least, the lengthening of the monomeric unit of each dendrimer generation should decrease the congestion at the surface. This can easily be observed by comparing the theoretical amine content for various chain lengths for up to four generations of PAMAM dendrimers on silica (Table 3.1). For example, with 1,12-diaminododecane as the linker the fourth generation dendrimer (3.8c; 1.84 mmol

67
NH₂/g SiO₂) has approximately half the amine content of its ethylenediamine counterpart (2.26; 3.55 mmol NH₂/g SiO₂).

Table 3.1 Theoretical and experimentally determined amine content (mmol NH₂/g SiO₂) of the C₂, C₄, C₆ and C₁₂ PAMAM dendrimers on silica.

<table>
<thead>
<tr>
<th>Generation</th>
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<th>G–4</th>
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<tr>
<td></td>
<td>Theo</td>
<td>Exp</td>
<td>Theo</td>
<td>Exp</td>
</tr>
<tr>
<td>C₂</td>
<td>1.50</td>
<td>1.34</td>
<td>2.23</td>
<td>1.54</td>
</tr>
<tr>
<td></td>
<td>(2.20)</td>
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<td>(2.22)</td>
<td></td>
</tr>
<tr>
<td>C₄</td>
<td>1.44</td>
<td>1.41</td>
<td>2.04</td>
<td>1.31</td>
</tr>
<tr>
<td></td>
<td>(3.2a)</td>
<td></td>
<td>(3.4a)</td>
<td></td>
</tr>
<tr>
<td>C₆</td>
<td>1.38</td>
<td>1.30</td>
<td>1.88</td>
<td>1.38</td>
</tr>
<tr>
<td></td>
<td>(3.2b)</td>
<td></td>
<td>(3.4b)</td>
<td></td>
</tr>
<tr>
<td>C₁₂</td>
<td>1.27</td>
<td>1.18</td>
<td>1.52</td>
<td>1.29</td>
</tr>
<tr>
<td></td>
<td>(3.2c)</td>
<td></td>
<td>(3.4c)</td>
<td></td>
</tr>
</tbody>
</table>

a Starting from aminopropylsilica with an initial amine loading of 0.90 mmol NH₂/g SiO₂ the theoretical amine content was calculated assuming perfect growth (see appendix 1). b Amine content determined experimentally by back titration with an standardized solution of NaOHₐq from HCl washed PAMAM silica (200 to 300 mg) in an aqueous methanol solution. Average from 3 trials except where indicated. c One trial.
3.2.1 THE C_4, C_6 AND C_12 PAMAM DENDRIMERS ON SILICA

To study the effect of chain length, 1,4-diaminobutane (3.1a), 1,6-diaminohexane (3.1b) and 1,12-diaminododecane (3.1c) were substituted for ethylenediamine (2.10) in the standard divergent growth strategy described in chapter 2 (Section 2.1.1). Henceforth, the PAMAM dendrimers on silica prepared using 2.10 will be referred to as the C_2 series. Correspondingly, dendrimers prepared from 3.1a, 3.1b and 3.1c will be labelled the C_4, C_6 and C_12 series respectively.

3.2.2 SYNTHESIS OF THE C_4, C_6 AND C_12 SERIES

PAMAM dendrimers, up to generation four, were constructed on the surface of aminopropylsilica employing a standard divergent growth strategy with 3.1a, 3.1b and 3.1c in lieu of 2.10 during the amidation step (Scheme 3.1). Longer reaction times (7 – 10 days) and higher reaction temperatures (50 °C) were also employed in an attempt to ensure a more exhaustive amidation reaction. Also, since 1,6-diaminohexane and 1,12-diaminododecane are both solids at room temperature, additional methanol was added to improve their solubility.

Figures 3.1 and 3.2 show the proposed structures of the third (2.24, 3.6a – c) and fourth (2.26, 3.8a – c) generation dendrimers respectively as the diamine linker increases from two carbons to twelve carbons. On paper at least, the proposed structures clearly show the gradual decongestion of the terminal groups as the diamine linker is extended.
Scheme 3.1 The synthesis of the longer linker PAMAM dendrimers on silica using diaminobutane (n = 2), diaminohexane (n = 3), and diaminododecane (n = 6).
Figure 3.1. Proposed structures for the third generation PAMAM dendrimers on silica with the a) $C_2$ (2.24) b) $C_4$ (3.6a) c) $C_6$ (3.6b) and d) $C_{12}$ (3.6c) linkers.
Figure 3.2. Proposed structures for the fourth generation PAMAM dendrimers on silica with the a) $C_2$ (2.26) b) $C_4$ (3.8a) c) $C_6$ (3.8b) and d) $C_{12}$ (3.8c) linkers.
3.2.3 ISOLATION OF THE $C_4$, $C_6$ AND $C_{12}$ PAMAM DENDRIMERS ON SILICA

The isolation of the dendrimers with the longer linkers proved to be extremely time consuming especially after the amidation step. The filters generally became clogged with precipitated diamine as the solvent evaporated under the nitrogen flow. In the case of the 1,12-diaminedodecane linker, isolation via filtration and washing took up to three days. As with the $C_2$ series, yield was sacrificed as the silica was allowed to compact at the bottom of the flask before the overlying diamine solution was decanted off prior to the addition of fresh methanol and filtration. In hindsight, Soxhlet extraction would probably have made recovery of the dendrimer-grafted silica from the diamine solution much faster, simpler and definitely less messy.

Also the problems encountered here make considering even longer linkers, such as a $C_{18}$ diamine, to be wholly impractical. At the isolation stage, the waxy solid would likely prove to be impossible to separate from the dendrimer silica matrix.

3.2.4 DETERMINATION OF THE AMINE CONTENT

The approximate amine contents were determined experimentally via the titration of the $RNH_2\cdot HCl$ salts with standardized $NaOH_{(aq)}$ (Table 3.1). As noted in the previous chapter, the experimental amine contents are much lower than the theoretical expectations indicating that dendrimer growth is far from perfect. However, a significant improvement in amine content was observed for the $C_6$ and $C_{12}$ linkers compared to the $C_2$ linker. The fourth generation $C_6$ (3.8b) and
C\textsubscript{12} (3.8c) dendrimers were determined to have 65 and 73 % of their theoretical amine contents respectively, while the fourth generation C\textsubscript{2} dendrimer (2.26) was found to have only 54 % of its theoretical amine content.

3.3 PREPARATION OF THE C\textsubscript{4}, C\textsubscript{6} AND C\textsubscript{12} LIGANDS AND RHODIUM COMPLEXES

The terminal amines of the C\textsubscript{4} (3.2a, 3.4a, 3.6a and 3.8a), C\textsubscript{6} (3.2b, 3.4b, 3.6b and 3.8b) and C\textsubscript{12} (3.2c, 3.4c, 3.6c and 3.8c) PAMAM dendrimers on silica were phosphonated with diphenylphosphanylmethanol (2.29), prepared \textit{in situ} from paraformaldehyde (2.27) and diphenylphosphine (2.28). The resulting bis-(diphenylphosphanyl methylated) dendrimers (3.9–3.12a–c) were then complexed with [Rh(CO)$_2$Cl]$_2$ in distilled and degassed hexanes at 40°C for 12 hours under argon to give complexes 3.13–3.16a–c (Scheme 3.2).

Scheme 3.2 The bisphosphinomethylation of the C\textsubscript{4}, C\textsubscript{6}, and C\textsubscript{12} PAMAM dendrimers on silica and subsequent complexation with rhodium.
Table 3.2 Compound index of bisdiphenylphosphinomethylated amines and rhodium complexed compounds for the various PAMAM dendrimers on silica.

<table>
<thead>
<tr>
<th></th>
<th>G-1</th>
<th>G-2</th>
<th>G-3</th>
<th>G-4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Phos(^a)</td>
<td>Rh(^b)</td>
<td>Phos</td>
<td>Rh</td>
</tr>
<tr>
<td>C(_2)</td>
<td>2.31</td>
<td>2.36</td>
<td>2.32</td>
<td>2.37</td>
</tr>
<tr>
<td>C(_4)</td>
<td>3.9a</td>
<td>3.13a</td>
<td>3.10a</td>
<td>3.14a</td>
</tr>
<tr>
<td>C(_6)</td>
<td>3.9b</td>
<td>3.13b</td>
<td>3.10b</td>
<td>3.14b</td>
</tr>
<tr>
<td>C(_{12})</td>
<td>3.9c</td>
<td>3.13c</td>
<td>3.10c</td>
<td>3.14c</td>
</tr>
</tbody>
</table>

\(^a\)N(CH\(_2\)PPh\(_2\))\(_2\). \(^b\)N(CH\(_2\)PPh\(_2\))\(_2\)Rh(CO)\(_2\)Cl.

3.4 CHARACTERIZATION OF THE C\(_4\), C\(_6\) AND C\(_{12}\) LIGAND AND RH COMPLEXES

Once more, the heterogeneity of the dendrimers on silica makes comprehensive characterization very difficult. Accepting that the backbones of our PAMAM dendrimers were imperfect was reasonable and we resolved ourselves to be satisfied with looking at the immediate environment around the metal centres. As before, solid state NMR was used to assess the purity of the bis-(diphenylphosphanyl)-methylation step. All phosphonated compounds gave satisfactory \(^{31}\)P NMR spectra showing only a broad singlet centred around \(-28\) ppm (see Figure 2.3) for the uncomplexed phosphines \((3.9 - 3.12a - c)\) while the rhodium complexed dendrimers \((3.13 - 3.16a - c)\) gave broader peaks centred around \(24\) to \(25\) ppm (see Figure 2.5).

The phosphonated compounds \((3.9 - 3.12a - c)\) were relatively stable when dry and could be easily manipulated in air for short periods of time without
oxidation. However, the phosphines oxidize slowly over time if the compounds are not stored under inert conditions (argon preferred). Also, using degassed solvents for all subsequent reactions is crucial as the compounds oxidize rapidly in any oxygenated solvent.

3.5 Evaluation of the $\text{C}_4$, $\text{C}_6$ and $\text{C}_{12}$ PAMAM Complexes as Catalysts

With the new series of rhodium complexes in hand, the hydroformylation of styrene (eq. 3.1) and other olefins was examined using a 1:1 mixture of CO and $\text{H}_2$ (total pressure $= 1000$ psi) in $\text{CH}_2\text{Cl}_2$. Improving the activity and recyclability of the third (3.15) and fourth (3.16) generation catalysts was one of our goals and results using 3.15 and 3.16 are highlighted below. Testing of the lower generations (3.13 and 3.14) revealed that they were also highly active and recyclable catalysts.

\[
\begin{align*}
\text{C}_6 & + \text{CO} / \text{H}_2 \\
\text{3.15 or 3.16} \\
\text{CH}_2\text{Cl}_2, 1000 \text{ psi} & \rightarrow \\
\text{2.40} & \rightarrow \text{2.41} \quad \text{and} \quad \text{2.42}
\end{align*}
\]
3.5.1 The Hydroformylation of Styrene: Recycling Study

The results for the third (3.15) and fourth (3.16) generation catalysts with styrene (2.40) are summarized in Table 3.3. The hydroformylation of 2.40 proceeds in up to quantitative yields, and in fine regioselectivity for all the new catalysts prepared.

These silica–supported catalysts are easily recovered by microporous filtration using a 0.45 μm Nylon membrane filter and are reusable for at least 3 more cycles. Generally, as the linker chain length is increased from 2 carbons (2.38 and 2.39; Table 3.3, entries 1 – 2 and 15 – 16) to 4 carbons (3.15a and 3.16a; Table 3.3, entries 3 – 6 and 17 – 20), the catalytic activity and recyclability increases dramatically as shown. There is another increase of activity going from the C₄ to the C₆ series (3.15b and 3.16b; Table 3.3, entries 7 – 10 and 21 – 24). However, there is no significant activity difference between the C₆ and the C₁₂ dendrimers series (3.15c and 3.16c; Table 3.3, entries 11 – 14 and 25 – 28).

The regioselectivities were observed to vary slightly from cycle to cycle and were generally between 85 and 92 % branched aldehyde. This observation is not consistent enough to say that selectivity improves or degenerates with recycling. Temperature is already known to greatly affect the branched to linear ratio when styrene is the substrate and small variances in the temperature of the reactor baths during the course of the reaction is a plausible explanation for this observation.
Table 3.3 The hydroformylation of styrene using 3.15 and 3.16.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Cycle\textsuperscript{c}</th>
<th>Time</th>
<th>Temp (\textdegree C)</th>
<th>Conversion\textsuperscript{d} (%)</th>
<th>Selectivity\textsuperscript{e}</th>
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<tr>
<td>1\textsuperscript{b}</td>
<td>2.38</td>
<td>1</td>
<td>22</td>
<td>75</td>
<td>99</td>
<td>8:1</td>
</tr>
<tr>
<td>2\textsuperscript{b}</td>
<td>2.38</td>
<td>2</td>
<td>22</td>
<td>75</td>
<td>5</td>
<td>ND\textsuperscript{f}</td>
</tr>
<tr>
<td>3</td>
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<td>65</td>
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## Chapter 3: Spacer Groups and Other Issues

*(Table 3.3 Cont.)*

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<td>3.16c</td>
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</tr>
</tbody>
</table>

\[a\] 10.0 mmol of 2.40 except where indicated, 10 ml CH\(_2\)Cl\(_2\), 22 h, 500 psi CO/500 psi H\(_2\), \[b\] 2.0 mmol 2.40 \[c\] Catalyst was recovered by microporous filtration after the first cycle, washed with CH\(_2\)Cl\(_2\) and reused in the next cycle. \[d\] Determined by \(^1\)H NMR and GC. \[e\] Determined by \(^1\)H NMR. \[f\] Not determined.
3.5.2 Low Conversion Recycling Study

Even with 10.0 mmol of substrate for only 25 mg of catalyst, it was apparent that the C\textsubscript{6} and C\textsubscript{12} series catalysts were very active after recycling. Observing the systems at lower conversions should give valuable insight into the relative activity of both systems and serve as a more meaningful comparison. Rhodium complexes 3.16\textsubscript{b} and 3.16\textsubscript{c} were employed for 2 hours and recycled normally resulting in a more dramatic decrease in activity between cycles. Under the conditions employed, the results indicate that catalyst 3.16\textsubscript{b} (Table 3.4, entries 1–3) is slightly more active than 3.16\textsubscript{c} (Table 3.4, entries 4–6).

Table 3.4 Low conversion recycling with complexes 3.16\textsubscript{b} and 3.16\textsubscript{c}. \textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Cycle\textsuperscript{b}</th>
<th>Conversion\textsuperscript{c} (%)</th>
<th>Selectivity\textsuperscript{d}</th>
<th>2.41:2.42</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.16\textsubscript{b}</td>
<td>1</td>
<td>23</td>
<td>8:1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3.16\textsubscript{b}</td>
<td>2</td>
<td>18</td>
<td>14:1</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3.16\textsubscript{b}</td>
<td>3</td>
<td>8</td>
<td>ND\textsuperscript{e}</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3.16\textsubscript{c}</td>
<td>1</td>
<td>20</td>
<td>10:1</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3.16\textsubscript{c}</td>
<td>2</td>
<td>14</td>
<td>11:1</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>3.16\textsubscript{c}</td>
<td>3</td>
<td>7</td>
<td>ND\textsuperscript{e}</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} 10.0 mmol 2.40, 10 ml CH\textsubscript{2}Cl\textsubscript{2}, 2 h, 65 °C, 25 mg catalyst. \textsuperscript{b} Catalyst was recovered by microporous membrane filtration after the first cycle, washed with CH\textsubscript{2}Cl\textsubscript{2} and reused in the next cycle. \textsuperscript{c} Determined by \textsuperscript{1}H NMR and GC. \textsuperscript{d} Determined by \textsuperscript{1}H NMR. \textsuperscript{e} Not determined.
3.5.3 The Hydroformylation of Vinyl Acetate: Recycling Study

The activities and regio-selectivities of 3.15 and 3.16 were also investigated with vinyl acetate (3.17) as the substrate (Eq. 3.2). Table 3.5 summarizes the results obtained.

\[
\begin{align*}
\text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O} \\
\text{3.17} & \quad \text{CH}_2\text{Cl}_2 & \quad 1000 \text{ psi} & \quad \text{3.15 or 3.16} \\
\end{align*}
\]

In general, the hydroformylation of 3.17 followed a similar trend as observed in the styrene trials where the C₆ (3.15b and 3.16b) and C₁₂ (3.15c and 3.16c) catalysts were found to be more active in later cycles than the C₄ (3.15a and 3.16a) catalysts. At 65 °C, all the catalysts tested gave excellent regio-selectivities varying from approximately 90 to 95 %, favouring 2-acetoxypropanal (3.18) over 3-acetoxypropanal (3.19). It was also observed that 3.17 is a less reactive substrate than styrene as the conversions drop lower than quantitative by the second cycle (Table 3.5, entries 2, 6, 10, 14, 18, 22) in all cases. In terms of recycling, 3.16 exhibited higher conversions (Table 3.5, entries 13 – 24) than 3.15 (Table 3.5, entries 1 – 12) suggesting a possible dendrimer effect.

With respect to comparing the relative activities of the C₆ and C₁₂ series catalysts, 3.16b (Table 3.5, entries 17 – 20) exhibited higher conversions after recycling then 3.16c its C₁₂ counterpart (Table 3.5, entries 21 – 24). However, a similar comparison with the third generation catalysts gives contradictory results where 3.15c (Table 3.5, entries 9 – 12) catalyst recycling is more effective than the 3.15b catalyst (Table 3.5, entries 5 – 8).
Table 3.5 The hydroformylation of vinyl acetate with 3.15 and 3.16.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Cycle\textsuperscript{b}</th>
<th>Temp (°C)</th>
<th>Conversion\textsuperscript{c} (%)</th>
<th>Selectivity\textsuperscript{d}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.15a</td>
<td>1</td>
<td>65</td>
<td>96</td>
<td>15:1</td>
</tr>
<tr>
<td>2</td>
<td>3.15a</td>
<td>2</td>
<td>65</td>
<td>79</td>
<td>15:1</td>
</tr>
<tr>
<td>3</td>
<td>3.15a</td>
<td>3</td>
<td>60</td>
<td>18</td>
<td>23:1</td>
</tr>
<tr>
<td>4</td>
<td>3.15a</td>
<td>4</td>
<td>65</td>
<td>8</td>
<td>13:1</td>
</tr>
<tr>
<td>5</td>
<td>3.15b</td>
<td>1</td>
<td>60</td>
<td>99</td>
<td>22:1</td>
</tr>
<tr>
<td>6</td>
<td>3.15b</td>
<td>2</td>
<td>65</td>
<td>95</td>
<td>17:1</td>
</tr>
<tr>
<td>7</td>
<td>3.15b</td>
<td>3</td>
<td>65</td>
<td>86</td>
<td>15:1</td>
</tr>
<tr>
<td>8</td>
<td>3.15b</td>
<td>4</td>
<td>65</td>
<td>36</td>
<td>15:1</td>
</tr>
<tr>
<td>9</td>
<td>3.15c</td>
<td>1</td>
<td>65</td>
<td>99</td>
<td>19:1</td>
</tr>
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<td>10</td>
<td>3.15c</td>
<td>2</td>
<td>65</td>
<td>93</td>
<td>18:1</td>
</tr>
<tr>
<td>11</td>
<td>3.15c</td>
<td>3</td>
<td>65</td>
<td>79</td>
<td>19:1</td>
</tr>
<tr>
<td>12</td>
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<td>4</td>
<td>65</td>
<td>65</td>
<td>17:1</td>
</tr>
<tr>
<td>13</td>
<td>3.16a</td>
<td>1</td>
<td>65</td>
<td>95</td>
<td>11:1</td>
</tr>
<tr>
<td>14</td>
<td>3.16a</td>
<td>2</td>
<td>65</td>
<td>89</td>
<td>13:1</td>
</tr>
<tr>
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<td>3.16a</td>
<td>3</td>
<td>65</td>
<td>85</td>
<td>15:1</td>
</tr>
<tr>
<td>16</td>
<td>3.16a</td>
<td>4</td>
<td>65</td>
<td>82</td>
<td>14:1</td>
</tr>
<tr>
<td>17</td>
<td>3.16b</td>
<td>1</td>
<td>60</td>
<td>99</td>
<td>21:1</td>
</tr>
<tr>
<td>18</td>
<td>3.16b</td>
<td>2</td>
<td>65</td>
<td>95</td>
<td>19:1</td>
</tr>
<tr>
<td>19</td>
<td>3.16b</td>
<td>3</td>
<td>65</td>
<td>91</td>
<td>13:1</td>
</tr>
<tr>
<td>20</td>
<td>3.16b</td>
<td>4</td>
<td>70</td>
<td>89</td>
<td>10:1</td>
</tr>
</tbody>
</table>
(Table 3.5 Cont.)

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
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</tr>
<tr>
<td>22</td>
<td><strong>3.16c</strong></td>
<td>2</td>
<td>65</td>
<td>87</td>
</tr>
<tr>
<td>23</td>
<td><strong>3.16c</strong></td>
<td>3</td>
<td>65</td>
<td>86</td>
</tr>
<tr>
<td>24</td>
<td><strong>3.16c</strong></td>
<td>4</td>
<td>65</td>
<td>80</td>
</tr>
</tbody>
</table>

\(^a\) 10.0 mmol of **3.17**, 10 ml CH\(_2\)Cl\(_2\), 22 h, 500 psi CO/ 500 psi H\(_2\), \(^b\) Catalyst was recovered by microporous membrane filtration, washed with CH\(_2\)Cl\(_2\) and reused in the next cycle. \(^c\) Determined by \(^1\)H NMR and GC. \(^d\) Determined by \(^1\)H NMR.
3.5.4 The Hydroformylation of 1-Octene: Recycling Study

The hydroformylation of 1-octene (3.20) (eq. 3.3) was briefly examined with the results summarized in Table 3.6. As observed before, catalyst 3.15c (Table 3.6, entries 1–3) is less active than catalyst 3.16c (Table 3.6, entries 4–6). After 7 hours, the first cycles (Table 3.6, entries 1 and 4) resulted in conversions of 62 and 98 % respectively. Regioselectivities remain very poor with nonanal (3.22) favoured slightly over the 2-methyloctanal (3.21).

![Chemical Reaction](image)

Table 3.6 Hydroformylation of 1-Octene with 3.15c and 3.16c.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cycle\textsuperscript{b}</th>
<th>Catalyst</th>
<th>Time (h)</th>
<th>Conversion (%)</th>
<th>Selectivity\textsuperscript{d}</th>
<th>3.21:3.22</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>3.15c</td>
<td>7</td>
<td>62</td>
<td>1:1.5</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>3.15c</td>
<td>14</td>
<td>97</td>
<td>1:1.2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>3.15c</td>
<td>21</td>
<td>77</td>
<td>1:1.4</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>3.16c</td>
<td>7</td>
<td>98</td>
<td>1:1.5</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>3.16c</td>
<td>14</td>
<td>95</td>
<td>1:1.2</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>3.16c</td>
<td>21</td>
<td>94</td>
<td>1:1.2</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} 10.0 mmol of 3.20, 10 ml CH\textsubscript{2}Cl\textsubscript{2}, 65 °C, 500 psi CO/500 psi H\textsubscript{2}.\textsuperscript{b} Catalyst was recovered by microporous membrane filtration, washed with CH\textsubscript{2}Cl\textsubscript{2} and reused in the next cycle.\textsuperscript{c} Determined by \textsuperscript{1}H NMR and GC.\textsuperscript{d} Determined by \textsuperscript{1}H NMR.
3.6 Modifying the Phosphine

A tremendous amount of research has been carried out investigating the effect of the phosphine ligand in the hydroformylation reaction\textsuperscript{101} and a general trend relating the basicity of the metal coordinating ligands to selectivity and activity of the rhodium catalysts is often reported. Typically, more basic phosphines, such as alkylphosphines when compared to tpp, demonstrate a decrease in activity but also show enhanced regio-selectivity.

3.6.1 The Preparation of the Bis-(dicyclohexylphosphanylmethyl)-PAMAM Ligands on Silica

In an effort to examine the effect of ligand basicity in our system, dicyclohexylphosphine (3.23) was substituted for diphenylphosphine (2.28) in the preparation of the C\textsubscript{6} series phosphonated PAMAM dendrimers on silica. 3.23 is much more air sensitive than 2.28 but can be handled with care under a generous flow of argon in rigorously degassed solvents.

In a very similar procedure to that previously mentioned, (Sections 2.1.4 and 3.2.5) dicyclohexylphosphanylmethanol (3.24) was prepared \textit{in situ} and used to phosphonated the C\textsubscript{6} series of PAMAM dendrimers on silica (3.2b, 3.4b, 3.6b and 3.8b) (Scheme 3.3). The resulting bis-(dicyclohexylphosphanylmethyl)-PAMAM ligands on silica (3.25 – 3.28) were characterized by solid state NMR. Figure 3.3 shows a representative solid-state \textsuperscript{31}P NMR spectra with a shift centred around \textasciitilde18 to \textasciitilde19 ppm.
Scheme 3.3 The phosphonation of the C₆ series of PAMAM dendrimers with dicyclohexylphosphanyl)methanol.

Figure 3.3 Solid state $^{31}$P NMR (CPMAS) spectra of the bis–
(dicyclohexylphosphanyl)methyl–PAMAM (C₆ series) dendrimer on Silica.
3.6.2 Preparation and Characterization of the Bis-
(dicyclohexylphosphanyl)methyl–PAMAM Rhodium Complexes

Ligands 3.25 – 3.28 were complexed with [Rh(CO)₂Cl]₂ in distilled and degassed hexanes at 40°C for 12 hours under argon to give four generations of the C₆ series bis–(dicyclohexylphosphanyl)methyl–PAMAM rhodium complexes on silica (3.29 – 3.32). Complexes 3.29 – 3.32 were also characterized by solid state NMR and gave broad shifts centred around 40 ppm. Figure 3.4 is a representative solid state ³¹P NMR spectrum of the rhodium complex (δ ≈ 40 ppm) which also shows a small amount of uncomplexed phosphine (δ ≈ 19 ppm).

Figure 3.4 Solid state ³¹P NMR (CPMAS) of the bis–(dicyclohexylphosphanyl methyl)–PAMAM (C₆ series) rhodium complexes on silica.
3.6.3 Evaluation of the Bis-(dicyclohexylphosphanylmethyl)-PAMAM Rhodium Complexes

All four generations of the rhodium complexes of the bis-(dicyclohexylphosphanylmethyl) terminated C₅ series dendrimers (3.29 – 3.32) were examined as hydroformylation catalysts. The results for styrene as the substrate are reported in table 3.7.

An apparent generation effect is observed as the first (3.29) (Table 3.7, entries 1 and 2) and second (3.30) generation catalysts (Table 3.7, entries 3–6) exhibit lower recycling capabilities when compared to the third (3.31) (Table 3.7, entries 7 – 10) and fourth (3.32) generation catalysts (Table 3.7, entries 11 – 14). Similar observations were previously noted when comparing the third (3.15) and fourth (3.16) generation catalysts of the corresponding bis-(diphenylphosphanylmethyl)-PAMAM system (Table 3.3). This result is reasonable as each generation is supposed to have twice as many metal centres as the previous generation.

In terms of regio-selectivity, the results obtained for 3.29 – 3.32 (Table 3.7) can be compared with the selectivities observed for the hydroformylation of 2.40 when the bis-(diphenylphosphanylmethyl)-PAMAM catalysts were employed (Table 3.3). In general, the observed regioselectivities were independent of generation, however the bis-(dicyclohexylphosphanylmethyl)-PAMAM catalysts (Table 3.7, entries 7 – 14) consistently gave higher branched to linear ratios than their bis-(diphenylphosphanylmethyl)-PAMAM counterparts (Table 3.3, entries 7 – 10 and 21 – 24).
Table 3.7 Hydroformylation of styrene with catalysts 3.29 – 3.32 at 85 °C.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Cycle\textsuperscript{b}</th>
<th>Conversion\textsuperscript{c} (%)</th>
<th>Selectivity\textsuperscript{d} 2.41:2.42</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.29</td>
<td>1</td>
<td>&gt;99</td>
<td>14:1</td>
</tr>
<tr>
<td>2</td>
<td>3.29</td>
<td>2</td>
<td>96</td>
<td>13:1</td>
</tr>
<tr>
<td>3</td>
<td>3.30</td>
<td>1</td>
<td>&gt;99</td>
<td>13:1</td>
</tr>
<tr>
<td>4</td>
<td>3.30</td>
<td>2</td>
<td>97</td>
<td>14:1</td>
</tr>
<tr>
<td>5</td>
<td>3.30</td>
<td>3</td>
<td>59</td>
<td>15:1</td>
</tr>
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<td>6</td>
<td>3.30</td>
<td>4</td>
<td>33</td>
<td>14:1</td>
</tr>
<tr>
<td>7</td>
<td>3.31</td>
<td>1</td>
<td>&gt;99</td>
<td>15:1</td>
</tr>
<tr>
<td>8</td>
<td>3.31</td>
<td>2</td>
<td>&gt;99</td>
<td>14:1</td>
</tr>
<tr>
<td>9</td>
<td>3.31</td>
<td>3</td>
<td>96</td>
<td>15:1</td>
</tr>
<tr>
<td>10</td>
<td>3.31</td>
<td>4</td>
<td>72</td>
<td>16:1</td>
</tr>
<tr>
<td>11</td>
<td>3.32</td>
<td>1</td>
<td>&gt;99</td>
<td>14:1</td>
</tr>
<tr>
<td>12</td>
<td>3.32</td>
<td>2</td>
<td>&gt;99</td>
<td>12:1</td>
</tr>
<tr>
<td>13</td>
<td>3.32</td>
<td>3</td>
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</tr>
<tr>
<td>14</td>
<td>3.32</td>
<td>4</td>
<td>88</td>
<td>15:1</td>
</tr>
</tbody>
</table>

\textsuperscript{a} 10.0 mmol of 2.40, 10 ml CH\textsubscript{2}Cl\textsubscript{2}, 22 h, 500 psi CO/ 500 psi H\textsubscript{2}. \textsuperscript{b} Catalyst was recovered by microporous filtration after the first cycle, washed with CH\textsubscript{2}Cl\textsubscript{2} and reused in the next cycle. \textsuperscript{c} Determined by \textsuperscript{1}H NMR and GC. \textsuperscript{d} Determined by \textsuperscript{1}H NMR.
These bis-(dicyclohexylphosphanylmethyl)-PAMAM catalysts still operate at lower temperatures, however the activity in the second cycle (Table 3.8, entries 2 and 4) are significantly lower than the first (Table 3.8, entries 1 and 3). Decreasing the temperature of the reaction to 35 °C also increases the regio-selectivity to greater than 96% favouring 2.41 (Table 3.8).

Table 3.8 Hydroformylation of styrene with catalysts 3.31 and 3.32 at 35 °C

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Cycle</th>
<th>Conversion</th>
<th>Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>3.31</td>
<td>1</td>
<td>&gt;99</td>
<td>&gt;25:1</td>
</tr>
<tr>
<td>16</td>
<td>3.31</td>
<td>2</td>
<td>22</td>
<td>&gt;25:1</td>
</tr>
<tr>
<td>17</td>
<td>3.32</td>
<td>1</td>
<td>&gt;99</td>
<td>&gt;25:1</td>
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<tr>
<td>18</td>
<td>3.32</td>
<td>2</td>
<td>46</td>
<td>&gt;25:1</td>
</tr>
</tbody>
</table>

a 10.0 mmol of 2.40, 10 ml CH₂Cl₂, 22 h, 500 psi CO/ 500 psi H₂, b Catalyst was recovered by microporous filtration after the first cycle, washed with CH₂Cl₂ and reused in the next cycle. c Determined by ¹H NMR and GC. d Determined by ¹H NMR.
3.7 Leaching and Preleaching Studies

After the hydroformylation reaction, the product solution is orange or yellow for the first few cycles indicating that slow leaching of rhodium from the silica occurs. Rinsing the catalyst with CH₂Cl₂ after complexation does not remove this excess rhodium, neither does Soxhlet extraction with CH₂Cl₂ or pressurizing the catalyst with H₂ (1000 psi) in CH₂Cl₂. However, pressurizing the catalyst with CO or mixtures of CO and H₂ (1000 psi total pressure) does promote the leaching of rhodium as observed by a coloured wash solution and a red or black residue after removal of solvent.

Several cycles of preleaching were performed by pressurizing the catalyst with CO (1000 psi) in CH₂Cl₂ and subsequent rinsing after depressurization washed away the soluble rhodium species. These preleached catalysts were still active under hydroformylation conditions however addition of substrate promotes further leaching of the metal.

Table 3.9 summarizes the activity of the fourth generation C₁₂ catalysts (3.16c) after 24 hours of Soxhlet extraction (entries 1 – 3) or 3 sessions of high pressure CO preleaching (entries 4 – 6). After 3 cycles, complete conversion is still achieved for the Soxhlet extraction treated catalyst (Table 3.9, entry 3), however only 78 % conversion is observed in the third cycle of the catalyst treated with CO (Table 3.9, entry 6).

The observations from this experiment would suggest that soluble rhodium carbonyl species are being formed under hydroformylation condition and may contribute to an unavoidable background reaction.
Table 3.9. Hydroformylation of styrene with preleached 3.16c.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>cycle\textsuperscript{b}</th>
<th>Catalyst</th>
<th>Conversion\textsuperscript{c} (%)</th>
<th>Selectivity\textsuperscript{d}</th>
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</thead>
<tbody>
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<td>1</td>
<td>1</td>
<td>3.16c Soxhlet\textsuperscript{e}</td>
<td>99</td>
<td>10:1</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>3.16c Soxhlet\textsuperscript{e}</td>
<td>99</td>
<td>13:1</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>3.16c Soxhlet\textsuperscript{e}</td>
<td>99</td>
<td>13:1</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>3.16c (pCO)\textsuperscript{f}</td>
<td>99</td>
<td>10:1</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>3.16c (pCO)\textsuperscript{f}</td>
<td>99</td>
<td>11:1</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>3.16c (pCO)\textsuperscript{f}</td>
<td>78</td>
<td>13:1</td>
</tr>
</tbody>
</table>

\textsuperscript{a} 10.0 mmol of 2.40, 10 ml CH\textsubscript{2}Cl\textsubscript{2}, 22 h, 65 °C, 500 psi CO/500 psi H\textsubscript{2}. \textsuperscript{b} Catalyst was recovered by microporous filtration after the first cycle, washed with CH\textsubscript{2}Cl\textsubscript{2} and reused in the next cycle. \textsuperscript{c} Determined by \textsuperscript{1}H NMR and GC. \textsuperscript{d} Determined by \textsuperscript{1}H NMR. \textsuperscript{e} Extraction for 24 h with refluxing CH\textsubscript{2}Cl\textsubscript{2}. \textsuperscript{f} Catalyst exposed to three 5 h cycles of 1000 psi CO.
3.8 Complexation of Platinum

The extent of rhodium leaching observed made us sceptical about the degree of metal complexation to the phosphines. It is very likely that some of the rhodium present in the system is not bound to the phosphines and the proximity of the phosphine oxide (δ = 29 ppm; P=O) peak to the broad rhodium complexed phosphine peak (δ ≈ 24 ppm, Ph₂P(CH₂N)Rh) in the ³¹P NMR brought a new uncertainty to our analyses. A simple experiment involving a metal with a large coupling constant with phosphine would show more clearly the extent of metal complexation to the phosphine via solid state NMR. PtCl₂(PhCN)₂ was used to prepare a series of platinum complexed phosphonated dendrimers (3.33 – 3.36). The spectra shown in figure 3.5 both show a triplet centred at −8.8 ppm with J(PL–P) equal to approximately 1705 hz. The observed multiplicity and coupling constant is consistent with a platinum centre bound to two phosphines. Also noticeable in both spectra are phosphine oxide peaks at 29 ppm and a broad hump of unidentified phosphorus species centred around 7 ppm.

The triplet in the fourth generation (3.36) spectrum (Figure 3.5b) is noticeably broader than the triplet observed in the first generation (3.33) spectrum (Figure 3.5a). This observation may be explained by the expected decrease in dendrimer purity with increasing generation. Synthetic defects during the construction of the dendrimers would place the terminal amines in slightly different environments prior to phosphonation and complexation and would result in peak broadening.
Figure 3.5 Solid state $^{31}$P NMR (CPMAS) of a) the C$_6$ G–1 (3.33) and b) C$_6$ G–4 (3.36) phosphorylated PAMAM dendrimer on silica complexed to platinum.
3.9 Recent Characterization Data of PAMAM on Silica

With a fresh perspective and industrial experience, Jan Reynhardt from our group has recently focused on the challenging task of finding new avenues for the characterization of these heterogeneous compounds. In this respect BET surface areas\textsuperscript{133,134} pore volumes and pore diameters of the different generations were determined. It was observed that the surface area of the support as well as the pore volumes and pore diameters all decreased with increasing generation (Table 3.10). This would support the notion that a substantial amount of dendrimer growth takes place within the pores of the silica.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Generation</th>
<th>Surface Area (m\textsuperscript{2}/g)</th>
<th>Total Pore Volume (cm\textsuperscript{3}/g)</th>
<th>Average Pore Diameter (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>305.59</td>
<td>0.70</td>
<td>7.68</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>248.06</td>
<td>0.51</td>
<td>7.04</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>225.16</td>
<td>0.46</td>
<td>7.05</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>190.32</td>
<td>0.39</td>
<td>6.90</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>147.92</td>
<td>0.33</td>
<td>6.98</td>
</tr>
</tbody>
</table>

It is difficult to say whether or not continuing the dendrimer to higher generations (past generation four) would actually see an increased degree of dendrimer growth on the surface based on the previous generation. Regardless,
it should be expected that incomplete reactions would become more significant
owing to statistical analyses.

3.10 SUMMARY

A series of PAMAM dendrimers were constructed using longer diamine
linkers in an effort to improve the dendrimer purity. Simple titrations of the new
$C_4$, $C_6$ and $C_{12}$ PAMAM dendrimers anchored on silica indicate that relieving
steric crowding allows for more complete dendrimer growth reactions.

The bis(diphenylphosphanyl)methyl)PAMAM ligands were prepared and
complexed to rhodium. These heterogeneous catalysts were found to be
effective for the hydroformylation of styrene and vinyl acetate showing good to
excellent regioselectivity for the branched aldehydes. $1$–octene was also easily
converted, however, only a slight excess of the linear product was observed. The
third and fourth generation $C_6$ and $C_{12}$ catalysts performed very well in various
recycling studies and could be reused up to four times.

Bis(dicyclohexylphosphanyl)methyl)PAMAM ligands and complexes were
also prepared to examine the effect of the phosphine ligand. Using the
alkyphosphine as a ligand resulted in improved regio–selectivities over the
arylphosphine ligands however an accompanying decrease in activity was
observed.
CHAPTER 4: POLYMER SUPPORTED CATALYSTS

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4.0 Polymer Supported Catalysts

In terms of organic synthesis, cross-linked polystyrene resins were originally used in the solid phase synthesis (SPS)\textsuperscript{135} of polypeptides following the seminal work of Bruce Merrifield for which he was awarded the Nobel Prize in chemistry.\textsuperscript{136-138} The field of SPS has since exploded and continual research has greatly improved the range of available synthetic targets, yields and purity by modifying the protecting groups, reagents, supports, and linkers. Naturally, the potential for these supports was expanded into the area of transition metal catalysis as well-defined ligands could be anchored on the polymer matrices and used as heterogeneous catalysts for a variety of metal catalyzed reactions.\textsuperscript{139,140}

Many of the potential advantages previously outlined for using silica as a support, such as ease of recovery \textit{via} filtration and the potential for recycling, can be extended to the use of polymers. From a pure research perspective, commercially available resins are an attractive alternative to the inorganic support since they typically have a cleavable linker and presents a valuable opportunity whereby any synthetic target grown on the polymer support can be cleaved off and characterized using the standard homogeneous techniques available in the organic chemist's repertoire. However, when considering SPS supported catalysts for industrial use, commercially available resins are typically prohibitively expensive as a catalyst support. To reduce the cost of preparing these catalysts, many research groups circumvent the commercially available resins entirely by designing and preparing their own cross-linked polystyrene supports based on functionalized divinylbenzene monomers.\textsuperscript{106,107}
4.1 PSEUDOPEPTIDE DENDRIMERS ON RESIN (NRC COLLABORATION)

During the course of our research, members from Prof. Alper’s Dendrimer Group had the occasion to work in partnership with colleagues from the National Research Council of Canada (NRC) on several projects. In one collaborative effort, the solid phase synthesis of several peptide based dendritic ligands anchored on beads was accomplished in the NRC labs via a straightforward synthetic strategy based on a building block approach. Under the direction of Dr. Prabhat Arya, with synthetic expertise in the field of peptide based chemistry and organic synthesis, Drs. Rao and Panda as well as Ms. Singkhronrat prepared several peptide based rhodium dendrimer complexes and submitted them to our labs at the University of Ottawa for catalyst testing in the hydroformylation reaction using our high-pressure facilities.\textsuperscript{141,142}

It was greatly anticipated that use of the commercially available rink-amide resin would offer allow us to evaluate the dendrimer growth by using the cleavable linker option. In this respect, meaningful numbers could be assigned to yield and purity after each stage of dendrimer growth, as facile and comprehensive characterization of the resulting dendrimer wedges and intermediates was now possible. In the case of a ligand supported on an SPS resin, a greater potential to elucidate the environment around the metal center exists with the added solution state characterization techniques. However the full potential of this advantage was not explored.
4.1.1 SYNTHESIS OF THE PSEUDOPEPTIDE BUILDING BLOCKS

As it was necessary to build up a stock of the building blocks which were used in excess during the dendrimer growth reactions, the solution phase synthesis of the pseudopeptide 4.1 was carried out on relatively large scale. As outlined in scheme 4.1, 3,5-diaminobenzoic acid was coupled with glycinebenzyl ester using diisopropylcarbodiimide (DIC) and 1-hydroxybenzotriazole (HOBT) at room temperature to give the benzyl ester derivative in excellent yield. The benzyl ester derivative was then coupled with Fmoc protected phenylalanine or Fmoc protected p-nitrophenylalanine under similar conditions. After purification using silica gel chromatography, the di-Fmoc pseudopeptide benzylesters were hydrogenated using 10% Pd/C to deprotect the carboxylic acid.

![Chemical structure](image)

4.1a \( R = \text{Ph} \)
4.1b \( R = p\text{-NO}_2\text{Ph} \)
Scheme 4.1 The synthesis of building block 4.1

\[ \text{COOH} \]

\[ \text{H}_2\text{N} \]

\[ \text{NH}_2 \]

\[ \text{4.2} \]

\[ \text{H}_3\text{N}^+\text{COOBn} \]

\[ \text{COOBn} \]

\[ \text{DCC, HOBT, DIPEA} \]

\[ \text{DMF, 12 h} \]

\[ \text{90\%} \]

\[ \text{R} \]

\[ \text{Fmoc-\text{COOH}} \]

\[ \text{H} \]

\[ 4.5a: \text{R} = \text{Ph} \]

\[ 4.5b: \text{R} = \text{p-NO}_2\text{Ph} \]

\[ \text{DIC, HOBT, DIPEA} \]

\[ \text{DMF, 48 h} \]

\[ 75-94\% \]

\[ \text{O} \]

\[ \text{N} \]

\[ \text{COOH} \]

\[ \text{NH} \]

\[ \text{NH} \]

\[ \text{Fmoc} \]

\[ \text{R} \]

\[ \text{NH} \]

\[ \text{NH} \]

\[ \text{Fmoc} \]

\[ \text{4.1} \]

\[ \text{H}_2, \text{Pd/C} \]

\[ \text{CH}_3\text{OH, 1 h} \]

\[ > 95\% \]

\[ \text{O} \]

\[ \text{N} \]

\[ \text{COOBn} \]

\[ \text{NH} \]

\[ \text{NH} \]

\[ \text{Fmoc} \]

\[ \text{Fmoc} \]

\[ \text{4.6} \]
4.1.2 FROM BUILDING BLOCKS TO DENDRIMERS ON THE RESIN

Employing a divergent growth strategy, three generations of the pseudopeptide-based dendrimers were assembled on a Rink Amide resin available from NovaBioChem. The Fmoc protected resin (4.7), with a loading of 0.45 mmol/g, was initially treated with piperidine to remove the protecting groups prior to coupling the free amine with the carboxylic acid of building block 4.1a using (7-azabenzo triazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) and DIEA as standard coupling reagents. The resulting compound 4.9 was deprotected with piperidine to yield the first generation amine terminated dendrimer on Rink Amide Resin (4.10). Further coupling of excess building block followed by the removal of the Fmoc groups led to the second-generation tetraamine (4.12) and the third-generation octaamine (4.14) dendrimers on resin (See scheme 4.2).

As with the silica examples reported in chapters 2 and 3, the dendrimer growth reactions are driven to completion by use of excess reagents. Filtration and subsequent washing with copious amounts of solvents facilitated 'purification' by means of removal of the excess building block, reagents and their by-products. To assess purity and yield of the desired products on the resin, small representative samples were subjected to cleavage conditions (95% TFA) and recovered. Reverse phase HPLC determined the yield of coupling for the first generation dendrimer to be 85% (90% purity) while that of the second and third generations were 80 (75% purity) and 50% (65% purity) respectively for the phenylalanine based building block.
Scheme 4.2 The solid phase synthesis of pseudopeptide dendrimers on resin.

$\text{NH}_2\text{Fmoc}$ → Piperidine, DMF, 2 h → $\text{NH}_2$ → HATU, DIEA, DMF, 12 h → $\text{NH}_2$ → HATU, DIEA, DMF, 12 h → $\text{NH}_2$ → Piperidine, DMF, 2 h → $\text{NH}_2$ → HATU, DIEA, DMF, 12 h → $\text{NH}_2$ → Piperidine, DMF, 2 h → $\text{NH}_2$ → Rink Amide Resin

104
4.1.3 Phosphonation and Complexation of the Pseudopeptide Dendrimers on a Resin

The pseudopeptide based dendrimers 4.10, 4.12 and 4.14 were phosphonated using a similar procedure to that previously reported (see scheme 4.3) with diphenylphosphinomethanol in toluene to yield the ligands 4.15, 4.16 and 4.17 respectively.

Scheme 4.3 The phosphorylation of the dendrimers on resin.
Phosphine ligands 4.15, 4.16 and 4.17 were characterized by solid state $^{31}$P NMR and gave chemical shifts centered around $-27$ ppm (Ph$_2$PCH$_2$N) as expected. Again, extreme care must be taken to exclude molecular oxygen from all solvents and the reaction must be carried out under an inert atmosphere of argon in order to obtain oxide free products.
The resin supported dendrimer ligands 4.15, 4.16 and 4.17 were then complexed with [Rh(CO)\textsubscript{2}Cl\textsubscript{2}] in CH\textsubscript{2}Cl\textsubscript{2}. The resulting rhodium complexes 4.18, 4.19 and 4.20 (see figure 4.1) resulted in broader \textsuperscript{31}P shifts centered around 24 to 26 ppm (Ph\textsubscript{2}P(CH\textsubscript{2}N–)Rh). Unfortunately complete characterization of the ligands and complexes cleaved from the resin was not accomplished.
Figure 4.1 a) The 1\textsuperscript{st} (4.18), b) 2\textsuperscript{nd} (4.19) and c) 3\textsuperscript{rd} (4.20) generation pseudopeptide based dendrimer rhodium complexes on resin.
4.2 RESIN SUPPORTED DENDRIMER COMPLEXES: EVALUATION AS CATALYSTS

4.2.1 THE HYDROFORMYLATION OF STYRENE

The rhodium complexes 4.18, 4.19 and 4.20 were evaluated as catalysts and found to be effective for the hydroformylation reaction (Table 4.1). In general, a generational effect was observed whereby the recyclability of the first generation catalyst (4.18) was significantly less efficient than the second (4.19) and third (4.20) generations catalysts.

Complete conversion of styrene (2.40) was observed after 5 cycles for 4.19 (Table 4.1, entry 13) and after 4 cycles for 4.20 (Table 4.1, entry 18) while the activity of 4.18 (Table 4.1, entry 3) started to drop off after only 3 cycles. In all cases, 10.0 mmol of substrate was used with 25 mg of the resin catalyst in CH₂Cl₂ at 1000 psi CO/H₂ (1:1) pressure.

As observed in the case of the silica-supported catalysts, temperature seriously affected the regioselective outcome of the reaction (see table 2.6 for comparison). Using 4.19 as the catalyst, the reaction at 25 °C is much slower yielding only 35 % conversion after 21 hours, however selectivities of greater than 25:1 favouring the 2–phenylpropionaldehyde (2.41) product are observed (Table 4.1, entry 7). Increasing the temperature to 45 and 65 °C resulted in decreased branched to linear ratios of 16:1 and 14:1 respectively (Table 4.1, entries 8 and 9).
Table 4.1 Hydroformylation of Styrene with 4.18, 4.19 and 4.20.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Cycle</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>Conversion (%)</th>
<th>Selectivity(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.18</td>
<td>1</td>
<td>5</td>
<td>65</td>
<td>42</td>
<td>13:1</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>2</td>
<td>18</td>
<td>65</td>
<td>70</td>
<td>12:1</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>3</td>
<td>23</td>
<td>65</td>
<td>85</td>
<td>10:1</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>4</td>
<td>24</td>
<td>65</td>
<td>51</td>
<td>15:1</td>
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<tr>
<td>5</td>
<td></td>
<td>5</td>
<td>24</td>
<td>65</td>
<td>22</td>
<td>9:1</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>6</td>
<td>24</td>
<td>65</td>
<td>8</td>
<td>10:1</td>
</tr>
<tr>
<td>7</td>
<td>4.19</td>
<td>1</td>
<td>21</td>
<td>25</td>
<td>35</td>
<td>&gt;25:1</td>
</tr>
<tr>
<td>8</td>
<td>4.19</td>
<td>1</td>
<td>16</td>
<td>45</td>
<td>&gt;99</td>
<td>16:1</td>
</tr>
<tr>
<td>9</td>
<td>4.19</td>
<td>1</td>
<td>5</td>
<td>65</td>
<td>57</td>
<td>14:1</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>2</td>
<td>22</td>
<td>65</td>
<td>&gt;99</td>
<td>11:1</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>3</td>
<td>22</td>
<td>65</td>
<td>&gt;99</td>
<td>12:1</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>4</td>
<td>22</td>
<td>65</td>
<td>&gt;99</td>
<td>12:1</td>
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<td>22</td>
<td>65</td>
<td>98</td>
<td>11:1</td>
</tr>
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<td>14</td>
<td></td>
<td>6</td>
<td>22</td>
<td>65</td>
<td>88</td>
<td>12:1</td>
</tr>
<tr>
<td>15</td>
<td>4.20</td>
<td>1</td>
<td>22</td>
<td>65</td>
<td>&gt;99</td>
<td>10:1</td>
</tr>
<tr>
<td>16</td>
<td></td>
<td>2</td>
<td>22</td>
<td>65</td>
<td>&gt;99</td>
<td>9:1</td>
</tr>
<tr>
<td>17</td>
<td></td>
<td>3</td>
<td>22</td>
<td>65</td>
<td>&gt;99</td>
<td>12:1</td>
</tr>
<tr>
<td>18</td>
<td></td>
<td>4</td>
<td>22</td>
<td>65</td>
<td>&gt;99</td>
<td>10:1</td>
</tr>
<tr>
<td>19</td>
<td></td>
<td>5</td>
<td>22</td>
<td>65</td>
<td>78</td>
<td>12:1</td>
</tr>
<tr>
<td>20</td>
<td></td>
<td>6</td>
<td>22</td>
<td>65</td>
<td>47</td>
<td>12:1</td>
</tr>
</tbody>
</table>
(Table 4.1 cont.)

\( ^{a} \) 10.0 mmol 2.40, 25 mg catalyst, 45 °C, 1000 psi CO/H\(_2\) (1:1), \(^{b}\) Determined by GC, \(^{c}\) Determined by \(^1\)H NMR.

4.2.2 The Hydroformylation of Various Olefins

Rhodium complex 4.19 was also used for a variety of olefins to show the versatility of these new resin supported dendrimer catalysts. Complete conversions of vinyl esters and substituted styrenes were observed after 3 cycles at 45 °C (see Table 4.2). Regioselectivities of 15:1 and greater than 22:1 were observed for vinyl acetate (Table 4.1, entries 1 - 3) and vinyl benzoate (Table 4.2, entries 4 - 6) respectively. When compared to the parent substrate styrene (Table 4.1, entry 8), the hydroformylation of \( p \)-methoxystyrene and \( 4-\text{tert-} \)butylstyrene resulted in lower observed regioselectivities. \( P \)-Methoxystyrene gave ratios of 10:1 and 11:1 (Table 4.2, entries 7 and 8) favouring the branched aldehyde while \( 4-\text{tert-} \)butylstyrene resulted in a ratio of 8:1 (Table 4.1, entry 9).
Table 4.2 Hydroformylation of various olefins with 4.19.<sup>a</sup>

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Cycle</th>
<th>Time (h)</th>
<th>Conversion (%)</th>
<th>Selectivity&lt;sub&gt;b&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>vinyl acetate</td>
<td>1</td>
<td>10</td>
<td>&gt;99</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>vinyl acetate</td>
<td>2</td>
<td>22</td>
<td>&gt;99</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>vinyl acetate</td>
<td>3</td>
<td>22</td>
<td>&gt;99</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>vinyl benzoate</td>
<td>1</td>
<td>10</td>
<td>&gt;99</td>
<td>&gt;25</td>
</tr>
<tr>
<td>5</td>
<td>vinyl benzoate</td>
<td>2</td>
<td>22</td>
<td>&gt;99</td>
<td>&gt;25</td>
</tr>
<tr>
<td>6</td>
<td>vinyl benzoate</td>
<td>3</td>
<td>22</td>
<td>&gt;99</td>
<td>22</td>
</tr>
<tr>
<td>7</td>
<td>p-methoxystyrene</td>
<td>1</td>
<td>10</td>
<td>&gt;99</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>p-methoxystyrene</td>
<td>2</td>
<td>22</td>
<td>&gt;99</td>
<td>11</td>
</tr>
<tr>
<td>9</td>
<td>4-tert-butylstyrene</td>
<td>3</td>
<td>22</td>
<td>&gt;99</td>
<td>8</td>
</tr>
</tbody>
</table>

<sup>a</sup> 10.0 mmol substrate, 25 mg catalyst, 45 ºC, 1000 psi CO/H₂ (1:1), <sup>b</sup>Determined by <sup>1</sup>H NMR.

4.2.3 LEACHING OF RHODIUM

Upon visual inspection of the product solutions after removal of 4.18, 4.19 and 4.20, red, orange or yellow solutions were observed indicating leaching of the rhodium from the supported dendrimer. A similar qualitative preleaching study to that described in section 3.6 was preformed with the result that pressures of CO encouraged the loss of rhodium from the support to the bulk solution. Another attempt to address this problem is described in section 4.3.
4.2.4 **ADDITIONAL OBSERVATIONS**

It was recognized early during the evaluation of these new resin anchored dendrimer catalysts that the nature of the support was quite different from the silica used in our previous examples. The beads were sensitive to mechanical degradation caused by stirring; through the recovery and reuse cycles, it was observed that the beads turned into a powder. Also, transfer of the dry catalyst was typically complicated by static buildup and the 'dry' resins were often sticky sometimes resembling a gel whereas the previously isolated silica supported catalysts were fine, free flowing powders.

4.3 **LIGAND EVOLUTION: RELOCATION OF THE CATALYTIC SITES**

When exploring options to address the leaching issue it was noted that all systems previously presented in this thesis possessed coordinating ligands that were located on the periphery of the immobilized dendrimers. Reports from Brunner\textsuperscript{74-77}, Moore and Suslick\textsuperscript{24,73} encouraged us that the body of the dendrimer backbone could serve as a cage and retard mass transport of the large metal centers into the bulk solution.

In an approach reminiscent of some enzyme active sites, it was proposed that the relocation of the catalyst sites from the periphery to the interior of the dendritic macromolecule should be investigated as a means to prevent loss of the metal center.
4.3.1 Preparation of Resin Supported Dendrimers with Interior Catalytic Sites

Using a building block approach paralleling that described in section 4.1, two generations of a new pseudopeptide based dendrimer catalyst were constructed via the procedure outlined in scheme 4.4. A para substituted nitro group introduced during the first generation growth step was the intended avenue for phosphine introduction for all generations prepared via this method. Note that both generations have only two metal centres per dendritic wedge, each of which is incorporated inside the bulk of the dendrimer backbone. This new design is also different from our previous systems using silica or a resin since the catalyst loading theoretically decreases with the added weight of the second-generation building blocks while the number of active sites remains the same.

Building block 4.1b derived from p-nitrophenylalanine was coupled to amine terminated Rink Amide resin using (HBTU) and diisopropylethylamine (DIPEA) as standard coupling reagents. The Fmoc protecting groups of the resulting compound 4.21 were exchanged for acetates prior to the reduction of the nitro groups with SnCl₂. The first generation diamine (4.23) was then phosphonated (4.25) with diphenylphosphinomethanol prior to complexation with rhodium to yield the first generation catalyst 4.27.

The Fmoc protecting groups of compound 4.21 were removed with piperidine prior to coupling with building block 4.1a. The second-generation Fmoc groups were then exchanged for acetates prior to reduction of the first
generation nitro groups. The resulting diamine (4.24) and was phosphonated (4.26) and complexed with rhodium to yield the second-generation catalyst 4.28.
Scheme 4.4 The placement of the metal centers in the dendrimer interior.

4.8 → 4.1b
HBTU, DIPEA, DMF, 20h.

4.21
i) piperidine, DMF
ii) 4.1a,
HBTU, DIPEA, DMF, 48h
iii) piperidine, DMF
iv) Ac₂O, DIPEA
v) SnCl₂, H₂O, DMF, 12 h

4.22
SnCl₂
H₂O, DMF, 10h

4.23
i) HOPPh₂,
CH₃OH, Toluene
(4.25)
ii) [Rh(CO)₂Cl]₂,
CH₂Cl₂, RT, 14h.

4.24
(4.26)

4.28
Figure 4.2 a) The first (4.27) and b) second (4.28) generations of the resin supported dendrimers with interior catalytic sites.
4.3.2 Evaluation of Resin Supported Catalysts with Interior Metal Sites

4.3.2.1 Hydroformylation of Styrene and p-Methoxystyrene

Both generations of the newly designed resin supported complexes with internal catalytic sites were evaluated in a series of recycling studies. In the first study, both catalyst generations were employed at 45°C to affect the conversion of 2.0 mmol of 2.40 to the corresponding branched (2.41) and linear (2.42) aldehydes at 1000 psi CO/H₂ (1:1). After 5 cycles, complete conversions were observed after 20 hours for both catalysts 4.27 and 4.28 (Table 4.3, entries 5 and 10 respectively). Excellent selectivities for 2.41 were observed ranging from 14:1 to 19:1. It should also be noted that upon visual inspection of the product solutions, leaching of rhodium was still observed for both generations of the catalysts.

As it is impossible to accurately compare the catalytic activities of the various generations after complete conversions, a second study using shorter reaction times was also performed with 2.40. At shorter reaction times of 1 or 2 hours, both generations gave comparable results of decreasing activity after recycling differing by at most 10% conversion between cycles. After 1 hour, a decrease of 6% conversion is observed between cycles 1 and 2 (Table 4.3, entries 11 and 12) for the first generation catalyst 4.27 while the second-generation catalyst, 4.28, exhibited a loss of 10% conversion (Table 4.3, entries 14 and 15). This result would seem to indicate that catalyst 4.28, which was initially more reactive than its first generation counterpart, was just as prone to
loss of its metal centers and activity as the theoretically more accessible metal centers in the 4.27 catalyst.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Cycle</th>
<th>Time (h)</th>
<th>Conversion (%)</th>
<th>Selectivity&lt;sup&gt;c&lt;/sup&gt; 2.41:2.42</th>
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<td>20</td>
<td>&gt;99</td>
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</tr>
<tr>
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<td>&gt;99</td>
<td>15:1</td>
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<td>5</td>
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<td>3</td>
<td>2</td>
<td>9</td>
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<sup>a</sup> 2.0 mmol 2.40, 25 mg catalyst, 45 °C, 1000 psi CO/H₂ (1:1), <sup>b</sup> Determined by GC, <sup>c</sup> Determined by <sup>1</sup>H NMR.
The recyclability of both generations was investigated further with p-methoxystyrene as the substrate. Complete conversions were observed after 4 cycles using both 4.27 and 4.28 (Table 4.4, entries 4 and 9) however a dramatic loss of activity was observed for the first generation catalyst 4.27 in the fifth cycle where only 56% conversion was obtained after 20 hours (Table 4.3, entry 5). Comparatively, the fifth cycle of the 4.28 catalyst yielded 85% conversion (Table 4.3, entry 10) to the aldehydes.

Table 4.4 Hydroformylation of p-methoxystyrene with 4.27 and 4.28.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Cycle</th>
<th>Time (h)</th>
<th>Conversion (%)</th>
<th>Selectivity B:L</th>
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<tbody>
<tr>
<td>1</td>
<td>4.27</td>
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<td>5</td>
<td>20</td>
<td>85</td>
<td>&gt;25:1</td>
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\(^a\) 2.0 mmol styrene, 25 mg catalyst, 45 °C, 1000 psi CO/H₂ (1:1), \(^b\) Determined by GC, \(^c\) Determined by \(^1\)H NMR.
4.3.2.2 Hydroformylation of Vinyl Acetate and Vinyl Benzoate

Vinyl acetate and vinyl benzoate were also tested as substrates in the hydroformylation reaction using 4.27 and 4.28 as catalysts. A more meaningful comparison of activities and recyclabilities, then that obtained in the previous example using styrene is presented in Table 4.5. Again, upon visual inspection, an orange to yellow product solution was observed after removal of the resin via filtration indicating that rhodium leaching was still occurring for both generations.

For both vinyl esters, catalyst 4.28 retains more of its activity upon recycling than catalyst 4.27. In the case of vinyl acetate as the substrate at 45 °C, a gradual loss of at most 3% conversion per cycle is observed for cycles 2 to 5 with catalyst 4.28 (Table 4.5, entries 7-10). For the same substrate, catalyst 4.27 also demonstrated very good recyclability with only a gradual loss of activity observed after each recycle; however, slightly lower conversions (Table 4.5, entries 2-5) are noted when compared to its second generation counterpart.

A more remarkable generational effect is demonstrated in the later cycles for the less reactive substrate vinyl benzoate. For both catalysts 4.27 and 4.28, complete conversion is observed in the third cycle (Table 4.5, entries 13 and 18 respectively) after which activity starts to decrease dramatically. The fourth and fifth cycles for the 4.27 catalyst gave only 43 and 20 % conversion, respectively (Table 4.5, entries 14 and 15), while the corresponding cycles for the 4.28 catalyst yielded 91 and 83 % conversion, respectively (Table 4.5, entries 19 and 20).
Table 4.5 Hydroformylation of vinyl acetate and vinyl benzoate with 4.27 and 4.28.

<table>
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<td>&gt;25</td>
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<tr>
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(Table 4.5 cont.)

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</table>

\(^a\) 2.0 mmol styrene, 25 mg catalyst, 45 °C to 50 °C, 1000 psi CO/H\(_2\) (1:1). \(^b\) Determined by GC, \(^c\) Determined by \(^1\)H NMR.

From the observations obtained in this last study, it would appear that the bulkier second-generation catalyst has a slightly better recyclability potential, however metal leaching is not avoided altogether, as demonstrated by the colored product solutions. The prolonged activity of the second-generation catalyst, even with a lower initial loading than its first generation counterpart, encourages the belief that the dendrimer backbone augments rhodium retention.

Future experiments involving at least the third generation catalyst would offer a more comprehensive evaluation of the concept under investigation.
4.4 SUMMARY

In summary, we have demonstrated that rhodium complexes of pseudopeptide-based ligands immobilized on a resin resulted in the hydroformylation of various olefins. These heterogeneous catalysts are recyclable, however leaching of the metal from the support and the accompanying loss of activity still presents a problem. Relocation of the metal centers from the periphery to the interior of the dendrimer did not inhibit metal leaching altogether. Work with higher generation analogues is needed to provide additional insight into these interesting observations.
CHAPTER 5: TOWARDS RECYCLABLE PHOSPHITE LIGANDS

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5.0 TOWARDS RECYCLABLE PHOSPHITE LIGANDS

The silica and resin supported dendritic complexes presented in the previous chapters are effective hydroformylation catalysts and exhibit great potential for catalyst recovery and recyclability. However, the obvious difficulties associated with the characterization of the solid supported complexes significantly obscure our understanding of the respective heterogeneous systems. The observed leaching of the metal off the support and related catalyst deactivation is of considerable concern and an essential area that should not be ignored. Equally, another significant element that needs to be addressed is the regioselective limitation experienced using important aliphatic substrates such as 1-octene.

This chapter will elaborate on some of the deficiencies observed with regards to the rhodium catalyzed hydroformylation reaction using supported phosphines as ligands and highlight some of the avenues considered and those ventured down in an attempt to address the recognized deficiencies.

5.0.1 CHARACTERIZATION POTENTIAL OF HETEROGENEOUS SYSTEMS

The difficulties associated with characterizing classical heterogeneous catalysts are well known and anticipated to be difficult to overcome. Similarly, the challenge of characterizing complicated dendrimer ligand–metal complexes anchored on inorganic supports is a daunting endeavour and is a thesis in itself. This project is currently pursued by Mr. Jan Reynhardt with encouraging results.¹⁴³ His efforts include the grafting of PAMAM onto various silicates of the
zeolite family including MCM–41 and SBA–15 as well as Davisol and the use of various analyses that are of a more industrial or chemical engineering nature. Changing the nature of the heterogeneous support from an amorphous structure to something more regular constitutes a promising avenue to approach the characterization problem. However, it must be recognized that changing the support may also be accompanied by unpredictable changes in activity and selectivity and may not serve as the parallel analogy that will explain all.

Another strategy to characterizing solid supported dendrimers and their corresponding ligand–metal complexes is to examine a parallel homogeneous system. By changing the nature of the support from solid particles of silica or beads of resin to something more organic and soluble, it is hoped that standard solution phase chemical techniques could be used to purify and characterize these resulting compounds, and parallels could be inferred to the solid supported systems.

5.0.2 Considering Regioselectivity: Access to the Linear Isomer

In all the systems presented thus far in this thesis, the regioselective outcome of the catalysts on silica or a resin have been very good to excellent in the case of aryl olefins and vinyl esters, favouring the branched aldehyde. However, in all cases, very poor selectivity for the desired linear products of aliphatic olefins was obtained. As there is genuine potential use of this domain of heterogeneous catalysts in the petrochemical industry, it was decided that
improving the regioselectivity of our catalysts towards the linear aldehydes is of paramount importance.

5.0.3 Leaching

Durability and longevity of the active species are both desirable characteristics of any ideal catalyst. In this regard, retention of the metal obviously promotes the system’s utility in industry. The leaching problem is a flaw that is inherent in many heterogeneous systems and the hydroformylation reaction is no exception. In the generalized mechanism depicted in figure 1.11 (page 24), ligand dissociation is necessary to form an active $16 \, e^{-}$ species. Under high pressures of carbon monoxide and hydrogen (e.g. 1000 psi CO/H$_2$), the lability of the coordinating ligands is promoted (see figure 1.12, page 25). With the increase in ligand exchange, the probability that CO ligands will replace the bidentate phosphines encourages loss of the metal from the support into the bulk solvent.

The dynamic nature of the hydroformylation reaction easily lends itself to a large variety of possibilities in attempts to change or improve the observed selectivity. Changing conditions and electronics through ligand manipulation are often the primary avenues taken to achieve the desired result. In our system, it was proposed that using a different metal ligand system under milder conditions was a promising avenue to explore with respect to this new goal.
5.1 Moving to a Soluble Support

It was anticipated that characterizing soluble analogues of the solid supported PAMAM dendrimers via standard solution phase and/or polymer techniques would provide a more detailed picture of the active catalyst and the dendritic environment around the ligand–metal complex. In particular, the degree of ligand purity of dendrimer growth was of interest and the use of a soluble support was accompanied with the hope that a soluble supported PAMAM dendrimer could be easily prepared, manipulated, isolated and characterized. With this in mind, a variety of organic polymers were considered as supports for the PAMAM ligand. Some inexpensive and readily available functionalized poly(ethylene) supports, such as poly (ethylene–co–acrylic acid) and poly(ethylene–co–methylacrylate) were tried initially but their solubility–precipitation properties proved uncooperative.

Transferring the dendrimer ligand preparation from the established solid phase techniques to a more soluble approach also proved to be a challenging task. It was during these trials that reports from Kim Janda\textsuperscript{144} regarding his work with soluble polymers based on poly(ethylene glycol) (PEG) caught our attention. Janda reported the use of PEG and mono–methoxy poly(ethylene glycol) (MPEG) as supports for the synthesis of small organic molecules. In one notable example, the linear polyether was used as a scaffold for a triphenylphosphine reagent (5.1) wherein the triphenylphosphine oxide byproduct is easily removed by filtration. Janda also reported a PEG supported Cinchona ligand and its use in the Sharpless asymmetric dihydroxylation reaction.\textsuperscript{144,145}
Figure 5.1 Janda's PEG supported triphenylphosphine reagent (5.1).

5.1.1 **Poly(ethylene glycol) (PEG) as a Support**

PEG was reported to have a particular solubility that can be easily manipulated to varying degrees, ultimately via the precipitation of the dissolved polymer using diethyl ether or hexanes from solutions of THF or chloroform. PEG is commercially available in a wide variety of molecular weights (MW); however, those in the range of 1000 to 3500 offer useful precipitation properties.

An obvious low loading problem was anticipated from the use of a linear polymer as the support. For all molecular weights of PEG, there are only two functional groups that can be modified into ligands and the weight of ligand required for catalysis would be quite large (100s of mg). However it was reasoned that the successful synthesis of a multivalent dendrimer ligand and corresponding complex should magnify the catalytic activity at each end of the linear polymer by exponentially increasing the available coordination sites, thus resulting in a smaller amount of ligand required.
5.1.2 The Preparation of PAMAM–PEG

As illustrated in Scheme 5.1, a standard divergent growth strategy employing iterative additions of methyl acrylate (2.8) and ethylenediamine (2.10) was applied toward the construction of the first and second generation PAMAM dendrimers supported on a PEG backbone\textsuperscript{146,147} (MW \(\approx 3400\)) (5.4 and 5.6 respectively) starting from diaminophane poly(ethylene glycol) \((\text{NH}_2\text{–PEG–NH}_2, 5.2)\).

Overall, removal of the reaction solvents and excess reagents proved time consuming, generally requiring several days under high vacuum to realize even a crude product, especially after the amidation step. Precipitation and centrifugation facilitated the removal of residual methylacrylate from the PEG half–generation product mixtures, however, the expected esters \(G_{0.5} (5.3)\) and \(G_{1.5} (5.5)\) were difficult to recover using silica gel chromatography, and there were large losses of product on the column.

Furthermore, the PEG support complicated all attempts to purify the amine-terminated products via chromatography. When solvents of higher polarity, such as methanol or chloroform, were used to push the highly polar polyamine through the silica gel or alumina matrix, either no separation was observed or new, unidentifiable peaks would emerge from reactions of the solvents with the silica. Even silica gel washed with solutions of TEA (up to 5%) in chloroform did not accomplish the desired separation. Preparatory HPLC with a size exclusion column was also tried. After a 250 mg injection, a broad baseline was obtained without any meaningful separation. Also, cleaning the column afterwards required two days of constant flushing and 6 liters of CHCl\(_3\).
Scheme 5.1 A divergent approach toward the preparation of PAMAM dendrimers on a PEG support.
5.1.3 The Convergent Approach

After failing to purify the PAMAM dendrimer supported on a soluble PEG, we were prompted to investigate a convergent strategy which would involve a final coupling step of a completed dendritic wedge onto an activated PEG backbone. The convergent route proposed involved a series of protecting and deprotecting steps. Coupling problems due to flexibility of the dendritic PAMAM wedge were expected however the attempt was tried regardless.

In theory, one would expect the primary amines of diethylenetriamine (5.7) to be more reactive towards modification than the secondary amine function. To achieve the desired protected secondary amine would involve protecting both primary amines, followed by the differential protection of the secondary amine (5.8) and subsequent removal of the primary protecting groups (5.9). Experimentally however, mixtures of mono, di and tri–protected products resulted from any attempt at carefully protecting the primary amines of 5.7 with Boc or Cbz protecting groups (PG).

![Chemical Structures](image)

Figure 5.2 The differential protection of diethylenetriamine (5.7).
Figure 5.3 A convergent route towards a PAMAM wedge.

Another convergent synthesis route of PAMAM involving the amidation of a monoproected ethylenediamine (5.10) was also considered. However, a similar route investigated by Dr. Helen Clark, involving the coupling of 5.12 to a much shorter bifunctional core, resulted in only the monoaddition product.\(^{148}\)

Figure 5.4 Clark's polyamide wedge 5.12.
5.1.3.1 (Polyaryl)ethers of PEG

Concurrent with the attempts to construct a soluble version of the PAMAM dendrimer on PEG, a different dendrimer scaffold was investigated. The difficulties encountered with the purification of the supported polyamines prompted us to consider a less polar dendrimer backbone. After looking at the available dendrimer systems reported in the literature, Fréchet’s polyaryl ether dendrimer was chosen because it had the potential to be constructed in a well-documented convergent manner and later attached, in a pure form, to the PEG support.149

The first generation of a poly(arylether) dendrimer wedge was easily synthesized using Fréchet’s convergent strategy (Scheme 5.2). Starting with 4-hydroxybenzyl alcohol (5.13), the phenol group was treated with di-tert-butyl dicarbonate. Bromination of the resulting Boc protected benzylic alcohol (5.14) was then accomplished with triphenylphosphine and carbon tetrabromide in THF. Two equivalents of the benzylbromide (5.15) were then coupled to 3,5-dihydroxybenzyl alcohol (5.16) under basic conditions in dry, refluxing acetone to yield the triarylether (5.17) in 42 % yield.

The coupling of even the first generation dendritic wedge to the PEG support proved to be non trivial. When excess alcohol 5.17 was added to mesylated–PEG (5.18) under basic conditions, very low conversions were observed and it was suspected that at most, only one of the two activated alcohols coupled with the excess wedge 5.17. In retrospect, the kinetics of the reaction would be expected to be low due to the relatively large size of the
molecules involved and the great potential for masking of the active sites, particularly of the spaghetti–like linear PEG molecule.

Eventually it was decided that PEG is an unsatisfactory support for the synthesis of dendrimers via both the convergent and divergent methods. After, considerable thought, the coupling problems encountered may be circumvented by the controlled polymerization of ethylene oxide \textit{in situ} with the dendritic wedge as an initiator and chain terminator.
Scheme 5.2 The preparation of (polyaryl)ether dendrimers on a PEG support via the convergent approach.
5.2 CONSIDERING REGIOSELECTIVITY: PHOSPHINES TO PHOSPHITES

Another aspect mentioned in the introduction to this chapter, namely the desire to improve the regioselectivity towards the linear aldehyde of 1-alkenes in the rhodium catalyzed hydroformylation reaction, was also investigated. A common way to alter the regioselective outcome of the reaction is to modify the ligand electronics. Increasing the basicity of the ligand by changing the phosphine to a phosphite was a feasible approach.

In many ways, phosphites are quite complimentary to phosphines. Not only do they offer alternative reactivities and selectivities as ligands, but they often react in a complimentary manner. Phosphines are typically sensitive to molecular oxygen and other oxidizing agents while phosphites are reasonably stable towards oxidation. Conversely, phosphites are extremely sensitive to moisture being less tolerant to water than phosphines.

5.2.1 SUPPORTED PHOSPHITE–PEG

With the desire to improve the regioselectivity of the recyclable hydroformylation reaction, the preparation of a supported phosphite was planned for both the soluble polyarylether (5.20) and PAMAM (5.21) dendrimers. However, as previously described in section 5.1, as the soluble dendrimers were never fully realized, their corresponding phosphites and complexes were not obtained. To circumvent the problems associated with dendrimer purification, the use of PEG as the support without the dendrimer was also investigated.
CHAPTER 5: TOWARDS RECYCLABLE PHOSPHITE LIGANDS

5.22

Figure 5.5 PEG supported triphenylphosphite 5.22.

5.2.2 SIMPLE NON–DENDRITIC TRIPHENYLPHOSPHITE SUPPORTED ON PEG

With a PEG supported triphenylphosphite ligand (5.22) in mind, PEG treated with methanesulfonyl chloride (5.18) was reacted with deprotonated hydroquinone (5.26) in THF to form the PEG supported diphenol 5.27. Several bases were tried for the deprotonation step, with varying results. A slight excess of triethylamine resulted in the desired product; however, removing the

Scheme 5.3 The Preparation of PEG diphenol.
triethylammonium chloride byproduct presented challenges. Removal of the contaminating triethylammonium chloride was attempted via the precipitation of the PEG product and centrifugation; however a pure product was not achieved.

Strong bases such as potassium $t$-butoxide and $n$-butyllithium resulted in an insoluble product. Carbonate bases such as cesium carbonate or potassium carbonate were also tried.

5.2.2.1 Preparation of the Chlorophosphite Intermediate and Phosphite

Alkyl and aryl phosphites can be prepared from phosphorus trichloride (5.29) and the corresponding alcohols under basic conditions. The preparation of $R^2OP(OR')_2$ phosphites via a two step process involves a chlorophosphite intermediate (5.31) and is outlined in Scheme 5.4. As previously mentioned, phosphites are extremely sensitive to moisture and tremendous care to dry all

![Scheme 5.4 The preparation of a chlorophosphite intermediate and phosphite.](image)

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glassware, reagents and solvents must be taken in order to achieve as clean a reaction as possible.

The chlorophosphite (\textit{5.31}) is generated from the slow addition of biphenol (\textit{5.28}) or binaphthol (1 equiv.), to a cold solution of triethylamine (\textit{5.30}) (2 equiv.) and phosphorus trichloride (\textit{5.29}) (10 equiv.) in THF. Removal of the resulting ammonium chloride salt (\textit{5.32}) can be accomplished by filtering the yellow suspension through a thick pad of oven dried Celite. The \textit{(1,1'-biphenyl-2,2'-diyl)chlorophosphite (5.31)} can be purified with care by distillation at 170 – 190 °C under an extremely good vacuum (30 – 50 mtorr) to yield \textit{5.31} as a colourless cloudy oil \textit{\textsuperscript{31}P NMR, δ = 179.5 ppm). Distillations at temperatures higher than 200 °C yield a white solid that doesn’t react further to yield the phosphite.

The chlorophosphite intermediates are extremely sensitive to hydrolysis and should be used as quickly as possible (within hours of distillation) as it is seemingly impossible to prevent the formation of various hydrolysis products as observed in the \textit{\textsuperscript{31}P NMR} in the 0 – 30 ppm range. The binaphthol version can undergo limited purification by trituration with pentane and subsequent canulation of the dissolved impurities, however, hydrolysis products are still observed in the NMR.

The chlorophosphite will form in the absence of any base, however the yield suffers and the residual hydrochloric acid needs to be removed to prevent decomposition back to the alcohol. Use of more than 2 equivalents of base results in the direct formation of the phosphites.
After isolation of the chlorophosphite, the phosphite is then prepared by the addition of base to a solution of the desired alcohol in THF. In our case, a solution of the chlorophosphite (5.31) in THF is added dropwise to the PEG diphenol (5.27) in THF at −40 °C.

Depending on the solubility of the alcohol used, the ammonium chloride salt may be removed by filtration through a short pad of oven dried Celite. However, in the case of PEG, Celite cannot be used as the long polar backbone is trapped in the clay matrix. Precipitation of the solubilized PEG supported phosphites with dried solvents was attempted but complete removal of the triethylammonium chloride salt and the hydrolysis products was never accomplished. Not surprisingly, the more manipulation of the components in the solvent, the more hydrolysis products were observed in the $^{31}$P NMR spectrum.

When using the PEG supported phenols, it is of vital importance to dry all glassware and solvents vigorously to prevent the decomposition of the resulting phosphites from hydrolysis, as purification is by no means trivial. Indeed, pure PEG supported phosphites were never isolated as removal of all the ammonium chloride salt from the PEG matrix was never achieved. Other bases were also tried in the expectation that the corresponding byproducts would be easier to remove from the supported phosphite using standard solubility and precipitation techniques. Strong bases such as $^1$butyllithium and potassium $^1$butoxide tended to attack the PEG backbone or the chlorophosphite while the use of carbonates under refluxing conditions was accompanied by an increase in hydrolysis products.
5.3 INTRODUCING ZWITTERIONIC RHODIUM: A NOVEL HYDROFORMYLATION CATALYST

The preparation of a variety of simple zwitterionic rhodium (\(\text{Rh}^{2+}\)) complexes was first described by Schrock and Osborn,\textsuperscript{150} in 1970, via the straightforward addition of rhodium chloride, sodium tetraphenylborate and a diolefin, such as 1,5-cyclooctadiene (cod), in methanol. While not widely used amongst rhodium catalysts thus far, these novel species offer unique reactivity and selectivity and have often been employed as catalyst in our labs.

\[ \text{BPh}_3^- \quad \text{+} \quad \text{Rh}^{2+} \quad \text{(5.33)} \]

Amer and Alper\textsuperscript{151} first employed the \((\eta^5-\text{C}_8\text{H}_8\text{BPh}_3)^-\text{Rh}^+(1,5-\text{cyclooctadiene})\) complex (5.33) in 1990, as a novel catalyst for the hydroformylation of a variety of olefins. Experiments at 200 psi of CO/H\(_2\) pressure in the absence of a ligand gave 25:1 selectivity favouring the branched aldehydes of a variety of substituted styrenes. Vinyl ethers and 1,1-disubstituted olefins also afforded excellent regioselectivity, however, aliphatic olefins such as 1-heptene gave a 1:1 ratio of aldehydes under the same conditions.

Zhou and Alper\textsuperscript{152} investigated the influence of phosphine on the activity and selectivity of 5.33 for the hydroformylation of \(\alpha,\beta\)-unsaturated esters at 600 psi CO/H\(_2\). The hydroformylation of vinyl sulphones\textsuperscript{153} and 4-vinyl-\(\beta\)-lactams
were also investigated with excellent results. Subsequent investigations reported Rh\textsuperscript{2w} to be an effective catalyst for the asymmetric hydrosilylation\textsuperscript{154} of prochiral ketones, the hydrogenation of imines\textsuperscript{155} and the reductive carbonylation of olefins. These initial reports described very promising results for various substrates under generally mild conditions. More recently, 5.33 was employed by Van den Hoven and Alper\textsuperscript{156-160} for the hydroformylation and cyclocarbonylation of enynes and related conjugated systems with simple phosphites as ligands.

It is known that using phosphites as ligands with rhodium often give better selectivity the corresponding phosphines. The generally accepted theory stems from the fact that phosphites are more basic then phosphines and thus direct a slower reaction.

5.3.1 Evaluating 5.33 Under Mild Hydroformylation Conditions

The recent hydroformylation and cyclocarbonylation results reported by Van den Hoven and Alper using 5.33 and simple phosphite ligands prompted us to determine how this catalyst system would behave with simple aliphatic olefins under mild hydroformylation conditions. As alluded to previously, milder conditions were expected to reduce the extent of observed leaching and limit the possibility of a background reaction occurring from soluble rhodium carbonyl species.

In an effort to estimate the significance of the background reaction, 1-octene was subjected to hydroformylation conditions with complex 5.33 in the absence of any phosphite ligand. The results displayed in Table 5.1 show that
the bare zwitterionic rhodium complex 5.33 is virtually inactive in benzene (Table 5.1, entry 1), CH₂Cl₂ (Table 5.1, entry 2) and THF (Table 5.1, entries 3 and 4) at CO/H₂ pressures lower than 50 psi. Only trace aldehydes were observed in each case. This result can be compared to the published result of hydroformylation activity using the same catalyst without ligand at 200 psi, (Table 5.1, entry 5). On a qualitative note, at temperatures above 100 °C, the catalyst was observed to blacken.

Table 5.1 Background reactions for the hydroformylation of 1-octene using 5.33.³⁴⁵

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pressure (psi)</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>benzene</td>
<td>90–100</td>
<td>12–18</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>CH₂Cl₂</td>
<td>60 – 110</td>
<td>12–48</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>THF</td>
<td>60 – 110</td>
<td>12–48</td>
<td>trace</td>
</tr>
<tr>
<td>4</td>
<td>45</td>
<td>THF</td>
<td>85</td>
<td>12</td>
<td>trace</td>
</tr>
<tr>
<td>5⁻</td>
<td>200</td>
<td>CH₃Cl</td>
<td>47</td>
<td>20</td>
<td>89</td>
</tr>
</tbody>
</table>

³ A 2.0 mmol 1-octene, 5 mg 5.33, no ligand, CO/H₂ (1:1), 2.5 ml solvent. ⁵ Reference result for 1-heptene¹⁵¹.
Table 5.2 summarizes some very promising results in terms of selectivity in the hydroformylation of 1-octene using complex 5.33 in the presence of triphenylphosphite (5.34) as a ligand. For the most part, a general trend of selectivity being inversely proportional to conversion is noted for the hydroformylation of 1-octene, however, it is also clear that this is truly a dynamic system with temperature, time and pressure all affecting the observed result.
Table 5.2 Hydroformylation of 1-octene with complex 5.33 and triphenylphosphite (5.34) or tri-n-butylphosphite (5.35).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand (\text{P(OPh)}_3)</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Selectivity L:B</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.34 (\text{P(OPh)}_3)</td>
<td>(\text{CH}_2\text{Cl}_2)</td>
<td>95</td>
<td>6</td>
<td>8 : 1</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>5.34 (\text{P(OPh)}_3)</td>
<td>(\text{CH}_2\text{Cl}_2)</td>
<td>70</td>
<td>6</td>
<td>8 : 1</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>5.34 (\text{P(OPh)}_3)</td>
<td>(\text{CH}_2\text{Cl}_2)</td>
<td>85</td>
<td>16</td>
<td>4.5 : 1</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>5.34 (\text{P(OPh)}_3)</td>
<td>THF</td>
<td>85</td>
<td>16</td>
<td>8.7 : 1</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>5.34 (\text{P(OPh)}_3)</td>
<td>THF</td>
<td>65</td>
<td>18</td>
<td>10 : 1</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>5.34 (\text{P(OPh)}_3)</td>
<td>THF</td>
<td>65</td>
<td>48</td>
<td>6.3 : 1</td>
<td>95</td>
</tr>
<tr>
<td>7</td>
<td>5.34 (\text{P(OPh)}_3)</td>
<td>THF</td>
<td>55</td>
<td>18</td>
<td>10 : 1</td>
<td>95</td>
</tr>
<tr>
<td>8</td>
<td>5.34 (\text{P(OPh)}_3)</td>
<td>THF</td>
<td>45</td>
<td>18</td>
<td>11 : 1</td>
<td>80</td>
</tr>
<tr>
<td>9</td>
<td>5.34 (\text{P(OPh)}_3)</td>
<td>THF</td>
<td>35</td>
<td>18</td>
<td>11 : 1</td>
<td>47</td>
</tr>
<tr>
<td>10</td>
<td>5.35 (\text{P(OBu)}_3)</td>
<td>THF</td>
<td>85</td>
<td>16</td>
<td>5.3 : 1</td>
<td>80</td>
</tr>
</tbody>
</table>

a 5.0 mmol 1-octene, 30 psi of CO/H\(_2\), 2.5 ml solvent, 2.5 mg of 5.33, 20 mg ligand.
After 6 hours, the hydroformylation of 1-octene in CH₂Cl₂ at 70 – 90 °C converted 35 % of the olefin in good selectivity, favoring the linear aldehyde in a 8:1 ratio (Table 5.2, entries 1 and 2). An increase of the conversion to 50 % resulted in a lower selectivity of 4.5:1 (Table 5.2, entry 3).

In THF at 85 °C, 85% of the substrate converted with good selectivity toward the linear aldehyde after 16 hours (Table 5.2, entry 4). Decreasing the temperature to 65 °C while increasing the reaction time to 18 hours resulted in 90 % conversion and an increased selectivity of 10:1 favouring 1-nonanal (Table 5.2, entry 5). Extending the reaction time to 48 hours allowed for significant isomerization of the product distribution to occur (Table 5.2, entry 6). Lowering the temperature further to 55, 45 and 35 °C (Table 5.2, entries 7, 8 and 9 respectively) did not have a significant impact on the selectivity; however 47 % conversion occurred at 35 °C (Table 5.2, entry 9). Going from triphenylphosphite (5.34) to tri-n-butylphosphite (5.35) as the ligand resulted in a lower selectivity of 5.3:1 for the hydroformylation of 1-octene (Table 5.2, entry 10).

It must be stated that reactions were not always reproducible due to phosphite hydrolysis in some cases and the correlation of conversion with temperature was somewhat inconsistent in such instances. As it is well known that phosphites are sensitive to hydrolysis, discrepancies in the reaction outcome under apparently similar conditions were attributed to unavoidable decomposition of the phosphite ligands necessary for activity despite attempts to maintain a dry reaction. Residual water molecules left over from the preparation of the zwitterionic rhodium complex were the culprits. At this point, it should also be
noted that sufficient pre-mixing of the $\text{Rh}^{\text{Zw}}$ complex with the phosphite prior to the addition of olefin is necessary, otherwise the catalyst–ligand mixture may be completely inactive.

Table 5.3 Hydroformylation$^a$ of various olefins with triphenylphosphite (5.34) and $\text{Rh}^{\text{Zw}}$ (5.33).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Pressure (psl)</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Selectivity L:B</th>
<th>Conversion %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-decene</td>
<td>30</td>
<td>60</td>
<td>14</td>
<td>12 : 1</td>
<td>38</td>
</tr>
<tr>
<td>2</td>
<td>trans–2–octene</td>
<td>30</td>
<td>80</td>
<td>24</td>
<td>1.6 : 1$^b$</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>cis–4–octene</td>
<td>30</td>
<td>80</td>
<td>24</td>
<td>–</td>
<td>trace</td>
</tr>
<tr>
<td>4</td>
<td>cyclohexene</td>
<td>40</td>
<td>85</td>
<td>24</td>
<td>0 : 1</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>cyclohexene</td>
<td>40</td>
<td>75</td>
<td>24</td>
<td>0 : 1</td>
<td>22</td>
</tr>
<tr>
<td>6</td>
<td>2–methyl–3–phenylpropene</td>
<td>40</td>
<td>85</td>
<td>24</td>
<td>–</td>
<td>n.r.$^c$</td>
</tr>
<tr>
<td>7</td>
<td>vinyl acetate</td>
<td>30</td>
<td>60</td>
<td>14</td>
<td>1 : 22</td>
<td>46</td>
</tr>
<tr>
<td>8</td>
<td>styrene</td>
<td>30</td>
<td>65</td>
<td>18</td>
<td>1 : 8</td>
<td>92</td>
</tr>
</tbody>
</table>

$^a$ 5.0 mmol substrate, 2.5 ml solvent, 2.5 mg of 5.33, 20 mg 5.34. $^b$ sum of branched isomers. $^c$ No reaction.
Table 5.3 expands on the versatility of the Rh\textsuperscript{Zw}–phosphite catalyst system for the hydroformylation of various olefins. Yielding results comparable to 1–octene, 1–decene produced the linear aldehyde in 12:1 selectivity and 38% conversion (Table 5.3, entry 1). Moving from a terminal double bond to an internal double bond, the hydroformylation of trans–2–octene resulted in a more sluggish reaction and poor selectivity when compared to 1–octene. However it should be noted that at 80 °C, the major product was the isomerized linear aldehyde (Table 5.3, entry 2). cis–4–Octene (Table 5.3, entry 3) gave only trace aldehydes, however, 62 % of cyclohexene converted to a single aldehyde product (Table 5.3, entry 4). trans–2,5–Dimethyl–3–hexene was also slow to convert (22 %) (Table 5.3, entry 5). Under similar conditions, no reaction was observed for 2–methyl–3–phenylpropene (Table 5.3, entry 6).

Vinyl acetate and styrene were also tested under mild hydroformylation conditions with triphenylphosphite (5.34) and complex 5.33, both affording excellent regioselectivities (Table 5.3, entries 7 and 8 respectively).

5.3.2 HYDROFORMYLATION WITH A CRUDE PEG PHOSPHITE LIGAND

As discussed in section 5.2, attempts to purify a phosphite ligand supported on PEG did not result in a pure compound. However, the crude ligand, still contaminated with triethylammoniumchloride was tested as a recyclablehydroformylation ligand.

The results for the hydroformylation of 1–octene with the zwitterionic rhodium complex 5.33 using the crude PEG supported phosphite (5.22) are
presented in Table 5.4. When appropriate, the crude ligand and catalyst system was recycled and reused up to 2 more times. To recycle the PEG based catalyst system (5.22/5.33), the ligand complex was precipitated with ether, compacted at the bottom of a centrifuge tube via centrifugation and the ether solution decanted away prior to redissolving the recovered ligand catalyst mixture in fresh THF for reuse in a new reactor. After each cycle, loss of the ligand and rhodium complex that would be soluble in the ether, and corresponding decreases in observed conversion, were anticipated.

At 60 °C and 30 psi CO/H₂, complete conversion of 1–octene was observed for the first 2 cycles (Table 5.4, entries 1 and 2), however, in the third cycle the conversion dropped to 63 %, accompanied by an increase in selectivity (Table 5.4, entry 3). By decreasing the pressure to 20 psi CO/H₂, excellent selectivity was observed accompanied by a sharp drop in conversion (< 20%) for the first 2 cycles (Table 5.4, entries 4 and 5). When the catalyst–ligand system was reused in a third cycle, aldehydes were formed in trace quantities (Table 5.4, entry 6). Decreasing the pressure again to 15 psi CO/H₂ gave only 5 % conversion (Table 5.4, entry 7). At 50 °C and 30 psi CO/H₂, complete conversion was observed for the first two cycles (Table 5.4, entries 8 and 9) while the third resulted in trace aldehydes (Table 5.4, entry 10). Similarly, at 30 °C and 30 psi CO/H₂, 1–octene was not converted (Table 5.4, entry 11). Overall, these results demonstrate that, under appropriate conditions, one can achieve very good selectivity for the linear aldehyde derived from 1–octene.
Table 5.4 Hydroformylation\textsuperscript{a} of 1-octene with a PEG–phosphite/Rh\textsuperscript{zw} system.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cycle\textsuperscript{b}</th>
<th>Pressure (psi)</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Selectivity L:B</th>
<th>Conversion %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>30</td>
<td>60</td>
<td>4</td>
<td>6 : 1</td>
<td>&gt;95</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>30</td>
<td>60</td>
<td>14</td>
<td>5 : 1</td>
<td>&gt;95</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>30</td>
<td>60</td>
<td>14</td>
<td>9 : 1</td>
<td>63</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>20</td>
<td>60</td>
<td>4</td>
<td>17 : 1</td>
<td>16</td>
</tr>
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<td>5</td>
<td>2</td>
<td>20</td>
<td>60</td>
<td>14</td>
<td>25 : 1</td>
<td>15</td>
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<tr>
<td>6</td>
<td>3</td>
<td>20</td>
<td>60</td>
<td>14</td>
<td>–</td>
<td>trace</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>15</td>
<td>60</td>
<td>14</td>
<td>25 : 1</td>
<td>5</td>
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<tr>
<td>8</td>
<td>1</td>
<td>30</td>
<td>50</td>
<td>4</td>
<td>4 : 1</td>
<td>&gt;95</td>
</tr>
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<td>9</td>
<td>2</td>
<td>30</td>
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<td>4 : 1</td>
<td>&gt;95</td>
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<td>11</td>
<td>1</td>
<td>30</td>
<td>40</td>
<td>14</td>
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</tbody>
</table>

\textsuperscript{a} 1-octene 5.0 mmol, 100 mg PEG–phosphite/Rh\textsuperscript{zw} (5.22/5.33) (1mol % Rh).\textsuperscript{b} Ligand/Catalyst recovered \textit{via} precipitation with ether followed by centrifugation and transfer to the reactor with fresh substrate.
5.4 SUMMARY

An effort to build a soluble phosphanylated PAMAM ligand via a divergent synthesis was attempted, and then abandoned, after encountering purification difficulties. A related convergent approach, involving the coupling of a purified polyarylether dendritic wedge to an activated PEG support, did not prove fruitful.

Preliminary investigations into the activity of zwitterionic rhodium phosphite complexes under extremely mild conditions resulted in a surprising regioselective outcome where the industrially more important linear aldehyde of 1-octene was favoured. The preparation of a soluble triphenylphosphite supported on PEG was attempted and the crude systems were evaluated as ligands for the hydroformylation of 1-octene.
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6.0 EXPERIMENTAL

6.1 GENERAL CONSIDERATIONS

Chemicals were purchased from Aldrich, Lancaster, Alfa Aesar, Strem and NovaBioChem Chemical companies and were used as received unless otherwise noted. Argon, carbon monoxide (CO), UHP hydrogen, and nitrogen were supplied by Air Products or Praxair. All reactions were carried out under an atmosphere of nitrogen (in house) unless otherwise stated. Solvents were purified and dried following standard procedures. Purification of compounds by flash chromatography was performed using recycled silica gel (230-400 mesh, 60 Å) supplied by Silicycle (Quebec, Canada) or EM Science. During work-up, concentration in vacuo refers to the removal of the solvent or reagent under vacuum using either a glass vacuum line and an N$_2$(l) trap coupled to an Edwards RV3 or RV5 pump or using a Büchi R–114 Rotavapor evacuated with an air aspirator.

All $^{13}$C and $^{31}$P (200 MHz) solid state spectra were recorded on a Bruker ASX-200 spectrometer under cross polarization magic angle spinning (CPMAS) conditions (5000 or 6000 Hz spin rate). $^1$H NMR solution state spectra were recorded on Varian Gemini 200 (200 MHz), Varian XL-300 (300 MHz), and Bruker Avance 300 (300 MHz) spectrometers. $^{13}$C NMR spectra were recorded at 50 MHz (Varian Gemini 200) and 75 MHz (Bruker Avance 300). Solution state $^{31}$P NMR spectra were recorded at 121 MHz (Bruker Avance 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 ($\delta$) are
reported in ppm relative to the external standard 85% H$_3$PO$_4$. Gas chromatography was carried out using a Varian 3400 or an HP 6890 series chromatograph using a DB–1 capillary column. FT–IR were obtained using a Shimadzu Advantage 8400 spectrometer equipped with an attenuated total reflectance (ATR) silver gate apparatus. HPLC were run on a Japan Analytical Instrument recycling semi–prep HPLC using a JAIGEL packed size exclusion column and 1% MeOH in CHCl$_3$ as the eluent and an refractive index (RI) detector to observe peaks.

High-pressure reactions (P > 50 psig) were conducted in dry 45 ml stainless steel autoclaves fitted with a glass liner, screw cap and pressure gauge from Parr Instrument Company (part numbers 4712 and 4316). Reactions at low pressure (P < 50 psig) were carried out in a dry 3 oz Fisher Porter Bottle (glass pressure reaction vessel available from Andrews Glass Company) equipped with a pressure gauge. All reported psi pressures are psig.

Carbon monoxide (CO), a powerful asphyxiant, should be used with care. To use and work with CO safely, reactions must be carried out in a properly working fumehood with CO detectors installed nearby. Tanks and lines should be inspected on a regular basis for leaks.
6.2 Experimental for Chapter 2

6.2.1 General Procedure for the Preparation of the PAMAM–SiO₂ Dendrimers 2.20, 2.22, 2.24, and 2.26 (C₂ Series).

Aminopropyl silica gel (2.14) (20.0 g, 18.0 mmol w.r.t. NH₂) and methyl acrylate (2.8) (15.65 g, 180 mmol) were stirred at 50 °C under nitrogen for 3 days in methanol (200 ml). The suspension was cooled and filtered through an HPLC solvent filter with a 0.45 μm nylon membrane, washed first with methanol (3 x 30 ml) and then with ether (3 x 30 ml). The residual solvent was removed in vacuo affording bis(methylpropionate) aminopropyl silica gel (2.19) (22.1 g, 96 % yield by weight, 34.2 mmol w.r.t. ester). FT-IR = 1730 cm⁻¹ (vCO). ¹³C NMR (solid state): δ = 10, 22, 28, 50, and 174 ppm.

The bis(methylpropionate) aminopropyl silica gel (2.19) (20.0 g, 31.3 mmol w.r.t. ester) was then added to ethylenediamine (2.10) (100 ml, 1.5 mol) in methanol (200 ml) and stirred at room temperature under nitrogen for 5 days. The resulting first generation PAMAM dendrimer on SiO₂ (2.20) was isolated by filtration with a medium pore glass frit then washed with methanol (3 x 30 ml) and dichloromethane (3 x 30 ml). Note: Use extra solvent (if needed) until product is substantially free of the diamine odour. The residual solvent was removed in vacuo (95 % yield by weight, 21.0 g). FT-IR (cm⁻¹) = 1655 (vCO). ¹³C NMR (Solid State): δ = 10, 21, 28, 50, and 173 ppm.

The second generation PAMAM dendrimer on SiO₂ 2.22 can be prepared by following the above procedure starting with the first generation dendrimer 2.20.
(20.0 g, 29.8 mmol w.r.t. NH₃ groups) and methyl acrylate (26.0 g, 0.3 mol), and by increasing the reaction time to 5 days. After isolation, the ester was added to ethylenediamine (100 ml) in methanol (200 ml) and stirred at room temperature under nitrogen for 7 days (24.3 g, 91 % yield by weight, 54 mmol w.r.t. NH₂). FT-IR = 1650 cm⁻¹ (vCO). ^{13}C δ (Solid State): = 10, 22, 28, 50, and 173 ppm.

The third (2.24, 83 % yield by weight) and fourth (2.26, 75 % yield by weight) generations were prepared in the same manner. ^{13}C δ (Solid State): = 11, 22, 29, 50, and 173 ppm.

6.2.2 GENERAL PROCEDURE FOR THE PREPARATION OF PHOSPHANYLATED PAMAM DENDRIMERS ON SiO₂: 2.31, 2.32, 2.33 AND 2.34

Under argon, diphenylphosphine (7.0 ml, 40 mmol) was added to a solution of paraformaldehyde (1.05g, 35.0 mmol) in degassed methanol (40 ml). The mixture was stirred at 70 °C for 30 to 90 minutes and then cooled to room temperature. 2.0 mmol w.r.t. NH₂ of the selected generation of the PAMAM dendrimer on SiO₂ (2.20, 2.22, 2.24, or 2.26) was added under a generous flow of argon along with degassed methanol (20 ml) and toluene (80 ml). The reaction mixture was refluxed for 18 hours. The pale yellow product was collected by filtration using a 0.45 μm nylon membrane filter under a stream of argon and washed with degassed methanol (100 ml). The residual solvent was removed in vacuo and the pale yellow powder (2.31, 2.32, 2.33 or 2.34
respectively) was stored under argon. $^{13}$C NMR (Solid State): $\delta = 11, 22, 28, 51, 88, 128 – 135, \text{ and } 173$. $^{31}$P NMR (Solid State): $\delta = – 28$ ppm.

6.2.3 GENERAL PROCEDURE FOR THE RHODIUM COMPLEXATION OF PPH$_2$–PAMAM–SiO$_2$ DENDRIMER LIGANDS: 2.36, 2.37, 2.38, AND 2.39

The PPH$_2$–PAMAM–SiO$_2$ dendrimer ligand (2.31, 2.32, 2.33 or 2.34: 1.0 mmol w.r.t PPH$_2$) was added to a solution of chloro(dicarbonyl)rhodium(I) dimer ([Rh(CO)$_2$Cl]$_2$) (97 mg, 0.25 mmol) in freshly distilled hexanes (40 ml) under

Figure 6.1 Diagram of the filtration apparatus used in the isolation of the phosphonated and rhodium complexed compounds.
argon. The mixture was stirred at room temperature overnight (12 to 18 h). The reddish brown product was collected using a 0.45 μm nylon membrane filter under a stream of argon (see Figure 6.1 for apparatus used) and washed with dry hexanes (50 ml). Residual solvent was removed \textit{in vacuo} to afford complexes 2.31, 2.32, 2.33 and 2.34. $^{31}$P NMR (Solid State): $\delta = 24$ to 25 ppm.

6.2.4 General Procedure for the Hydroformylation Reaction

A glass liner containing the substrate (generally 2.0 mmol), catalyst (25 mg) and solvent (10 ml) was placed in a dry 45 ml stainless steel autoclave equipped with a magnetic stirring bar. The autoclave was flushed three times with CO and then pressurized to the desired level (generally 500 psi). The H$_2$ line was then attached to the autoclave and purged before pressuring the autoclave to the total pressure (generally 1000 psi). The pressurized autoclave was secured in an oil bath preset to the desired temperature on a stirring hot plate. After the appropriate reaction time (refer to Tables 2.4 to 2.9 for specific conditions), the autoclave was removed from the oil bath and cooled to room temperature prior to the careful release of the excess CO and H$_2$ gases in a properly vented fumehood. The resulting solution was filtered to remove the catalyst and the solvent was evaporated \textit{in vacuo} with a Rotavapor. The product aldehydes were analyzed by $^1$H NMR spectroscopy and gas chromatography and identified by comparison of spectral results with literature data and authentic samples. The branched to linear distribution was easily identified by the doublet-
triplet splitting patterns for the respective aldehyde protons on the $^1$H NMR spectra.
6.3 EXPERIMENTAL FOR CHAPTER 3

6.3.1 GENERAL PROCEDURE FOR THE PREPARATION OF THE C₄ (3.2A, 3.4A, 3.6A AND 3.8A), C₆ (3.2B, 3.4B, 3.6B AND 3.8B) AND C₁₂ (3.2C, 3.4C, 3.6C AND 3.8C) PAMAM DENDRIMERS ON SiO₂

Bis(methylpropionate) aminopropyl silica gel (2.19) was added to a flask containing the appropriate diamine (1,4-diaminobutane (3.1a), 1,6-diaminohexane (3.1b), or 1,12-diaminododecane (3.1c), refer to Table 6.1 for quantities) dissolved in methanol (10 – 20 ml per g SiO₂). The resulting suspension was stirred at 50 °C for 7 to 10 days. The first generation of the C₄ (3.2a), C₆ (3.2b) and C₁₂ (3.2c) PAMAM dendrimers on SiO₂ were isolated by filtration and washed with methanol (3 x 100 ml) and dichloromethane (3 x 50 ml). In the case of the C₆ and C₁₂ diamines, the silica product was allowed to compact at the bottom of the rbf and the reaction solvent containing the excess diamine was decanted off prior to redilution and filtration of the solid. The residual solvent was removed in vacuo to give 3.2a (94 % yield by weight), 3.2b (96 % yield by weight), and 3.2c (92 % yield by weight). The second (3.4a – c) (88 – 91 % yield by weight), third (3.6a – c) (80 – 86 % yield by weight) and fourth (3.8a – c) (73 – 77 % yield by weight) generation dendrimers were prepared in as per the iterative steps outlined in section 6.2.1. FT-IR (cm⁻¹) = 1640 (vCO). ¹³C NMR (Solid State): δ = 11, 21, 29, 51, and 174 ppm.
Table 6.1 Grams\(^a\) of methylacrylate (MA) and diamine (DA) used per g SiO\(_2\) scale reaction.

<table>
<thead>
<tr>
<th>Diamine</th>
<th>Generation</th>
<th>MA</th>
<th>DA</th>
<th>Generation</th>
<th>MA</th>
<th>DA</th>
<th>Generation</th>
<th>MA</th>
<th>DA</th>
<th>Generation</th>
<th>MA</th>
<th>DA</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(_2)N–C(_4)H(_8)–NH(_2)</td>
<td>G–1</td>
<td>0.8</td>
<td>1.6</td>
<td>G–2</td>
<td>1.4</td>
<td>2.5</td>
<td>G–3</td>
<td>2.1</td>
<td>3.6</td>
<td>G–4</td>
<td>2.6</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.2a</td>
<td></td>
<td></td>
<td>3.4a</td>
<td></td>
<td></td>
<td>3.6a</td>
<td></td>
<td></td>
<td>3.8a</td>
<td></td>
</tr>
<tr>
<td>H(_2)N–C(<em>6)H(</em>{12})–NH(_2)</td>
<td>G–1</td>
<td>0.8</td>
<td>2.1</td>
<td>G–2</td>
<td>1.4</td>
<td>3.2</td>
<td>G–3</td>
<td>1.9</td>
<td>4.4</td>
<td>G–4</td>
<td>2.3</td>
<td>5.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.2b</td>
<td></td>
<td></td>
<td>3.4b</td>
<td></td>
<td></td>
<td>3.6b</td>
<td></td>
<td></td>
<td>3.8b</td>
<td></td>
</tr>
<tr>
<td>H(<em>2)N–C(</em>{12})H(_{24})–NH(_2)</td>
<td>G–1</td>
<td>0.8</td>
<td>3.6</td>
<td>G–2</td>
<td>1.2</td>
<td>4.9</td>
<td>G–3</td>
<td>1.5</td>
<td>6.1</td>
<td>G–4</td>
<td>1.7</td>
<td>6.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.2c</td>
<td></td>
<td></td>
<td>3.4c</td>
<td></td>
<td></td>
<td>3.6c</td>
<td></td>
<td></td>
<td>3.8c</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Amounts determined based on theoretical loading of starting amine.

6.3.2 GENERAL PROCEDURE FOR THE PREPARATION OF PHOSPHANYLATED PAMAM DENDRIMERS ON SiO\(_2\): 3.9 – 3.12 A – C

As per section 6.2.2.

6.3.3 GENERAL PROCEDURE FOR THE RHODIUM COMPLEXATION OF PPH\(_2\)–PAMAM–SiO\(_2\) DENDRIMER LIGANDS: 3.13 – 3.16 A – C

As per section 6.2.3.
6.3.4 General Procedure for the Hydroformylation Reaction and Catalyst Recycling:

A glass liner containing the substrate (generally 10.0 mmol), catalyst (25 mg) and CH₂Cl₂ (10 ml) was placed in a 45 ml stainless steel autoclave equipped with a magnetic stirring bar. The autoclave was flushed three times with CO, then pressurized to 500 psi. The H₂ line was attached and the line purged before pressurizing the autoclave up to 1000 psi. The autoclave was then placed in an oil bath preset to the desired temperature on a stirring hot plate. After the desired reaction time, (refer to Tables 3.3 to 3.9 for specific conditions) the autoclave was removed from the oil bath and cooled to room temperature prior to the careful release of the excess CO and H₂. The resulting solution was filtered using a 0.45 μm membrane filter to remove the catalyst and the solvent evaporated in vacuo. The product aldehydes were analyzed by ¹H NMR and GC and identified by comparison with literature data and authentic samples.

The recovered catalyst was washed with distilled CH₂Cl₂ under a stream of argon or nitrogen. The dry catalyst on the membrane filter was carefully transferred to a clean glass liner and the membrane rinsed with a fresh aliquot of distilled CH₂Cl₂ (reaction solvent). Substrate and a stirring bar were added to the glass liner, which was then sealed within an autoclave. The reactor was pressurized and subjected to the desired conditions as described above.
6.3.5 Preparation of Dicyclohexylphosphanyl Ligands 3.25–3.28 (G₁₄ C₆)

Under argon, dicyclohexylphosphine (4.0 ml, 20.0 mmol) was added to a solution of paraformaldehyde (0.450 g, 15.0 mmol) in degassed methanol (30 ml) and the mixture stirred at 70 °C for 30 min. The reaction flask containing dicyclohexylphosphanyl methanol (3.24) produced in situ was removed from the heat source prior to the addition of the C₆ series of PAMAM dendrimers on silica (3.2b, 3.4b, 3.6b and 3.8b) (1.0 mmol. w.r.t NH₂) along with more degassed methanol (30 ml) and toluene (50 ml). The reaction was refluxed for 16 h and the resulting bis-(dicyclohexylphosphanylmethyl)-PAMAM ligands on silica (3.25, 3.26, 3.27 and 3.28) were isolated by filtration using a 0.45 µm membrane filter under a generous stream of argon and washed with degassed methanol (100 ml). The residual solvent was removed in vacuo and the product stored under argon. ³¹P NMR: δ (Solid State): = −18.5 ppm. ¹³C NMR: δ (Solid State): = 11, 27, 52, and 176 ppm.

6.3.6 Preparation of Dicyclohexylphosphanyl Rhodium Complexes 3.29–3.32

Rhodium complexes prepared as per sections 6.2.3
6.3.7 The complexation of 3.2b, 3.4b, 3.6b and 3.8b with PtCl₂(C₆H₅CN)₂

250 mg of 3.2b (0.17 mmol), 3.4b (0.23 mmol), 3.6b (0.29 mmol), or 3.8b (0.32 mmol) was added to 1.0 equivalents of dichlorobis(benzonitrile)platinum(II) (80 mg, 108 mg, 135 mg, 150 mg respectively) dissolved in freshly distilled and degassed acetonitrile (60 ml) under argon. The red mixture was stirred at room temperature for 12 hours. The brownish-orange solid was filtered through a 0.45 μm nylon membrane filter under a stream of argon and washed with dry acetonitrile (60 ml). Residual acetonitrile was removed in vacuo to yield the platinum complexed phosphonated dendrimers 3.33 (0.308g, G1–C₆), 3.34 (0.295g, G2–C₆), 3.35 (0.287g, G3–C₆), and 3.36 (0.266g, G4–C₆). ¹³C δ NMR (Solid State): = 11, 28, 43, 51, 130, 173, and 219 ppm. ³¹P NMR δ (Solid State): = −8.8 ppm (t, J₉₅₃ = 1705 Hz).
6.4 EXPERIMENTAL FOR CHAPTER 4

General Remarks: The synthesis all of the resin supported dendrimers and complexes discussed in chapter 4 was carried out at the NRC facility. For the sake of completeness, the details of the resin supported dendrimer synthesis are reported herein.

6.4.1 SYNTHESIS OF PSEUDOPEPTIDE BUILDING BLOCK 4.1A

A solution of 3,5-diaminobenzoic acid (4.2) (50.0 mmol), GlyOBz (4.3) (60.0 mmol), DCC (60.0 mmol), HOBT (60.0 mmol) in CH₂Cl₂:DMF (100ml) was stirred under nitrogen at room temperature for 14 – 16h. The precipitated solid was filtered, washed thoroughly with CH₂Cl₂ and the mother liquor collected, washed thoroughly with a saturated solution of NaHCO₃ and the solvent removed in vacuo to give the crude product. 3,5-diamino N-benzamide glycine benzyl ester (4.4) was obtained (72% yield) after purification by flash chromatography over silica gel (CH₂Cl₂:MeOH 20:1). ^1H NMR (DMSO-d₆): δ = 7.35 (m, 5H, Ar-H), 5.75 (s, 2H, -OCH₂-Ar), 4.95 (bs, 1H, O=CNHCH₂), 3.95 (bs, 4H, ArNH₂) and 3.3 (m, 2H, -NHCH₂C=O-). LRMS (FAB, positive ion mode, m/z) C₁₆H₁₇N₂O₃ 299.1 (M+).

To a solution of Fmoc-Phe-OH (4.5a) (60.0 mmol) in CH₂Cl₂ (100ml) were added DIC (60.0 mmol), HOBT (60mmol) and 4.4 (20 mmol). The mixture was stirred under nitrogen at room temperature for 30 – 40 h. The precipitated solid was filtered and washed thoroughly with CH₂Cl₂ and the mother liquor collected, washed with a saturated solution of NaHCO₃ and evaporated to give the crude
product. The benzyl ester derivative (4.6a) of building block 4.1a was obtained in 76 % isolated yield after purification: $^1$H NMR (DMSO-d$_6$) δ 2.89 (m, 2H), 3.05-3.10 (m, 2H), 4.00-4.24 (m, 2H), 4.42-4.48 (m, 2H), 5.17 (s, 2H), 7.08-7.88 (m, 34H), 8.31 (bs, 2H) and 10.34 (bs, 2H); $^{13}$C NMR (DMSO-d6) δ 38.2, 42.2, 47.4, 60.6, 66.6, 66.7, 114.5, 120.9, 126.1, 127.3, 127.9, 128.5, 128.7, 128.9, 129.0, 129.3, 136.1, 136.8, 138.8, 140.0, 141.5, 141.5, 144.6, 156.8, 167.8, 170.6 and 171.7. LRMS (electrospray, positive ion mode, m/z) for C$_{64}$H$_{55}$N$_5$O$_9$ 1038 (MH$^+$).

The benzyl derivative of the building block (4.6a) (10.0 mmol) was dissolved in DMF (50 ml) and hydrogenated in the presence of Pd/C (10 mol %) for 35 – 45 minutes. The catalyst was filtered off using Celite and the solvent removed in vacuo to give the building block 4.1a in 95% yield. $^1$H NMR (DMSO-

d$_6$): δ = 2.88-2.94 (m, 2H), 3.08-3.17 (m, 2H), 3.76 (s, 2H), 4.10-4.18 (m, 6H), 4.45-4.54 (m, 2H), 7.08-7.94 (m, 29H), 8.31 (bs, 2H), and 10.60 (bs, 2H); $^{13}$C NMR (DMSO-d$_6$): δ = 39.8, 45.0, 47.4, 58.0, 66.6, 114.1, 120.9, 122.3, 128.9, 129.7, 130.2, 138.2, 140.2, 141.5, 141.5, 144.5, 144.6, 156.8 and 171.7; LRMS (electrospray, positive ion mode, m/z) for C$_{57}$H$_{49}$N$_5$O$_9$ = 948 (MH$^+$)

6.4.2 SYNTHESIS OF PSEUDOPEPTIDE BUILDING BLOCK 4.1b

A solution of 3,5-diaminobenzoic acid (46.0 mmol), GlyOMe (73.0 mmol), DCC (73.0 mmol), HOBt (73.0 mmol) and DIPEA (230.0 mmol) in DMF (110 mL) was stirred under nitrogen at room temperature for 24h. The precipitated solid was filtered and washed thoroughly with DMF. The mother liquor was evaporated to give the crude compound that was subjected to flash chromatography over
Chapter 6: Experimental

silica gel. Elution with ethyl acetate furnished glycine methyl ester derivative (74% yield). LRMS (electrospray, positive ion mode, m/z) C_{10}H_{13}N_{3}O_{3} 223 (M^+).

To a solution of Fmoc-Phe-(p-NO_{2})-OH (4.5b) (5.78 mmol) in DMF (60 mL) was added HBTU (7.77 mmol), DIPEA (7.77 mmol) and 3,5-diamino-N-benzamide glycine methyl ester (2.59 mmol). The mixture was stirred under nitrogen at room temperature for 30 h. DMF was evaporated to give the crude compound that was extracted with ethyl acetate. The organic layer was washed with a saturated solution of NaHCO_{3} and brine. The methyl ester derivative of the building block 3 was obtained in 80% isolated yield after purification. \(^1\)H NMR (DMSO-d_{6}) \(\delta\) 2.89 (m, 2H), 3.05-3.10 (m, 2H), 3.7 (s, 3H), 3.8-4.1 (m, 10H), 4.3-4.4 (m, 2H), 7.00-8.1 (m, 30 H). LRMS (FAB, positive ion mode, m/z) C_{58}H_{49}N_{7}O_{13} 1052 (MH^+).

The methyl ester derivative (2.94 mmol) was dissolved in 3:1 THF/H_{2}O (20 mL) and treated with 30% H_{2}O_{2} (8.0 equiv.) and LiOH (2.0 equiv.) for 4 h at 0°C. The excess of H_{2}O_{2} was quenched at 0°C with 1.5 N Na_{2}SO_{3}. The solution was buffered to pH 9-10 with aqueous NaHCO_{3} and the THF evaporated. The remaining solution was acidified (pH 1-2), the carboxylic acid derived building block 4.1b was extracted from the aqueous phase using EtOAc (75% yield). \(^1\)H NMR (DMSO-d_{6}) \(\delta\) 2.89 (m, 2H), 3.05-3.10 (m, 2H), 3.8-4.1 (m, 10H), 4.3-4.4 (m, 2H), 7.00-8.1 (m, 28 H). LRMS (FAB, positive ion mode, m/z) C_{57}H_{48}N_{7}O_{13} 1038 (M^+).

169
6.4.3 General Procedure for Solid Phase Synthesis

Part I: 4.10, 4.12 and 4.14

Rink amide MBHA resin (4.7) (loading 0.4 – 0.5 mmol/g) was suspended in DMF for 30-45 minutes under argon. After filtration, a solution of 20 % piperidine in DMF was added and the mixture stirred for 40 minutes (2 cycles) to afford the deprotected resin (4.8). The coupling of the building block 4.1a (4.0 eq) to the deprotected resin (4.8) was aided by the addition of DIC (4.0 eq), HOBt (4.0 eq), and DIPEA (8.0 eq), with stirring for 12 h. After filtration, compound 4.9 was subjected to Fmoc removal with 20% piperidine in DMF as discussed above to yield the first generation amine terminated dendrimer 4.10. Repetition of the coupling step and Fmoc deprotection step yields the G2 (4.12) and G3 (4.14) amine terminated dendrimers on resin.

Part II: 4.23 and 4.24

Building block 4.1b (4.0 equiv) was coupled to deprotected Rink amide MBHA resin (4.8) using HBTU (4.0 equiv), DIPEA (8.0 equiv) in DMF and stirred for 20 h. After filtration, compound 4.21 was subjected to the Fmoc group removal by using 20 % piperidine in DMF and the resulting amine terminated derivative was divided into two parts. For the first half, the NH2 group was protected by treatment with Ac2O (8.0 equiv) and DIPEA (10.0 equiv) in DCM. This was followed by the reduction of both nitro groups to amine groups using SnCl2/H2O (12.0 equiv) in DMF (10h) to afford the first generation amine terminated dendrimer on resin (4.23). The second half was coupled with more
building block 4.1b (10.0 equiv) using HBTU (10.0 equiv), DIPEA (16.0 equiv.) in DMF for 48 h. After filtration, the compound was subjected to the Fmoc group removal as discussed above. The free amino derivative thus obtained was re-protected by treatment with Ac₂O (8.0 equiv) and DIPEA (10.0 equiv) in DCM. The dinitro groups were reduced to di-amino groups by SnCl₂/H₂O (12.0 equiv) reduction in DMF (10h) to yield the second generation amine terminated dendrimer on resin (4.24).

6.4.4 GENERAL PROCEDURE FOR THE PREPARATION OF LIGANDS 4.15, 4.16, 4.17, 4.25, AND 4.26 AND COMPLEXES 4.18, 4.19, 4.20, 4.27 AND 4.28

Paraformaldehyde (10.0 mmol) and diphenylphosphine (10.0 mmol) in degassed MeOH (20 ml) were stirred at 70°C for 45 min under argon. Beads from the solid-phase synthesis of 4.10, 4.12, 4.14, 4.25 or 4.26 were transferred into the flask and the heterogeneous reaction mixture was stirred for 24 h at room temperature. The beads were filtered under argon and complexed with [Rh(CO)₂Cl]₂ (1.0 equiv. Rh per bisphosphinomethyamino group) in DCM for 14 h at room temperature to complete the synthesis of the dendrimer catalysts on resin.

6.4.5 GENERAL PROCEDURE FOR HYDROFORMYLLATION

As per sections 6.2.4 and 6.3.3. Refer to Tables 4.1 to 4.5 for specific conditions.
6.5 EXPERIMENTAL FOR CHAPTER 5

6.5.1 ATTEMPTED SYNTHESIS OF PAMAM–PEG: DENDRIMERS 5.4 AND 5.6

Poly(ethylene glycol) diamine (5.2) (MW 3400: 1.5 g, 0.90 mmol w.r.t NH₂) and methyl acrylate (2.8) (8.2 ml, 90 mmol) were stirred at 40 °C under nitrogen for 3 days in distilled CH₂Cl₂ (80 ml). The solution was concentrated to remove the solvent and excess methyl acrylate then diluted with THF (5 ml) prior to precipitation with distilled ether (50 ml). The brown precipitate was collected via gravity filtration, transferred into a dry rfb and the volatiles were removed in vacuo (36 h). Crude ester 5.3 was purified via silica gel chromatography with CHCl₃/MeOH (10:1) as the eluent (0.60 g, 36 % yield, 0.65 mmol w.r.t. ester). FT–IR (cm⁻¹) = 1736 (vCO). ¹H NMR: δ = 1.55 (8H), 1.64 (12H), 1.90 (8H), 2.28 (8H), 3.50 (12H), and 3.65 (backbone) ppm. ¹³C NMR: δ = 35, 41, 52, 70.5 (backbone), 80.4, and 175 ppm.

```
O
\_____/\nO         O
N           N
O         O
\_____/\nO
```

Ester 5.3 was then added to ethylenediamine (4.0 ml, 60 mmol) in CH₂Cl₂ (50 ml) and stirred under nitrogen at room temperature for 3 days. The resulting product was concentrated and the majority of excess diamine distilled off using a Kugelrhor distillation apparatus. The product was diluted with chloroform (5 ml) and precipitated with ether (50 ml). Filtration yielded a viscous brown gel (1.1 g crude). FT-IR: 1650 cm⁻¹ (vCO).
Crude 5.4 (MW_{theo} 4670: 1.1 g, 0.47 mmol w.r.t NH₂) and methyl acrylate (2.8) (4.3 g, 50 mmol) were stirred at 40 °C under nitrogen for 3 days in distilled CH₂Cl₂ (50 ml). The solution was concentrated to remove the solvent and excess methyl acrylate then diluted to a 5 ml volume (THF) prior to precipitation with distilled ether (50 ml). Filtration of the precipitate was carried out under a stream of nitrogen and the brown paste was transferred into a dry rbf. Crude ester 5.5 was purified via silica gel chromatography with CHCl₃/MeOH (8:1) as the eluent. FT–IR (cm⁻¹) = 1648, 1732 (vCO). ¹H NMR: δ = 1.55, 1.64, 1.90, 2.28, 2.63, 3.50, and 3.65 (backbone) ppm. ¹³C NMR: δ = 35.0, 41.2, 49.9, 51.9, 55.0, 70.5 (backbone), 80.4, 172.2 and 174.9.

5.5 was added to a solution of ethylene diamine in CH₂Cl₂ and stirred for 3 days at room temperature. The resulting yellow product was concentrated and the majority of excess diamine distilled off. The product was diluted with
chloroform (5 ml) and precipitated with ether (50 ml). Collection of the yellow gel yielded 0.44 g crude 5.6. FT-IR: \( = 1650 \text{ cm}^{-1} \) (vCO).
6.5.2 TOWARDS POLYARYL ETHER ON PEG

6.5.2.1 PREPARATION OF TRIARYLETHER 5.17

A solution of \( p \)-hydroxybenzylalcohol (5.13) (20 mmol, 2.48 g), potassium carbonate (4.0 g) and 18–crown–6 ether (20 mg) was stirred at 60 °C for 30 minutes in THF (90 ml). Di-\(^3\)-butyl dicarbonate (5.0 ml, 21 mmol) was added to the reaction and the mixture was then refluxed under nitrogen overnight (16 h). The THF was removed \textit{in vacuo} and the residue was purified by silica gel chromatography (3:2 pentane ether) affording \( p \)-(\(^1\)butoxycarbonylhydroxy)benzylalcohol (5.14) as a colourless oil in 95% yield (4.28 g, 19.0 mmol). \(^1\)H NMR (CDCl\(_3\)): \( \delta = 1.50 \) (s, 9H), 1.8 (s, 1H), 4.65 (s, 2H), 7.13 (d, 2H), and 7.37 (d, 2H).

5.14 (4.0 g, 18 mmol) was then added to a solution of triphenylphosphine (5.25 g, 20 mmol) and carbon tetrabromide (3.3 g, 10 mmol) in THF (70 ml) and stirred at room temperature for 3 h. The solvent was removed \textit{in vacuo} and the residue purified by silica gel chromatography (2:1 pentane ether) to give 95% yield (4.86g, 17.0 mmol) of \( p \)-(\(^1\)butoxycarbonylhydroxy)benzylobromide (5.15) as a white solid. \(^1\)H NMR (CDCl\(_3\)): \( \delta = 1.54 \) (s, 9H), 4.46 (s, 2H), 7.12 (d, 2H), and 7.38 (d, 2H) ppm.

\[
\begin{array}{c}
\text{Br} \\
\text{OBoc}
\end{array}
\]

5.15
5.15 (2.37g, 8.25 mmol) was coupled to 3,5-dihydroxybenzylalcohol (5.16) (0.56g, 4.0 mmol) using K$_2$CO$_3$ (10 mmol) and 18-crown-6 (20 mg) in dry, refluxing acetone (50 ml). The acetone was removed in vacuo and the residue was purified by silica gel chromatography (1:1 pentane:ether) affording 3,5-bis-(4-4-butoxycarbonyl-benzyloxy)-benzyl alcohol (5.17) as a white solid in 42% yield (0.93 g, 1.7 mmol). $^1$H NMR (CDCl$_3$): $\delta = 1.54$ (18H, s), 1.9 (1H, s), 4.62 (2H, s), 4.95 (4H, s), 6.45 (1H, t), 6.58 (2H, d), 7.18 (4H, d), 7.40 (4H, d) ppm.

![Chemical Structure Image]

6.5.2.2 Preparation of Mesylated PEG 5.18

TEA (0.80 ml, 10 mmol) was added to PEG 2000 or 3400 (4.0 or 6.8 g respectively, 5.0 mmol w.r.t. OH) dissolved in THF (50 ml). The mixture was stirred for 5 minutes at room temperature before the slow addition of methanesulfonyl chloride (4.0 ml, 50 mmol). After 6 hours of stirring, the solvent and excess reagents were removed in vacuo. The resulting white residue was dissolved in THF, (~5 ml) and slowly added to stirring ether (~250 ml). A white precipitate (HNE$_3$Cl) formed over the gelled PEG product. The solution and
precipitate were decanted from the gel product. (Note: product still contaminated with HNEt₃Cl salt.) ¹H NMR: δ = 2.9, 3.5 – 3.7 (backbone). ¹³C NMR: δ = 39, 62, 70, and 70.5 (backbone) ppm.

![Chemical Structure](image)

**5.18**

**ALTERNATE ACTIVATED PEG**

PEG–3400 (6.8g, 4.0 mmol w.r.t. OH) or PEG–2000 (4.0 g, 4.0 mmol w.r.t. OH) was dissolved in neat SOCl₂ (23.8 g, 14.6 ml, 0.20 mol) and allowed to stir for 12 hours. Excess reagent and HCl were removed *in vacuo* and the residue dissolved in a minimal amount of distilled THF (~5ml) prior to precipitation in distilled ether (~50 ml). The sticky white precipitate was collected *via* gravity filtration under a stream of nitrogen and removal of residual solvent (4.3 g, 63% yield or 2.3 g, 55%). ¹H δ (CDCl₃): = 3.65 (backbone). ¹³C δ (CDCl₃): = 70.5 (backbone).
6.5.3 TOWARDS THE SYNTHESIS OF PEG–PHOSPHITE (5.22)

6.5.3.1 PREPARATION OF PEG–PHENOL (5.27)

\[
\text{HO-} \begin{array}{c}
\text{C} \text{H}_3 \\
\text{O} \\
\text{O} \\
\text{O} \\
\text{C} \text{H}_3 \\
\end{array} \text{O} \begin{array}{c}
\text{C} \text{H}_3 \\
\text{OH} \\
\end{array}
\]

Cesium carbonate (3.5 g, 10 mmol) was added to a solution of hydroquinone (1.1 g, 10 mmol) in THF (100 ml) and the mixture refluxed for 1 hour. Mesylated PEG (5.18, 2.3 g, 2.1 mmol w.r.t. OH) was added to the bluish solution and refluxed for a further 18 hours. While still warm, the reaction solution was decanted from the undissolved carbonate and concentrated to a 5 ml volume. The product solution was added slowly to a stirring solution of ether (80 ml). The resulting brown gel was filtered off via gravity filtration, the product redissolved in a further aliquot of hot THF (5 ml) and the precipitation procedure repeated. The residual solvent was removed in vacuo to yield 5.27 (1.4 g, 1.3 mmol w.r.t. OH). $^{13}$C NMR (CDCl$_3$): $\delta = 70.2$ (backbone), 116.4, 116.9, 123.6, 124, and 150.1 ppm. $^1$H NMR: $^1$H $\delta$ (CDCl$_3$): = 3.6 (backbone), 6.7, and 7.2 ppm.
6.5.3.2 Preparation of (1,1'-biphenyl-2,2'-diyl)chlorophosphite

\[ \text{5.31} \]

To a solution of distilled trichlorophosphine (8.7 ml, 100 mmol) in THF (100 ml) at \(-40\, ^\circ\text{C}\) was added triethylamine (2.8 ml, 20 mmol). A solution of 1,1'-biphenol (5.28) (1.86 g, 10.0 mmol) in THF (50 ml) was added drop wise while the temperature was maintained at \(-40\, ^\circ\text{C}\). The resulting cream coloured suspension was stirred for an additional twelve hours at room temperature before the precipitate was removed by filtration through oven dried celite under nitrogen. The solvent and excess trichlorophosphine were removed in vacuo to yield a yellow oil. The product (5.31) is a colourless oil after vacuum distillation at between 170 and 180 \(^\circ\text{C}\) at 30 to 50 mtorr and can be stored in a THF solution for several days. (1.9 g, 76% Yield). \(^{31}\text{P}\) NMR (CDCl\(_3\)): \(\delta = 180\, \text{ppm}\). \(^1\text{H}\) NMR (CDCl\(_3\)): \(\delta = 7.2 - 7.5\, \text{ppm}\) (8H, m). \(^{13}\text{C}\) NMR (CDCl\(_3\)): \(\delta = 122, 126, 129, 130, 131,\) and 149 ppm.
To a solution of PCl₃ (8.7 ml, 100 mmol) in THF (50 mmol) at −40 °C was added NEt₃ (2.8 ml, 20 mmol). The resulting solution was allowed to stir at −40 °C for 30 minutes prior to the drop wise addition of 1,1′-binaphthyl-2,2′-diol (2.86 g, 10.0 mmol) in THF (50 ml). The thick cream coloured slurry was stirred at −40 °C for 2 hours then allowed to warm up to room temperature and stir for an addition 12 hours. The triethylamine hydrochloride salt was removed via filtration through a thick pad of oven dried Celite and the excess PCl₃ and solvent removed in vacuo. The yellow residue was treated with freshly distilled pentane (20 ml) and the dissolved impurities removed by canulation of the wash solvent. The residual solvent was removed in vacuo to yield a yellow solid (2.5 g, 71% yield). (92 % pure by ³¹P NMR.) ³¹P NMR (CDCl₃): δ = 180 ppm. ¹H NMR δ (CDCl₃): = 7.2 – 7.7 and 7.8 – 8.2 ppm. ¹³C NMR δ (CDCl₃): = 121, 125, 126, 126, 128, 130, 131, 132, and 147 ppm.
6.5.3.4  Preparation of PEG–Phosphite 5.22

![Chemical Structure](image)

5.22

Triethylamine (2.8 ml, 20 mmol) was slowly added to chlorophosphite 5.31 (5.01 g, 20.0 mmol) in THF (50 ml) at −40 °C. The white precipitate was stirred for 10 minutes prior to the slow addition of the PEG-phenol (5.27) (1.1 g, 1.0 mmol w.r.t. OH) in THF (100 ml). The suspension was stirred for 12 hours at 50 °C. The solvent was removed in vacuo and the yellow gel was dissolved in hot distilled THF (5 ml) prior to precipitation with distilled ether (50 ml). The product was compacted via centrifugation and the solid subjected to a second precipitation step (2 ml THF and 25 ml ether). 1.86 g of crude 5.22 was achieved (72 % pure phosphite by $^{31}$P NMR, $^1$H and $^{13}$C show TEA contamination). $^1$H (CDCl$_3$) δ = 3.65 (backbone), and 6.9 – 7.4 ppm. $^{13}$C (CDCl$_3$) δ = 67.8, 70.4 (backbone), 121.8, 122.1, 124.9, 125.4, 129.1, and 129.8 ppm. $^{31}$P (CDCl$_3$) δ = 127.6 ppm.
6.5.4 General Procedure for the Low Pressure Hydroformylation

Phosphite (20 mg, 65 μmol) and solvent (5 ml) were placed in a dry 3 oz glass autoclave equipped with a magnetic stirring bar. 53 (5.3 mg, 10 μmol) was introduced and the mixture allowed to stir under N₂ for 20 minutes prior to the addition of the substrate. The pressure gauge was attached and the glass reactor was flushed three times with a 1:1 mixture of CO:H₂ gas then pressurized to the desired level. The pressurized reactor was then secured in an oil bath preset to the desired temperature on a stirring hot plate. After the appropriate reaction time (refer to tables 5.1 to 5.3 for specific conditions), the autoclave was removed from the oil bath, cooled to room temperature then the gases released carefully in a properly vented fumehood. In the case of triphenylphosphite, the crude solution was analyzed without purification.

In the case of the PEG–phosphite (refer to Table 5.4), the catalyst and ligand were precipitated out of solution with dry ether, and compacted by centrifugation. The product solution was then concentrated and analyzed by ¹H NMR spectroscopy and gas chromatography. The compacted PEG–catalyst complex was transferred to a clean, dry reactor with fresh solvent for further reaction with another aliquot of substrate.
7.0 RHODIUM CATALYZED HYDROFORMYLATION: THE ADVENTURE REMEMBERED ........................................... 184

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7.0 Rhodium Catalyzed Hydroformylation: The Adventure Remembered

In considering the research presented on the rhodium catalyzed hydroformylation using heterogeneous and recyclable systems, we reflect now on the achievements, insights gained during our quest, and suggest considerations for future work.

7.1 Remembering the Destination

An ideal hydroformylation catalyst can be described as a catalyst offering efficiency under mild conditions, versatile selectivity towards either the desired branched or linear product, longevity of use, and is of profitable accessibility. In terms of longevity, a durable and reusable catalyst, which retains the active metal under the reaction conditions, is desired.

In moving towards this mythical catalyst, we sought to unite the stability and recoverability of a heterogeneous support, e.g. silica or resin, with the high activity and selectivity offered by a multivalent homogeneous ligand. It was further theorized that supported multivalent dendritic catalysts would behave with similar selectivities and kinetics as the classical homogeneous systems after which they were modeled.

7.2 Silica Supported Hydroformylation Catalysts

To summarize chapters 2 and 3, four generations of PAMAM dendrimers derived from C₄, C₆, and C₁₂ diamines were anchored on silica, phosphanylated, and complexed to rhodium. These heterogeneous systems
were found to be effective catalysts in the hydroformylation of various olefinic substrates. No obvious dendrimer effect was observed in terms of regioselectivity, and comparatively inferior activities were attributed to decreased metal loadings stemming from lower amine and phosphine contents. Regioselectivity largely depended on the complex dynamics presented by the substrate and metal–phosphine ligand electronics, as well as pressure and temperature conditions.

Chapter 2 proposes the threshold of dendrimer growth theory based on the observation that the third and fourth generation complexes of the C₂ diamine series suffered lower amine contents and rhodium loadings when compared to the first and second generation counterparts. In order to access the higher generations, longer (C₄, C₆, and C₁₂) diamine linkers were employed in chapter 3 as a means to relieve steric hindrance by decreasing the volume to surface area ratio of the PAMAM dendrimers on silica.

7.2.1 PAMAM ON SILICA: ASSESSING DENDRIMER PURITY

In assessing dendrimer purity, complete characterization of the ligands on silica is obviously expected to give a better picture of what is actually assembled on the support. The limited solid phase characterization techniques available to us were insufficient to accurately elucidate the structure of the ligands prepared. One possible avenue to overcome the limitations associated with characterizing the silica supported systems would be to cleave off the dendritic ligand in its entirety and determine the ligand structure via standard solution phase
techniques. Incorporating a selectively cleavable linker in between the silica core and the first generation of growth would realize this prospect. Linkers that have been developed for use in solid phase synthesis are envisioned. Consideration of a linker that would survive the catalytic hydroformylation conditions, yet require cleavage conditions mild enough to avoid attack of the PAMAM amide bonds would aid in the selection of such a tool. Photo labile linkers that can be selectively cleaved at a particular wavelength of light are also envisioned.

7.2.2 PAMAM ON SILICA: SIMPLIFYING THE ISOLATION

As discussed in chapters 2 and 3, the problems encountered with the isolation of the amine terminated dendrimers via filtration can be surpassed by using Soxhlet extraction with refluxing solvent. This extraction method can also be readily applied to the ester terminated half generations to ensure complete removal of any residual methacrylate. The same procedure can be applied to the phosphine and rhodium complexed dendrimers; however extreme care must be applied to eliminate oxygen from the system in order to avoid undesirable oxide formation. In this respect, filtration of the phosphines may provide a cleaner ligand than Soxhlet extraction.

7.3 POLYMER SUPPORTED CATALYSTS

Chapter 4 explored resin as an alternate catalyst support for the heterogeneous hydroformylation reaction. Rhodium complexed pseudopeptide–based ligands immobilized on Rink–amide resin were recyclable catalysts and
demonstrated similar selectivities to those observed in the silica supported systems previously mentioned.

7.3.1 The Leaching Problem

In the silica and resin supported systems presented above, the hydroformylation product solutions were typically orange or yellow, indicating that slow leaching of the rhodium, from the dendrimer ligands, occurs. The rhodium surrendered to the bulk solution is likely the result of phosphine ligand lability promoted by high pressures of CO. Use of milder conditions, i.e. lower CO pressures, in combination with more basic phosphines located in the core of a large dendritic structure may help in decreasing the extent of permanent metal loss.

Relocation of the metal centres from the periphery to the interior of the resin supported dendrimer was accomplished in chapter 4, however the effort did not inhibit metal leaching. A slight dendrimer effect was observed, in that the activity of the second generation ligand was greater than the first generation. Third and fourth generation analogues of these interiorly located metal sites would provide additional insight and confirmation of any generational effect with regard to leaching and sustained activity.

It should be mentioned that industry applies various methods to accommodate the inherent problem metal leaching causes, often by employing catalytic–product stream separations and in–reactor catalyst recycling. These solutions, however, are largely mechanical fixes for a chemical problem.
7.4 Towards Recyclable Phosphites

In chapter 5, we recognized that the true potential of the heterogeneous hydroformylation reaction related to industry’s preference for the production of linear aliphatic aldehydes. Phosphites are known to be more selective for the linear aldehyde than phosphines and a phosphite terminated dendrimer was envisioned as a ligand worthy of development. Preliminary investigations into the activity of zwitterionic rhodium–phosphite complexes under mild conditions resulted in excellent regioselectivities.

Originally PAMAM was chosen as the dendritic component because of our familiarity with the motif. However in retrospect, Newkome’s polyol or any alcohol terminated dendrimer, preferably one with a hydrophobic scaffold, would likely have proven to be more appropriate systems on which to build our phosphites. Additionally, in terms of addressing phosphite stability, adapting Bukwald bulky phosphite, which is reported to have improved resistance to moisture, may lead toward a more robust and recyclable dendritic phosphite ligand.

7.5 Effective Catalyst Evaluation

While all the supported dendrimer catalysts prepared proved to be successful in the hydroformylation reaction, the relative activities and turnover numbers for each series was not assessed as accurately as possible. On a purely comparative basis, evaluating the catalytic efficiency at 50 % conversion, rather than at complete conversion, would give a more truthful picture of the relative activity and recycling potential for each member of the dendrimer series.
Shorter reaction times, or increasing the substrate to catalyst ratio are two methods to achieve this effect. In the batch recycles, mechanical loss of catalyst during the filtration and transfer step is difficult to avoid. Thus, in addition to increasing the amount of substrate provided, it would be preferable to use larger autoclaves loaded with more catalyst, e.g. 50 mg and 100 mmol substrate, in order to decrease the significance of any possible mechanical loss.

In the case of the recycling reactions, turnover numbers based on the initial rhodium content of the starting complex seemed meaningless since leaching was a significant problem and the catalyst activity after subsequent recycles would not be reflective of the actual amount of rhodium available in each reaction cycle. Determining the extent of rhodium leaching from each cycle on a quantitative basis by analyzing the rhodium content of the product solutions should provide insight into the degree of metal loss per recycle and relate back to a corresponding metal retention.

7.6 Expanding Supported Dendrimer Catalysts to Industry.

The practical use of supported catalysts in industry is well established, and the adaptation of our supported dendritic catalysts to industry is easily envisaged by using a flow reactor. One possible reactor design involves passing a gaseous or liquid olefin stream with CO/H₂ through a catalyst bed bounded by nano-porous membranes in a continuous flow system.

If a high pressure, continuous flow, reactor system could be developed and implemented in the lab, or at a sponsoring industrial research facility, hourly
monitoring of the catalyst selectivity and activity would provide a more representative assessment of the industrial relevance of our catalysts.

7.7 Final Reflections

In the final survey of our adventure, the heterogeneous silica and resin supports clearly served their purpose, providing stability, ease of recovery via membrane filtration, and the opportunity for recycling. Less clear was the advantage presented from using the dendrimer based multivalent phosphine ligands. Periphery derived, multivalent, dendritic catalysts may indeed present a highly active and selective system, however, in retrospect, a controlled polymerization towards building a hyperbranched polymer scaffold and phosphorylation of terminal amine groups, without regard to dendritic perfection, may result in a more easily accessible catalyst with similar properties. Indeed, in calculating the industrial profitability of the silica and resin supported dendritic catalysts, the most significant hurdle present is likely the length of time invested in the preparation of these ligands.

It must be also be stated, that the leaching and characterization problems encountered herein did not allow us to adequately evaluate the ultimate potential of supported dendrimers as catalysts in every catalytic reaction. The broad aspect of supported dendrimer catalysts may be further studied, by investigating alternate supports, ligand construction, and different catalytic transformation.
THEORETICAL AMINE CONTENT.

For every \( \text{NH}_2 \) group, one generation of growth adds a considerable amount of mass.

For ethylenediamine... \[ \text{F.wt.}_{\text{C}_2} = 228.29 \text{ g/mol} \ (\text{C}_{10}\text{H}_{22}\text{N}_5\text{O}_2) \]

For 1,4–diaminobutane... \[ \text{F.wt.}_{\text{C}_4} = 284.40 \text{ g/mol} \ (\text{C}_{14}\text{H}_{30}\text{N}_5\text{O}_2) \]

For 1,6–diaminohexane... \[ \text{F.wt.}_{\text{C}_6} = 340.51 \text{ g/mol} \ (\text{C}_{18}\text{H}_{38}\text{N}_5\text{O}_2) \]

For 1,12–diaminedodecane... \[ \text{F.wt.}_{\text{C}_{12}} = 508.83 \text{ g/mol} \ (\text{C}_{30}\text{H}_{62}\text{N}_5\text{O}_2) \]

Also, the number of \( \text{NH}_2 \) groups doubles with every generation.

\[ G_0 = 1 \text{ NH}_2 \]
\[ G_1 = 2 \text{ NH}_2 \]
\[ G_2 = 4 \text{ NH}_2 \]
\[ G_3 = 8 \text{ NH}_2 \]
\[ G_4 = 16 \text{ NH}_2 \]
The general formula for the determination of the theoretical amine content is as follows...

\[
c_x = \frac{n_x}{m_0 + c_0 \times \frac{F.Wt. \cdot c_x}{1000} \times \sum_1^x 2^{x-1}}
\]

where...

\( x = \) generation
\( c_0 = \) initial amine content \( (\text{mmol/g}) \)
\( m_0 = \) initial mass of the silica \( (\text{g}) \)
\( c_x = \) amine content of the generation \( (\text{mmol/g}) \)
\( F.Wt. = \) formula weight added per amine \( (\text{g/mol}) \)
\( n_x = \) moles of amines \( (\text{mmol} \cdot \text{NH}_2) \)

So, to calculate the amine content of the fourth generation \( C_{12} \) dendrimer starting from aminopropyl silica with 1.00g of 0.9 mmol NH\(_2\)/g SiO\(_2\) ...

\( x = 4 \)
\( n_x = 16 \text{ mmol} \cdot \text{NH}_2 \)
\( F.Wt. C_{12} = 508.83 \text{ g/mol} \)

\[
c_4 = \frac{n_4}{m_0 + c_0 \times \frac{F.Wt. \cdot c_{12}}{1000} \times (2^0 + 2^1 + 2^2 + 2^3)}
\]

\[
= \frac{16 \times 0.90 \text{ mmol} \cdot \text{NH}_2}{1.00 \text{g} + 0.90 \text{ mmol/g} \times \frac{508.83 \text{ g/mol}}{1000 \text{ mmol/mol}} \times (1 + 2 + 4 + 8)}
\]

\[
= 1.83 \text{ mmol NH}_2/\text{g SiO}_2
\]
Table A.1 Determination of the theoretical amine content for the various PAMAM dendrimers on silica.

<table>
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<th>Series</th>
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<th>$n_x$ of NH$_2$ (mmol)</th>
<th># of NH$_2$</th>
<th>$m_x$ (g)</th>
<th>Amine content (mmol NH$_2$/g SiO$_2$)</th>
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<td>x</td>
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<td></td>
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</table>
Figure A.1 Theoretical amine content of PAMAM on silica as a function of linker length and generation.
THEORETICAL ESTER CONTENT: HALF GENERATION

\[ \text{NH}_2 \quad \text{C}_8\text{H}_{16}\text{NO}_4 \]
Mol. Wt.: 16.02 \quad \text{Mol. wt.: 188.09}

So for every NH$_2$ group, 174.19 g/mol is added to yield 2 esters.

The general formula used for the determination of the theoretical ester content is as follows ...

\[
c_{x,5} = \frac{2}{m_o + c_x} \times \frac{n_x}{F.Wt._e} \times \frac{1000}{1000}
\]

where...
\[x = \text{generation}\]
\[c_{x,5} = \text{ester content} \ (\text{mmol/g})\]
\[m_o = \text{initial mass of the silica (g)}\]
\[c_x = \text{amine content of the generation (mmol/g)}\]
\[F.Wt._e = \text{Formula weight of ester added per amine (g/mol)}\]
\[n_x = \text{moles of amines (mmol \cdot NH}_2\text{)}\]
So, to calculate the ester content of the G–4.5 C_{12} dendrimer...

\[ C_{4.5} = \frac{2 \left( \frac{\text{mmol OCH}_3}{\text{mmol NH}_2} \right) \cdot 1.83 \left( \frac{\text{mmol NH}_2}{\text{g } \text{SiO}_2} \right)}{1.0 \left( \frac{\text{g } \text{SiO}_2}{\text{g } \text{SiO}_2} \right) + 1.83 \left( \frac{\text{mmol } \text{SiO}_2}{\text{g } \text{SiO}_2} \right) \times \frac{174.19 \left( \frac{\text{g}}{\text{mol OCH}_3} \right)}{1000 \left( \frac{\text{mg}}{\text{g}} \right)}} \]

\[ C_{4.5} = 2.79 \frac{\text{mmol OCH}_3}{\text{g } \text{SiO}_2} \]

Table A.2 Determination of the theoretical ester content for the various PAMAM half generations on silica.

<table>
<thead>
<tr>
<th>Series</th>
<th>Generation</th>
<th>( n_x ) of OCH(_3)</th>
<th># of OCH(_3)</th>
<th>( m_x ) (g)</th>
<th>Ester content (mmol OCH(_3)/g SiO(_2))</th>
</tr>
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<tr>
<td>G(_x)-C(_2)</td>
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<td>1.8</td>
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<td>1.16</td>
<td>1.56</td>
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</table>

\( ^a \) Calculated from 1.0 g of silica with an initial amine content of 0.9 mmol NH\(_2\)/g SiO\(_2\).
Figure A.2  Theoretical ester content of the PAMAM half generations on silica as a function of amine linker length and generation.
THEORETICAL PHOSPHINE CONTENT

\[ \text{NH}_2 \quad \text{C}_{26}\text{H}_{24}\text{NP}_2 \]

\[ \text{Mol. Wt.:} \quad 16.02 \quad \text{Mol. Wt.:} \quad 412.42 \]

So for every \( \text{NH}_2 \) group, \( 412.42 \text{ g/mol} \) is added, yielding 2 phosphine groups.

The general formula for the determination of the theoretical phosphine content is as follows...

\[ c_{xPPh_2} = \frac{2 \times n_x}{m_o + c_x \times \frac{F.Wt.\_PPh_2}{1000}} \]

where...

- \( x \) = generation
- \( c_{xPPh_2} \) = phosphine content \( (\text{mmol/g}) \)
- \( m_o \) = initial mass of the silica \( (\text{g}) \)
- \( c_x \) = amine content of the generation \( (\text{mmol/g}) \)
- \( F.Wt.\_PPh_2 \) = Formula weight of phosphine added per amine \( (\%/\text{mol}) \)
- \( n_x \) = moles of amines \( (\text{mmol} \cdot \text{NH}_2) \)

So, to calculate the phosphine content of the G–4 \( \text{C}_{12} \) dendrimer...

\[ c_{4PPh_2} = \frac{2 \times \left( \frac{\text{mmol} \_PPh_2}{\text{mmol} \_\text{SiO}_2} \right) \times 1.83 \left( \frac{\text{mmol} \_\text{NH}_2}{\text{g} \_\text{SiO}_2} \right)}{1.0 \left( \frac{\text{g} \_\text{SiO}_2}{\text{SiO}_2} \right) + 1.83 \left( \frac{\text{mmol} \_\text{SiO}_2}{\text{mol} \_\text{SiO}_2} \right) \times \frac{412.42 \left( \frac{\text{g}}{\text{mol} \_\text{PPh}_2} \right)}{1000 \left( \frac{\text{mg}}{\text{g}} \right)}} \]

\[ c_{4PPh_2} = 2.09 \left( \frac{\text{mmol} \_\text{PPh}_2}{\text{g} \_\text{SiO}_2} \right) \]
### Table A.3 Determination of the theoretical phosphine content for the various PAMAM dendrimers on silica.

<table>
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<tr>
<th>Series</th>
<th>Generation x</th>
<th>n_x of PPh₂ (mmol)</th>
<th># of PPh₂</th>
<th>m_x (g)</th>
<th>Phosphine content (mmol OCH₃/g SiO₂)</th>
</tr>
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</table>
Figure A.3  Theoretical Phosphine content of the PAMAM generations on silica as a function of amine linker length and generation.
REFERENCES AND FOOTNOTES


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(125) Note: Manufactured by DSM, 1 g of Astramol-64 (DAB-AM-64) is listed in the Aldrich catalogue at $248.00 (Cat#46,909-2).
(126) Note: Manufactured by Dendritech Inc., 2 g of the 10th generation PAMAM dendrimer (5% solution in methanol) is listed in the Aldrich catalog at $3722.70 (Cat# 53,677-6).

(127) Note: It should be possible to design and synthesize a cleavable linker which would allow for the selective cleavage of the dendron from the support. Subsequent to isolation of the dendron, standard characterization techniques could be used to elucidate the structure. This route was not attempted.

(128) Note: Amine content was determined via back titration with 0.10 M NaOH from the 0.10 M HCl washed Amine generation using phenolphthalein as the indicator. Method was developed via the back titration of commercial aminopropylsilica gel with known amine content.


(130) Note: The authors neglect to take into consideration the added mass of the growing dendrimer on silica when they calculate the theoretical amine content.


(133) Note: The Brunauer, Emmett, and Teller (BET) method, based on the isothermal adsorption of nitrogen, is a standard industrial method used for
determining the total surface area and pore size distributions of solid catalysts and particles.


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CLAIMS TO ORIGINAL RESEARCH:

1. Four series of bis-(diphenylphosphanylmethyl)-polyamidoamine dendrimers anchored on silica were prepared, complexed to rhodium and evaluated in the hydroformylation of aryl olefins and vinyl esters. The effect of linker length (C₂, C₄, C₆, and C₁₂) and dendrimer generation (G₁, G₂, G₃, and G₄) was investigated.

2. Rhodium complexes of pseudopeptide-based ligands immobilized on resin were also studied in the hydroformylation of various olefins. The effect of catalyst center placement, on the periphery or in the interior of the dendrimer, was studied.

3. The recycling potential of the aforementioned silica and resin based catalysts was investigated.

4. The synthesis and purification of PEG-supported dendrimers was attempted.

5. The preparation and purification of a soluble triphenylphosphite supported on PEG was attempted. The crude systems were evaluated as ligands for the hydroformylation of 1-octene using a Zwitterionic Rhodium complex under mild hydroformylation conditions.
6. The activity of a homogeneous triphenylphosphite – zwitterionic rhodium catalyst system toward the hydroformylation of 1-octene under mild conditions was also studied.
LIST OF PUBLICATIONS


